APPLICATIONS OF RONGALITE, THIOUREA DIOXIDE AND SODIUM DITHIONITE FOR THE SYNTHESIS OF FUNCTIONALIZED 2-OXINDOLES, PHENOLS, α-HYDROXY ESTERS/AMIDES AND α-DIAZO ESTERS

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BY

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Dedicated
To
My Beloved Family
&
My Supervisor

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CERTIFICATE

This is to certify that the research work presented in this thesis entitled **"Applications of Rongalite, Thiourea Dioxide and Sodium Dithionite for the Synthesis of Functionalized 2-Oxindoles, Phenols, *α*-Hydroxy Esters/Amides and *α*-Diazo Esters"** submitted by **Miss. Golla Sivaparwathi** for the degree of Doctor of Philosophy in Chemistry, National Institute of Technology, Warangal (Telangana), under my supervision and that the same has not been submitted elsewhere for any degree.

Date: 21-09-2022
Place: NIT Warangal

Dr. K. Hari Prasad
Thesis Supervisor

DECLARATION

I hereby declare that the matter embodied in this thesis entitled **"Applications of Rongalite, Thiourea Dioxide and Sodium Dithionite for the Synthesis of Functionalized 2-Oxindoles, Phenols, *α*-Hydroxy Esters/Amides and *α*-Diazo Esters"** is based entirely on the results of the investigations and research work carried out by me under the supervision of **Dr. K. Hari Prasad**, Department of Chemistry, National Institute of Technology, Warangal. I declare that this work is original and has not been submitted in part or full, for any degree or diploma to this or any other University.

Date: 21-09-2022 (**Golla Sivaparwathi)**

Place: NIT Warangal

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V. R. Parvathiwan

(Golla Sivaparwathi)

ABBREVIATIONS

Ag(OAc)	:	Silver acetate
$AsPh_3$	:	Triphenylarsine
$B(C_6F_5)_3$	:	Tris(pentafluorophenyl)borane
β-CD	:	*β*-Cyclodextrin
B_2pin_2	:	Bis(pinacolato)diboron
Bu_4NPF_6	:	Tetrabutylammonium hexafluorophosphate
CCl_4	:	Carbon tetrachloride
$CeBr_3$	:	Cerium(III) bromide
$(CF_3CO)_2O$	:	Trifluoroacetic anhydride
CFC reactor	:	Convection Flow-Coil reactor
CH_2Cl_2	:	Dichloromethane
CH_3CN	:	Acetonitrile
CH_3CO_2H	:	Acetic acid
Co	:	Cobalt
CO_2	:	Carbon dioxide
CoI_2	:	Cobalt(II) iodide
Cs_2CO_3	:	Cesium carbonate
CsF	:	Cesium fluoride
Cu	:	copper
$Cu(NO_3)_2.3H_2O$	:	Copper(II) nitrate trihydrate
$Cu(OAc)_2.H_2O$	:	Copper(II) acetate
$Cu(OTf)_2$	:	Copper(II) trifluoromethanesulfonate
Cu_2O	:	Copper(I) oxide
CuCl	:	Copper(I) chloride
CuI	:	Copper(I) iodide
CuO	:	Copper(II) oxide
$CuSO_4.5H_2O$	:	Copper(II) sulfate pentahydrate
Cz-POF-1	:	carbazolic porous organic frameworks
DBU	:	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCDMH	:	1,3-Dichloro-5,5-dimethylhydantoin
DCE	:	1,2-Dichlorethane
DFT	:	Density-functional theory
DIPEA	:	*N*,*N*-Diisopropylethylamine
DMC	:	Dimethyl carbonate
DMEDA	:	*N*,*N'*-Dimethylethylenediamine
DMF	:	*N*,*N*-Dimethylformamide
DMSO	:	Dimethyl sulfoxide
DMSO-d_6	:	Deuterated dimethyl sulfoxide

DPPM	:	Bis(diphenylphosphino)methane
EtOAc	:	Ethyl acetate
EtOH	:	Ethanol
Fe(TCP)Cl	:	Iron(tetra(*p*-chlorophenyl)porphyrinato) chloride
$FeBr_2$	:	Iron(II) bromide
$FeCl_3$	:	Iron(III) chloride
FT-IR	:	Fourier transform infrared
h	:	Hours
$(HCHO)_n$	:	Paraformaldehyde
H_2O	:	Water
H_2O_2	:	Hydrogen peroxide
H_3PO_4	:	Phosphoric acid
$HBF_4.OEt_2$	:	Tetrafluoroboric acid diethyl ether complex
HI	:	Hydrogen iodide
$HPO(OEt)_2$	:	Diethyl phosphite
HRMS	:	High-resolution mass spectrometry
$HSiEt_3$	:	Triethylsilane
Hz	:	Hertz
$^{i}Pr_2NEt$	:	*N*,*N*-Diisopropylethylamine
i-PrOH	:	Isopropanol
Ir	:	Iridium
$[Ir(COD)Cl]_2$	:	Bis(1,5-cyclooctadiene)diiridium(I) dichloride
J	:	Coupling constant
K_2CO_3	:	Potassium carbonate
$K_2S_2O_8$	:	Potassium persulfate
KI	:	Potassium iodide
KOH	:	Potassium hydroxide
L-DOPA	:	L-3,4-dihydroxyphenylalanine
$LiClO_4$	:	Lithium perchlorate
m	:	Multiplet
m-CPBA	:	*meta*-Chloroperoxybenzoic acid
Me_3NO	:	Trimethylamine *N*-oxide
MeOH	:	Methanol
mg	:	Milligram
min	:	Minutes
mL	:	Millilitre
mmol	:	Milli mole
$Mo(CO)_6$	:	Hexacarbonylmolybdenum(0)
mp	:	Melting point
MW	:	Microwaves

$N_2H_4.H_2O$	:	Hydrazine Hydrate
Na_2CO_3	:	Sodium carbonate
$Na_2S_2O_3$	:	Sodium thiosulfate
$NaBH_4$	:	Sodium borohydride
$NaHCO_3$	:	Sodium bicarbonate
NaOAc	:	Sodium acetate
NaOH	:	Sodium hydroxide
n-Bu_4NCl	:	Tetrabutylammonium chloride
NCS	:	N-Chlorosuccinimide
NEt_3	:	Triethylamine
NFSI	:	*N*-Fluorobenzenesulfonimide
NH_4OAc	:	Ammonium acetate
NHPI	:	*N*-Hydroxyphthalimide
Ni	:	Nickel
$Ni(OAc)_2$	:	Nickel(II) acetate
NMR	:	Nuclear Magnetic Resonance
NS-CeO_2	:	Nanosphere cerium(IV) oxide
O_2	:	Molecular oxygen
O_3	:	Ozone
$Pb(OAc)_4$	:	Lead(IV) acetate
Pd	:	Palladium
$Pd(dppf)Cl_2$	:	1,1′Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
PDI	:	Perylene diimide
Ph	:	Phenyl
PIFA	:	(Bis(trifluoroacetoxy)iodo)benzene
PMHS	:	Polymethylhydrosiloxane
PMP	:	1,2,2,6,6-Pentamethylpiperidine
P_{red}	:	Red phosphorus
q	:	Quartet
Rh	:	Rhodium
$Rh_2(OAc)_4$	:	Rhodium(II) acetate
rt	:	Room temperature
Ru	:	Ruthenium
RVC electrode	:	Reticulated Vitreous Carbon electrode
s	:	Singlet
SiO_2	:	Silicon dioxide
t	:	Triplet
TBAB	:	Tetrabutylammonium bromide
TBAHS	:	Tetrabutylammonium hydrogen sulfate
TBAI	:	Tetrabutylammonium iodide

^{t}BuONa	:	Sodium *tert*-butoxide
TDO	:	Thiourea dioxide
TEMPO	:	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA	:	Trifluoroacetic acid
THF	:	Tetrahydrofuran
$TiCl_4$	:	Titanium tetrachloride
TLC	:	Thin Layer Chromatography
TMEDA	:	Tetramethylethylenediamine
TMS	:	Tetramethyl silane
UV-Vis	:	Ultraviolet-visible
Zn	:	Zinc
$ZnCl_2$	:	Zinc(II) chloride
ZnO	:	Zinc(II) oxide
ZrO_2	:	Zirconium(IV) oxide

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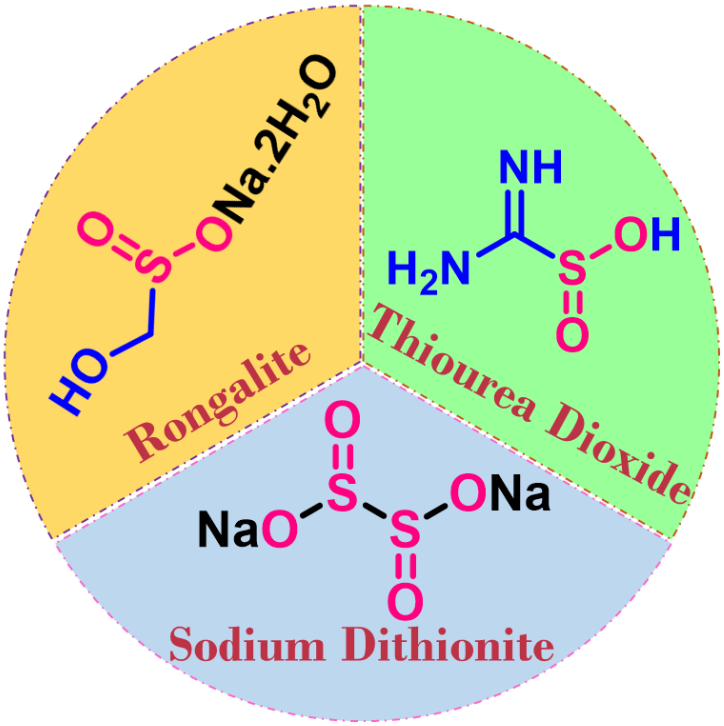
CHAPTER-I

INTRODUCTION



1.1. Introduction

Sulfur containing reducing agents with C–S and S–S bonds are ubiquitous in nature and found numerous applications. Mainly, these are divided into three categories such as *α*-hydroxyalkanesulfinates, thiourea oxides and dithionites, which include more than eighty number of reagents and among all, sodium hydroxymethanesulfinate dihydrate (rongalite), sodium dithionite and thiourea dioxide are the versatile reductants in the chemistry and also captivated the synthetic community.[1] The development of these reagents was started in the 18th century. In 1870, on the basis of Schönbein's observations,[2] Schützenberger prepared the sodium dithionite successfully for the first time.[3] Later, in the beginning of 20th century, even more stable reductants were invented like *α*-hydroxyalkanesulfinates (rongalite).[4] In 1910, thiourea dioxide was synthesized directly from the thiourea and hydrogen peroxide by Barnett.[5]

1.2. Rongalite

Rongalite is a white crystalline solid with the chemical formula $HOCH_2SO_2Na.2H_2O$. It is also called as sodium hydroxymethanesulfinate dihydrate or sodium formaldehyde sulfoxylate or rongalite C. In addition to sodium, zinc and calcium hydroxymethanesulfinate salts are also available, and commercially called them as decroline and rongalite H, respectively. Sodium hydroxymethanesulfinate is an industrial reagent and is available in the form of powder, lumps and granules. In 1993, Mulliez et al., synthesized the rongalite from sodium dithionite and formaldehyde using NaOH.[6] The X-ray crystal structure of rongalite has been investigated by Truter in 1955 and found that sulfur exists in the IV oxidation state and the two oxygen atoms are pyramidally bonded to sulfur atom with S–O bond length 1.50 Å and C–S bond length 1.84 Å. The exact structure of rongalite is represented in the Figure 1.1.[7,8]

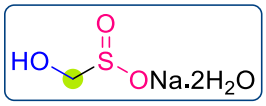
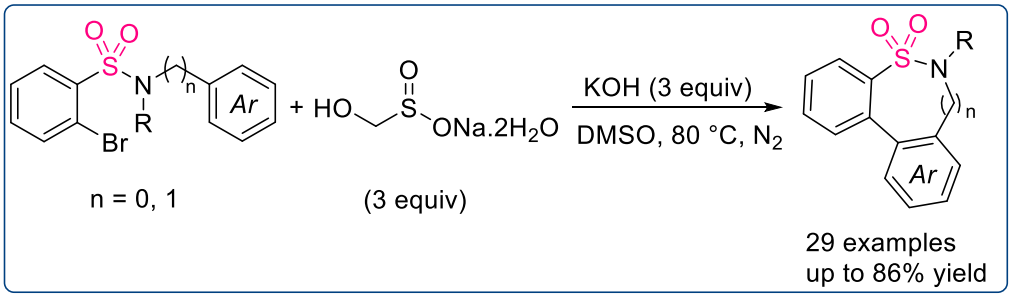


Figure 1.1

The name of the rongalite came from the French, which means discharge. It is used as a bleaching agent in the textile industry,[9] and was also employed in the emulsion polymerization of acrylates.[10] It works as an antidote for acute mercury poisoning,[11] and utilized in the anticancer formulations.[12] Also, it is a potential substitute for toxic formaldehyde.[13,14] In addition to above

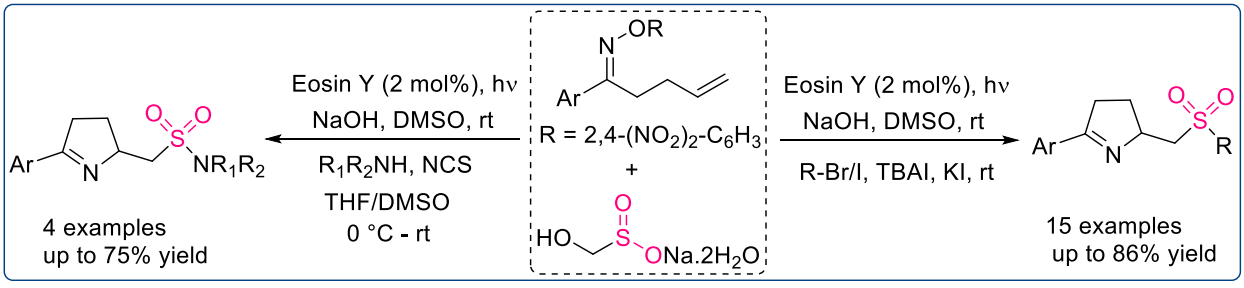
industrial and medicinal applications, reducing property of rongalite was also explored in the material science which includes, preparation of CdTe-quantum dots and thin films,[15] PbSe films,[16] carbon nanostructures,[17] cobalt telluride nanostructures,[18] cobalt selenide nanostructures,[19] silver selenide thin films,[20] copper nanoparticles,[21] and zinc sulfide nanoparticles.[22] Besides the applications of rongalite in material science, it also found a great number of applications in the synthetic chemistry due to the multifaceted reactivity of rongalite such as sulfone surrogate, C1 unit source and as reductant *via* single electron transfer. The recent applications of rongalite in the synthesis of useful molecules were discussed below.

Laha and co-workers have developed a protocol for the synthesis of six- and seven-membered biarylsultams from sulfonamides using rongalite in the presence of potassium hydroxide (KOH) in DMSO at 80 °C under inert atmosphere for 24 h. Here, rongalite used for the generation of aryl radicals from aryl bromides, later subsequent intramolecular arylation afforded the biarylsultams with good yields (Scheme 1.1).[23]



Scheme 1.1

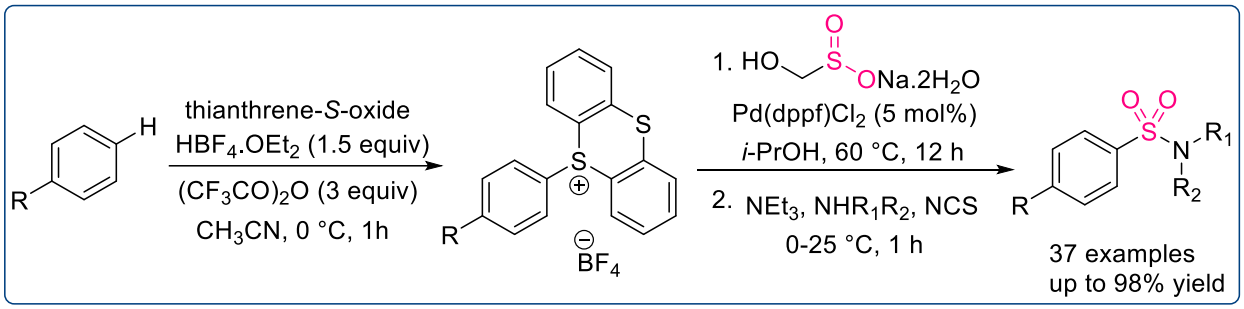
He et al. reported a photoredox-catalyzed strategy for the synthesis of aliphatic sulfones and sulfonamides from the oximes under visible light irradiation. The first step of this protocol involves the formation of sulfinate salts using rongalite as sulfone source, eosin Y as a photocatalyst. The second step is the trapping of electrophile by sulfinate anion to form the



Scheme 1.2

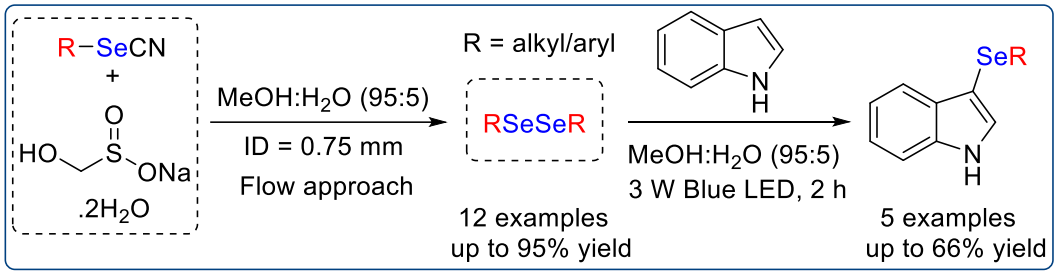
aliphatic sulfones and sulfonamides with moderate to good yields under different reaction conditions (Scheme 1.2).[24]

Ritter and co-workers described the generation of aryl sulfonamides form thianthrenium salts which are formed *via* site selective C–H thianthrenation of arenes using thianthrene-*S*-oxide and $HBF_4.OEt_2$ in the presence of trifluoroacetic anhydride in CH_3CN at 0 °C for 1 h. This protocol involves two steps, the first step is about the coupling of rongalite with thianthrenium salt in the presence of $Pd(dppf)Cl_2$ in isopropanol at 60 °C for 12 h. Later, the *in situ* formed aryl hydroxymethyl sulfone reacts with secondary amine to form the corresponding aryl sulfonamides with moderate to excellent yields (Scheme 1.3).[25]



Scheme 1.3

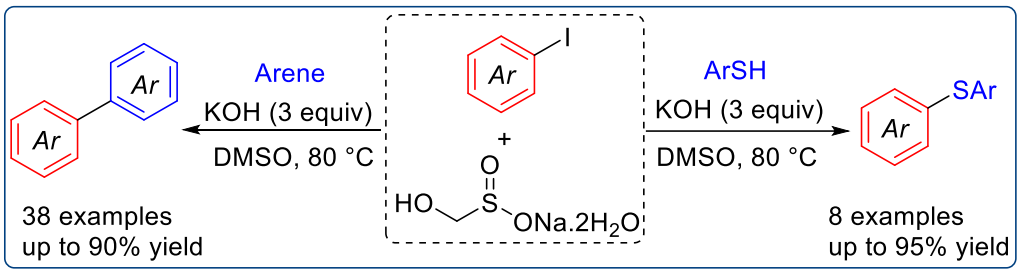
Heredia et al. developed a two-step protocol for the synthesis of organic selenides *via* continuous-flow chemistry. The first step involves the reduction of aryl/alkyl selenocyanates to diselenides using rongalite in $MeOH:H_2O$. The second is about the formation of organic selenides from the electron rich arenes like indoles, using *in situ* generated alkyl/aryl selenyl radical under photochemical conditions (Scheme 1.4).[26]



Scheme 1.4

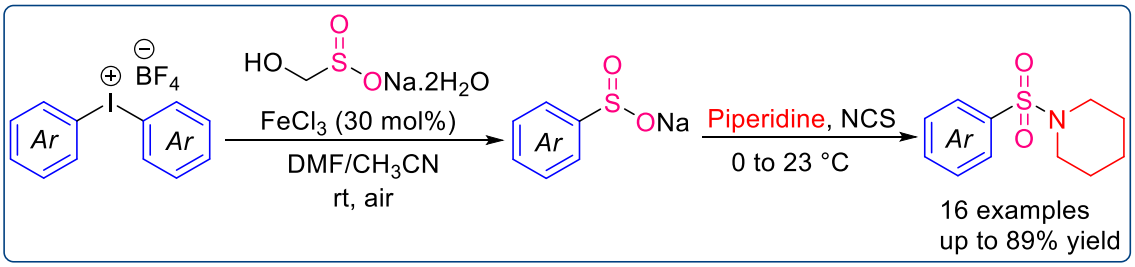
Wang and co-workers described the generation of aryl radicals from aryl iodides using rongalite as a single electron transfer reagent. Later, the formed aryl radicals were employed for the synthesis of biaryls and diaryl sulfides *via* $S_{RN}1$ or homolytic aromatic substitution in the

presence of potassium hydroxide (KOH) in DMSO at 80 °C under transition metal-free condition. Also, this protocol allows the arylation of diphenylphosphine, sodium benzene sulfinate, sodium hydrosulfide and triethylphosphite with moderate to excellent yields (Scheme 1.5).[27]



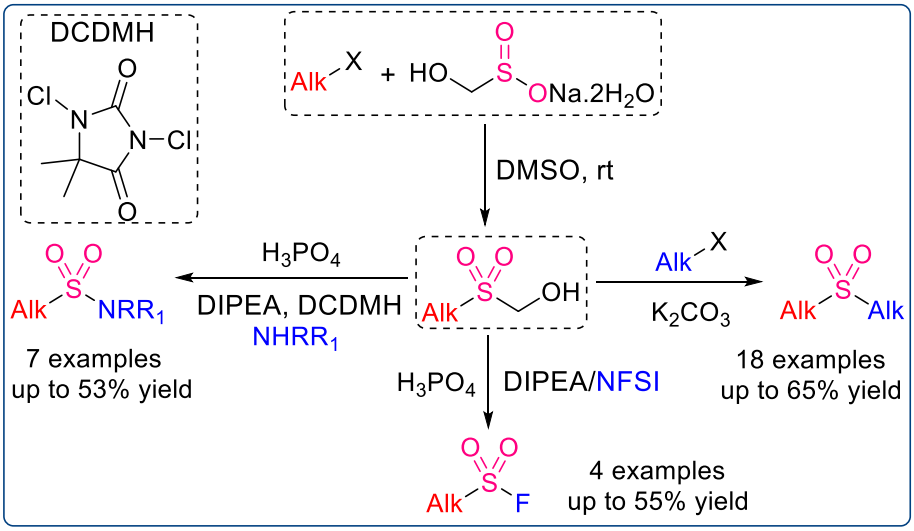
Scheme 1.5

Luo and co-workers developed an iron-catalyzed strategy for the generation of arylsulfinates form the diaryliodonium salts using rongalite in 1:1 mixture of DMF:CH_3CN under open air at room temperature. Here, rongalite functions as a single electron transfer reagent and a source of sulfoxylate radical anion. Further, they have synthesized the arylsulfonamides from arylsulfinates using piperidine as an amine source in the presence of *N*-chlorosuccinimide (Scheme 1.6).[28]



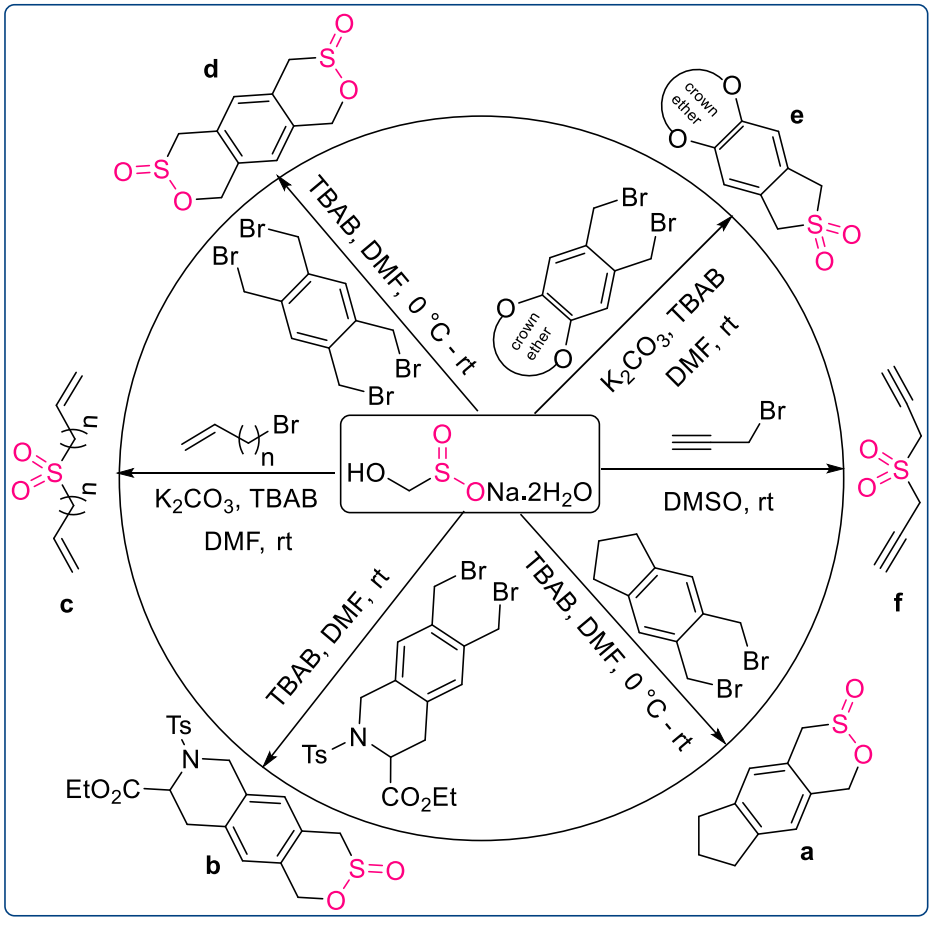
Scheme 1.6

Shavnya and co-workers reported a protocol for the synthesis of hydroxymethyl sulfone from alkyl halides using rongalite in DMSO at room temperature. Later, they have prepared unsymmetrical dialkylsulfones using *in situ* generated alkylsulfinate from hydroxymethyl sulfone in the presence of potassium carbonate (K_2CO_3). Also, they synthesized various sulfonyl fluorides in the presence of phosphoric acid (H_3PO_4) using DIPEA and *N*-Fluorobenzenesulfonimide. In a similar way, alkylsulfonamides were also prepared by employing DCDMH and various amines (Scheme 1.7).[29]



Scheme 1.7

Kotha and co-workers diversely utilized the rongalite for the preparation of various sultines from the corresponding alkyl bromides in the presence of tetrabutylammonium bromide.



Scheme 1.8

In addition to sultines, several sulfones were also reported under similar conditions using potassium carbonate such as dipropargyl sulfones,[30] symmetric and cyclic sulfones *via* ring-closing metathesis.[31] Later, they employed these sultines/sulfones as the synthetic precursors to *o*-xylylenes, which are the versatile reactants in the Diels-Alder chemistry (Scheme 1.8).

Further, they have utilized the prepared sultines/sulfones to synthesize various functionalized molecules such as i) tetralin-based α-amino acid derivatives **A**,[32] using sultine **a** and methyl 2-acetamidoacrylate in toluene under reflux for 30 h, ii) quinone-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid hybrids **B**,[33] using sultine **b** and 1,4-benzoquinone derivative in toluene at 90 °C for 12 h and later subsequent aromatization in the presence of MnO_2 in dry dioxane for 30 h, iii) annulated benzocrowns **C**,[34] using sulfone **e** and acetylene derivative in *o*-dichlorobenzene at 160 °C, iv) annulated benzocycloalkanes **D**,[35] using sultine **a** and dimethyl acetylenedicarboxylate under N_2 bubbling in toluene at 100 °C, v) various spirooxindoles **E**,[36] and vi) fullerene-based unnatural amino acids **F**,[37] using the *in situ* generated *o*-xylylenes by applying Diels-Alder chemistry (Figure 1.2).

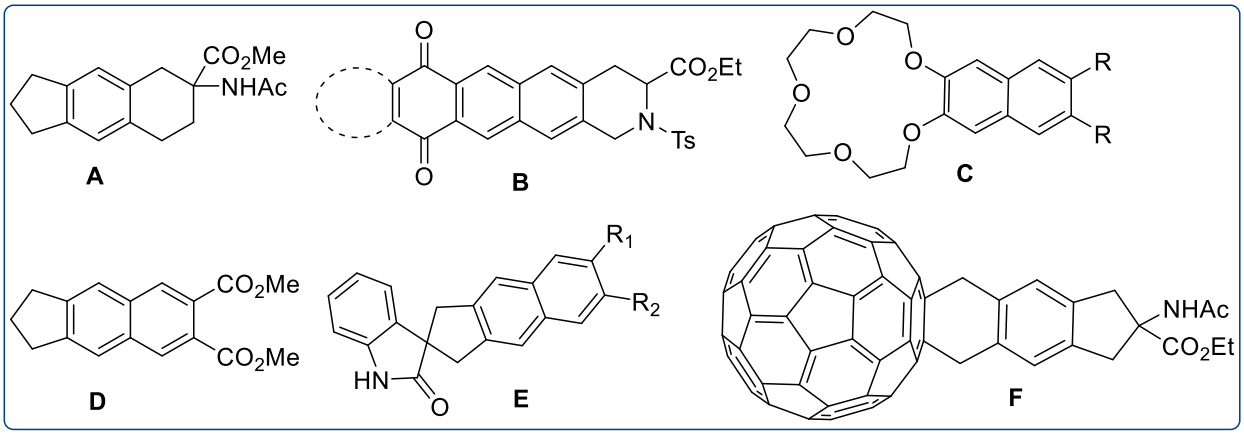
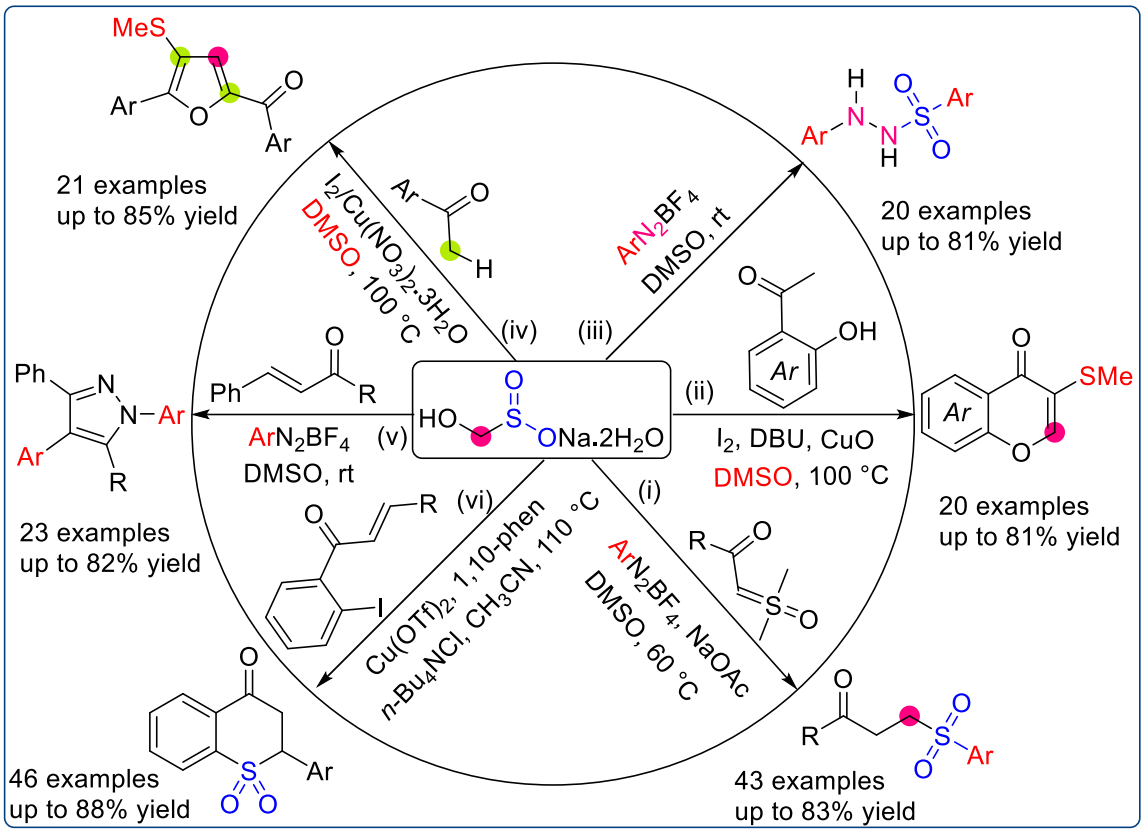


Figure 1.2. Various functionalized molecules generated form sultines/sulfones

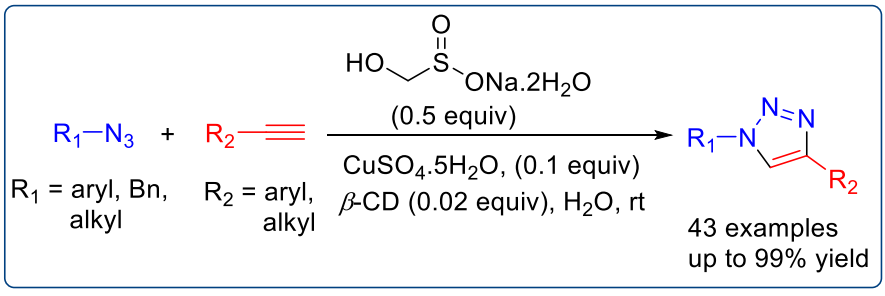
Wu and co-workers extensively used the rongalite as a C1 unit source, sulfone surrogate and single electron transfer reagent to prepare multifunctional molecules such as i) sulfonylmethylated compounds,[38] synthesized from sulfoxonium ylides and aryldiazonium salts in the presence of sodium acetate in DMSO at 60 °C, ii) C3-sulfenylated chromones,[39] prepared using *o*-hydroxyaryl methyl ketones, I_2/DMSO reagent system and CuO as a catalyst in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 100 °C, iii) *N*-aminosulfonamides,[40] from aryldiazonium tetrafluoroborates in DMSO at room temperature, iv) 2,4,5-trisubstituted

furans,[41] using Cu as a catalyst *via* triple C(sp3)-H functionalization in DMSO (acts as both reagent and solvent) at 100 °C, v) fully substituted pyrazoles,[42] from aryldiazonium tetrafluoroborates and *α,β*-unsaturated aldehydes or ketones *via* radical annulation reaction and vi) 1-thiaflavanone sulfones,[43] using rongalite as sulfone source, 2´-iodochalcones, Cu as a catalyst and tetrabutylammonium chloride in CH_3CN at 110 °C (Scheme 1.9).



Scheme 1.9. Applications of rongalite as C1 unit and sulfone source

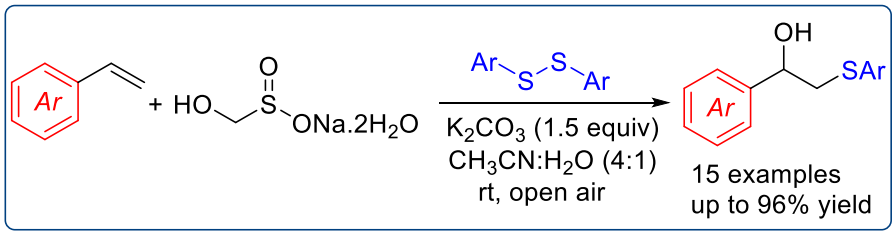
Kokatla and co-workers introduced a green protocol for the synthesis of regiospecific 1,4-disubstituted 1,2,3-triazoles from alkyl/benzyl/aryl azides with terminal alkynes using *in situ* generated Cu nanoparticles from $CuSO_4.5H_2O$ and rongalite in the presence of *β*-cyclodextrin in



Scheme 1.10

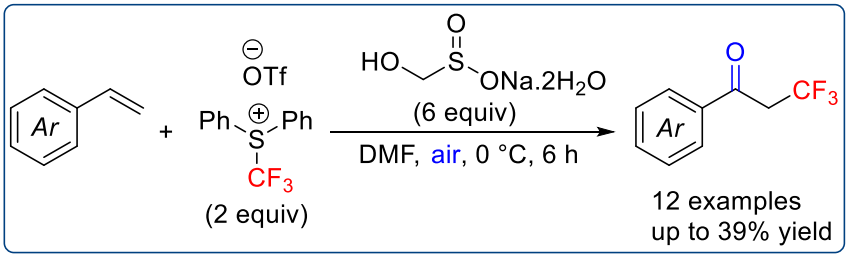
water at room temperature. Here, rongalite reduces the Cu(II) to Cu(0) NPs and *β*-CD acts as a stabilizing agent. This protocol offers the synthesis of wide range of 1,4-disubstituted 1,2,3-triazoles up to 99% yields (Scheme 1.10).[44]

Yadav and co-workers described the regioselective synthesis of *β*-hydroxy sulfides by employing styrenes, rongalite and diaryl disulfides in the presence of potassium carbonate (K_2CO_3) in a mixture of CH_3CN:H_2O (4:1) at room temperature in open air. Here, rongalite generates the thiyl radicals from disulfides *via* single electron transfer pathway. The formed thiyl radicals regioselectively attacks on the styrene and undergoes subsequent oxidation with atmospheric oxygen to produce *β*-hydroxy sulfides with good to excellent yields (Scheme 1.11).[45]



Scheme 1.11

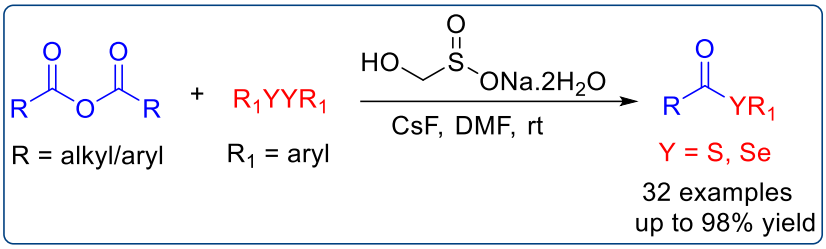
Zhang et al. introduced a novel protocol for the synthesis of *α*-trifluoromethylated ketones by utilizing styrenes and *S*-(trifluoromethyl)diphenylsulfonium triflate using 6 equiv of rongalite in DMF at 0 °C in open air for 6 h. Here, rongalite acts as a single electron transfer agent, helps in the production of trifluoromethyl radical source from its salt, later it attacks on the styrene and further undergoes oxidation with molecular oxygen present in air to generate *α*-trifluoromethylated ketones with 20-40% yields (Scheme 1.12).[46]



Scheme 1.12

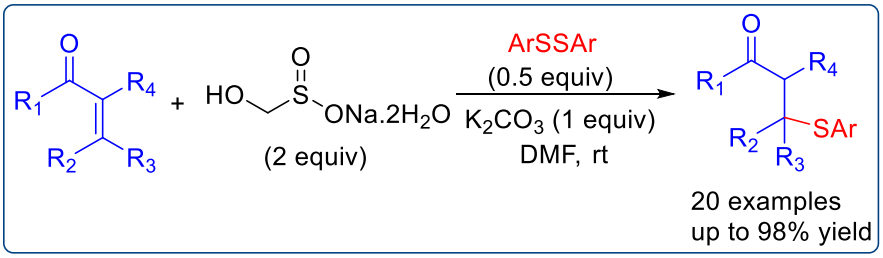
Dan et al. reported a methodology for the synthesis of thioesters and selenoesters with good to excellent yields by employing corresponding alkyl/aryl anhydrides and diaryl disulfides/diselanes using rongalite and cesium fluoride in DMF at ambient temperature. Here,

rongalite functions as a single electron transfer reagent, and generates the chalcogenolate anions from disulfides/diselanes, which further undergoes the acylation with anhydrides to generate thioesters and selenoesters (Scheme 1.13).[47]



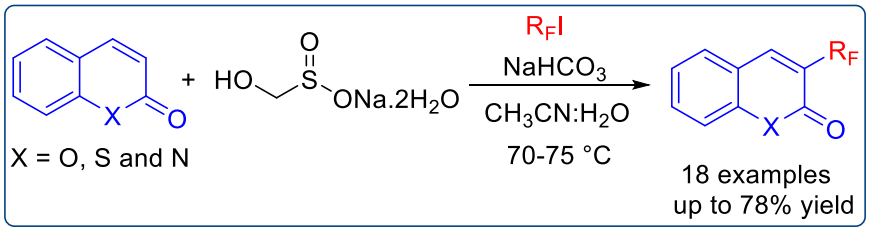
Scheme 1.13

Wu and co-workers introduced an odorless protocol to produce *β*-sulfido carbonyl compounds form *α,β*-unsaturated carbonyl compounds using rongalite, diaryl disulfides and K_2CO_3 in DMF at ambient temperature. Here, rongalite helps to generate the thiolate anion from disulfide *via* single electron transfer pathway. Later, the formed thiolate anion undergoes thia-Michael addition to afford *β*-sulfido carbonyl compounds with good to excellent yields (Scheme 1.14).[48]



Scheme 1.14

Huang and co-workers described the synthesis of 3-perfluoroalkylated coumarins, 2-quinolones and thiocoumarins using perfluoroalkyl iodides and rongalite in the presence of sodium bicarbonate ($NaHCO_3$) in a mixture of CH_3CN and H_2O at 70-75 °C. Rongalite helps to generate the perfluoroalkyl radical from respective iodides *via* SET pathway and afforded products with moderate to good yields (Scheme 1.15).[49]



Scheme 1.15

Here, we discuss some more applications of rongalite in addition to the aforementioned synthetic transformations. Harries et al., used rongalite as a reductant in the reductive dehalogenation of α-halo ketones to form the respective products.[50] Later, Suzuki et al., reported the other reduction protocols using rongalite in combination with tellurium powder, *in situ* it generates the Na_2Te, which is the potential reagent for the reduction of nitro aromatics to amines and also this protocol applicable to substrates which contain acid-sensitive functional groups.[51] Also, Na_2Te generates the olefins from their 1,2-dibromo alkanes in stereoselective manner and tolerates the other reducible functional groups such as nitro, carbonyl, carboxyl and ester moieties.[52] Nagakura's group employed rongalite in the deprotection chemistry in the presence of $Pd(PPh_3)_4$, to deprotect the allyl groups of carboxylic acids, amines and alcohols.[53] Dittmer's group prepared the allylic alcohols from oxiranes utilizing rongalite and tellurium chemistry under ultrasound or microwave irradiation in the solid phase synthesis.[54] Tang's group prepared the *N*-difluoromethyl thioureas from azoles using rongalite and bromodifluoroacetate in the presence of elemental sulfur.[55] Recently, Zhang et al., synthesized thiosulfonates from sulfonyl hydrazides and benzotrifluoride using rongalite at 80 °C under air.[56]

1.3. Thiourea dioxide

Thiourea dioxide is also called as formamidinesulfinic acid or aminoiminomethanesulfinic acid. In 1962, Sullivan's group investigated the X-ray crystal structure of thiourea dioxide and found that, the solid state of thiourea dioxide exists as $(NH_2)_2CSO_2$ and the two oxygen atoms and one carbon atom pyramidally bonded to sulfur atom. The S–O bond length is 1.496 Å, the C–N bond length is 1.296 Å and the C–S bond length is 1.867 Å, which is higher when compared to the C–S bond length of thiourea (1.716 Å). The large C–S bond length is attributed to the antibonding interaction between the lone pair on sulfur atom and the filled p-orbitals of carbon atom.[57] In 2003, Lough's group reported that the thiourea dioxides are the Lewis acid-base adducts of diamino carbens and sulfur dioxide based on the quantum chemical calculations (Figure 1.3).[58]

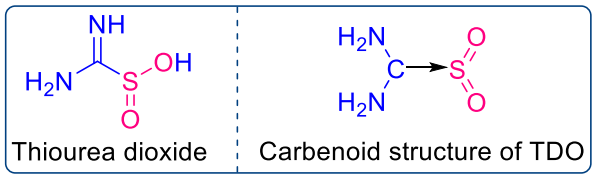
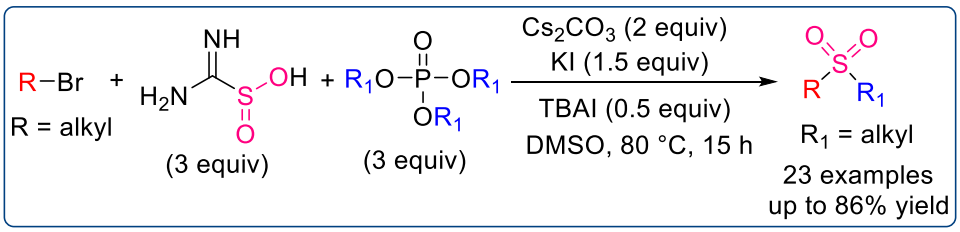


Figure 1.3

Thiourea dioxide is a well-known reducing agent, and found numerous applications in chemistry, biology, textile industry, etc. For example, thiourea dioxide acts as a well co-reactant with lucigenin for chemiluminescence, and this system is useful for the selective detection of dopamine. Thiourea dioxide is found to be more compatible with lucigenin compared to other reagents such as uric acid, amino acids, sugars, and ascorbic acid.[59] Also, thiourea dioxide successfully employed for the recycling of keratin (protein macromolecule) from waste wool, which is very difficult due to dense structure of wool.[60] Thiourea dioxide in combination with chitosan acts as an effective cleaning gel for the manganese blue and black stains on glass and granite materials.[61] Thiourea dioxide with traces of Cu(II) is an effective system for treating diatrizoate, which is present in hospital waste water.[62] It is also useful for removal of nitric oxide from Fe(II)EDTA-NO,[63] and helps in the chemical modification of bitumen to work with improved properties. In addition to reduction properties of thiourea dioxide, it is also utilized in the synthesis of guanidines and its derivatives.[64] The applications of thiourea dioxide as reducing agent, sulfone source and as an organocatalyst in the synthetic chemistry are discussed below.

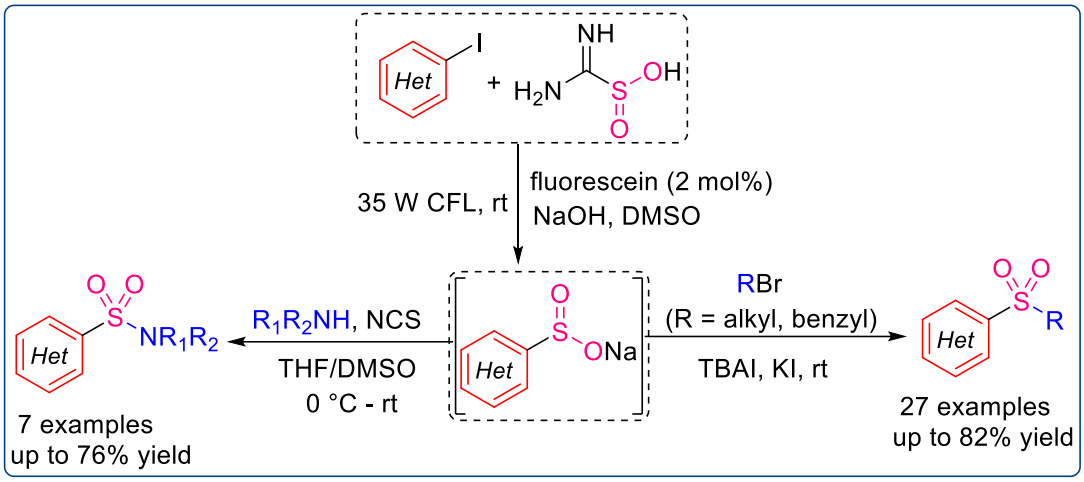
Jiang and co-workers developed a methodology for the synthesis of dialkyl sulfones from alkyl bromides and trialkyl phosphate using thiourea dioxide in the presence of cesium carbonate, KI and TBAI in DMSO at 80 °C for 15 h. This protocol offers the synthesis of wide range of dialkyl sulfones with moderate to good yields. Here, thiourea dioxide acts as a sulfone source. Late-stage modification was also performed on cholesterol and estrone to produce the corresponding sulfones using this method (Scheme 1.16).[65]



Scheme 1.16

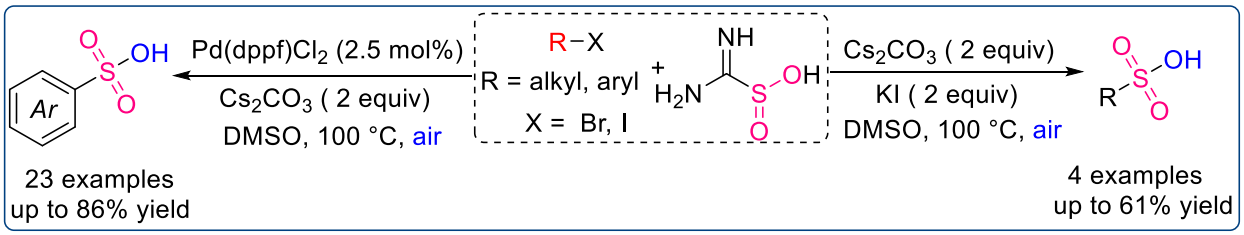
Ye et al. described the synthesis of diversified heteroaryl sulfones or heteroaryl sulfonamides from heteroaryl iodides using thiourea dioxide as sulfone source with good yields. It is a one-pot two-step process, first step involves the formation of heteroaryl sulfinate, in the presence of 2 mol% of fluorescein as a photocatalyst, sodium hydroxide (NaOH) with 35 W CFL bulb in DMSO at room temperature. The second step is about the formation of i) heteroaryl sulfones,

from the sulfinates using alkyl/benzyl bromide in the presence of TBAI and KI at room temperature, and ii) heteroaryl sulfonamides, from heteroaryl sulfinates using amine and *N*-chlorosuccinimide in a mixture THF and DMSO at 0 °C to room temperature (Scheme 1.17).[66]



Scheme 1.17

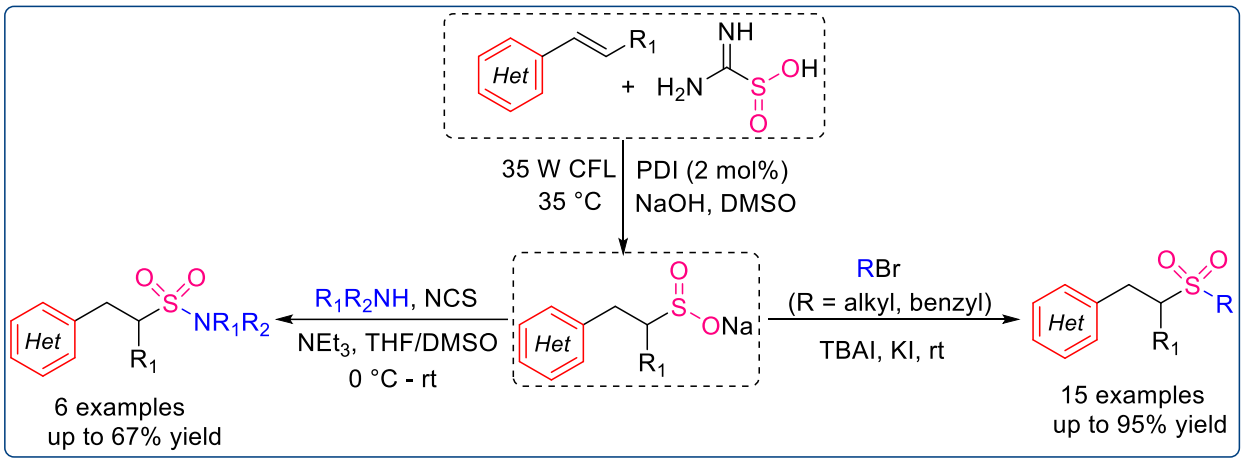
Jiang and co-workers synthesized the aryl sulfonic acids using transition metal ($Pd(dppf)Cl_2$) and alkyl sulfonic acids under transition metal-free conditions, respectively by employing aryl iodides/alkyl bromides using thiourea dioxide as sulfone source in the presence of cesium carbonate (Cs_2CO_3) in DMSO at 100 °C under open air for 14 h. The *in situ* generated aryl/alkyl sulfinate reacts with the molecular oxygen present in air and produced the sulfonic acids. The oxygen atom in the sulfonic acid is coming from the molecular oxygen present in the air (Scheme 1.18).[67]



Scheme 1.18

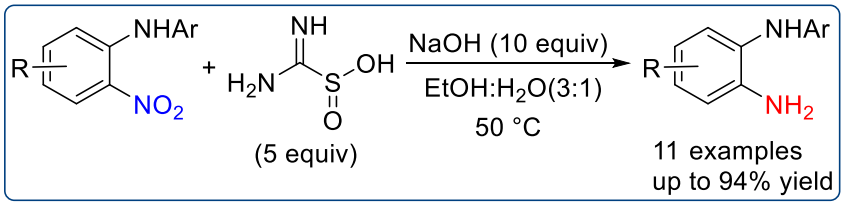
Li et al. developed a photoredox-catalyzed protocol for the functionalization of alkenes to produce alkyl sulfones and alkyl sulfonamides using thiourea dioxide. Here, thiourea dioxide functions as a sulfone source and single electron transfer reagent. It is a one-pot two-step process, first step involves the formation of alkyl sulfinate in regioselectively in the presence of 2 mol% of perylene diimide (PDI) as a photocatalyst, sodium hydroxide (NaOH) with 35 W CFL

bulb in DMSO at 35 °C. The second step is about the formation of i) alkyl sulfones, from the sulfinates using alkyl/benzyl bromide in the presence of TBAI and KI at room temperature, and ii) alkyl sulfonamides, from the sulfinates using amine, *N*-chlorosuccinimide and triethyl amine (NEt_3) in a mixture THF and DMSO at 0 °C to room temperature. Fluorescence quenching experiments suggested that the oxidation of sulfur dioxide dianion to sulfur dioxide radical anion (Scheme 1.19).[68]



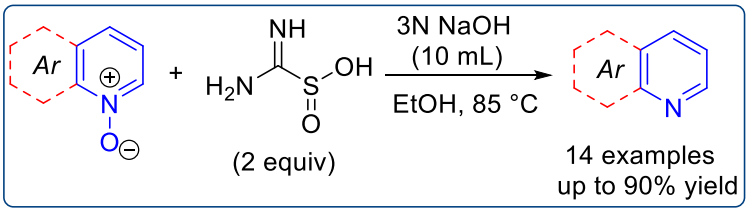
Scheme 1.19

Zhong et al. have described an effective strategy for the synthesis of *N*-substituted-benzene-1,2-diamines using *N*-substituted-2-nitroanilines and thiourea dioxide as a reducing agent in the presence of sodium hydroxide (NaOH) in EtOH+H_2O system at 50 °C. Finally, the products are purified by simple filtration. The key features of this method include, inexpensive reducing agent and produced urea as by-product, which is an environmentally benign (Scheme 1.20).[69]



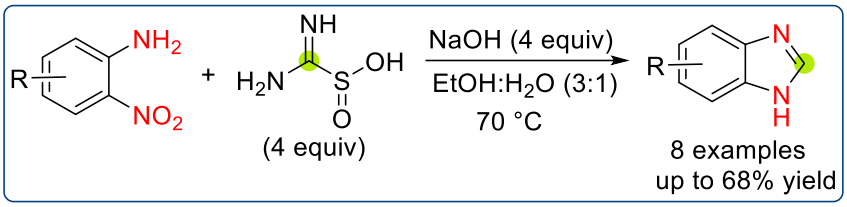
Scheme 1.20

Chmielowiec and co-workers have developed a protocol for the deoxygenation of aromatic *N*-oxides using thiourea dioxide and 3N sodium hydroxide in EtOH at 85 °C and produces the corresponding amines in good yields in 1-4 h. This protocol is also applicable to various quinolines, isoquinolines and acridine *N*-oxides. In addition to this, *N*,*N*-dioxides also underwent deoxygenation readily and afforded the respective products (Scheme 1.21).[70]



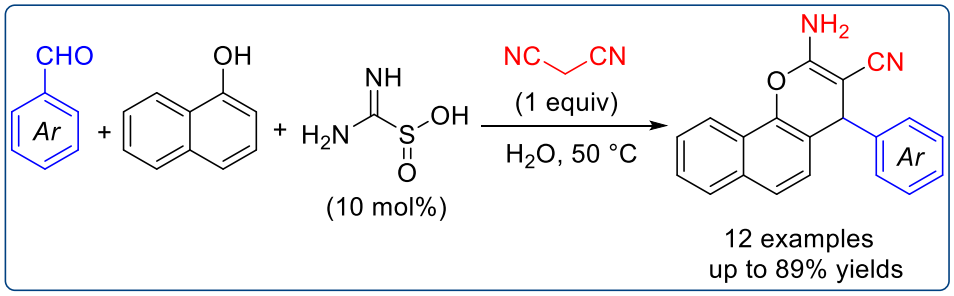
Scheme 1.21

Luo and co-workers developed a procedure for the synthesis of benzimidazoles with moderate to good yields from 2-nitroanilines using thiourea dioxide in the presence of sodium hydroxide in a mixture of EtOH and H_2O at 70 °C. Here, 2-nitroaniline undergoes reduction with thiourea dioxide to from *o*-phenylenediamine, which further again reacts with thiourea dioxide and produces the benzimidazoles (Scheme 1.22).[71]



Scheme 1.22

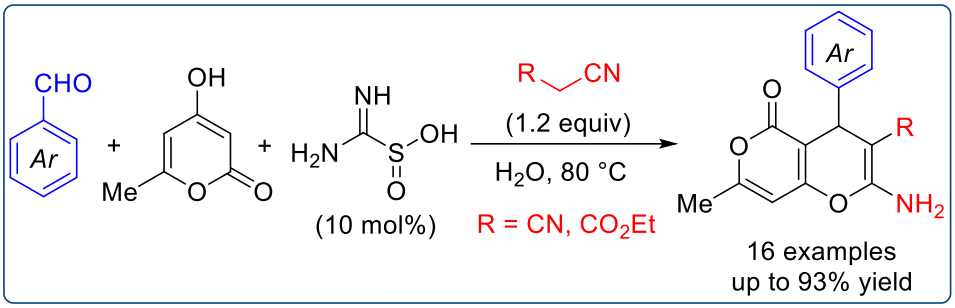
Jain and co-workers described a thiourea dioxide catalyzed multi-component reaction of aromatic aldehydes, *α* or *β*-naphthol and malononitrile in water (H_2O) at 50 °C to produce the naphthopyran derivatives with 80-89% yields. The products were purified by simple filtration and the filtrate contains the thiourea dioxide, which can be reused up to several times (Scheme 1.23).[72]



Scheme 1.23

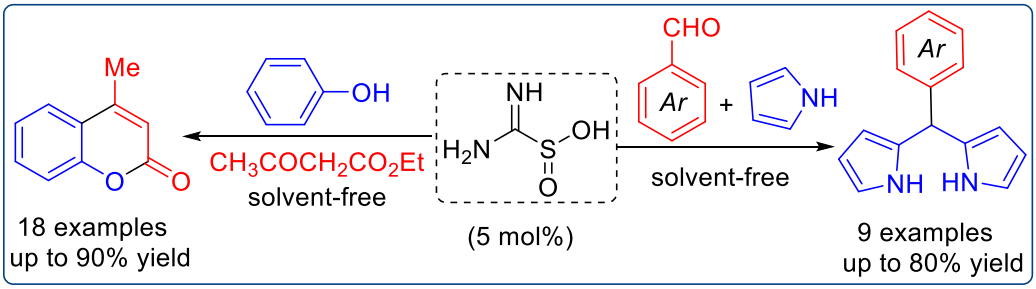
Aswin and co-workers developed a multi-component protocol for the synthesis of pyrano[4,3-*b*]pyran derivatives using aromatic aldehydes, cyano acetate or malononitrile and 4-hydroxy-6-methylpyran-2-one by employing 10 mol% of thiourea dioxide as a catalyst in

water at 80 °C. In this protocol, the products were purified by simple filtration and the filtrate contains the thiourea dioxide, which can be reused up to several times (Scheme 1.24).[73]



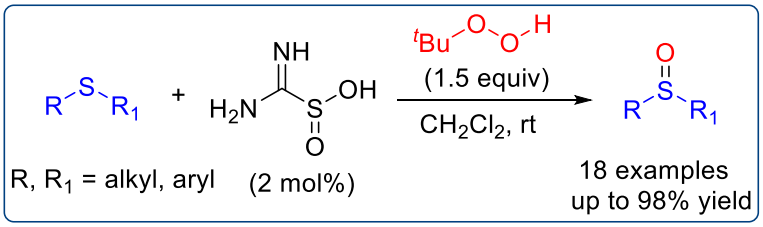
Scheme 1.24

Verma et al. reported a solvent-free protocol for the synthesis of heterocycles such as substituted coumarins and dipyrromethanes utilizing thiourea dioxide as a recyclable catalyst. Coumarins are prepared from the phenols and ethyl acetoacetate under stirring, and dipyrromethanes are prepared using aromatic aldehydes and pyrroles in a similar way. At the end of the reaction, organic compound was extracted with organic solvent and water contains the thiourea dioxide, which will be reused for further reactions (Scheme 1.25).[74]



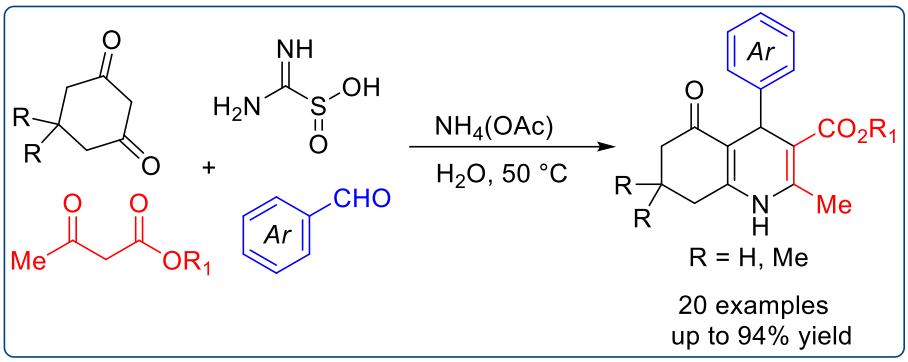
Scheme 1.25

Jain and co-workers reported a method for the oxidation of aryl/alkyl sulfides to respective sulfoxides using thiourea dioxide as an efficient organocatalyst and *tert*-butyl hydroperoxide as an oxidizing agent in dichloromethane (CH_2Cl_2) at room temperature. Here, the possibility of forming hydrogen bonds between thiourea dioxide and *tert*-butyl hydroperoxide facilitates the oxidation of sulfides to sulfoxides with good to excellent yields (Scheme 1.26).[75]



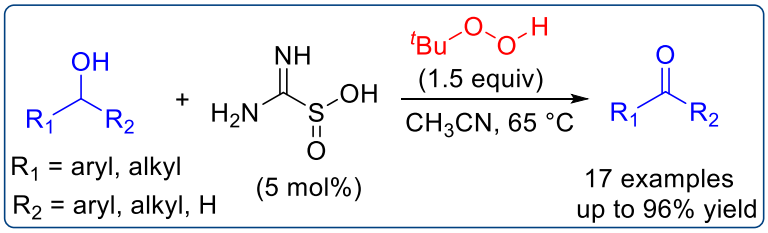
Scheme 1.26

Kumar et al. developed a multicomponent reaction for the synthesis of polyhydroquinolines using dimedone, aldehyde, ethyl acetoacetate and ammonium acetate by employing thiourea dioxide as an organic catalyst in water at 50 °C *via* Hantzsch multicomponent coupling. This protocol allows the synthesis of diverse polyhydroquinolines with 85-94% yields (Scheme 1.27).[76]



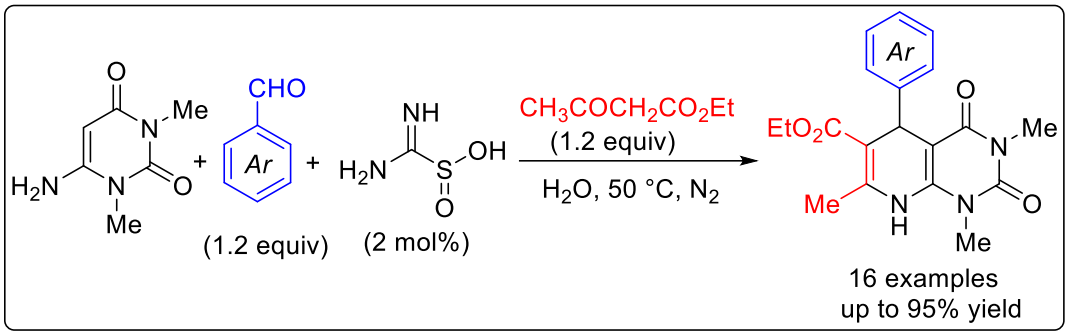
Scheme 1.27

Jain and co-workers developed a protocol for the oxidation of primary/secondary alcohols to the respective aldehydes/ketones using thiourea dioxide as an organocatalyst with *tert*-butyl hydroperoxide as an oxidizing agent in CH_3CN at 65 °C. This protocol offers the synthesis of a wide range of carbonyl compounds from their respective alcohols with 76-96% yields (Scheme 1.28).[77]



Scheme 1.28

Verma et al. described the synthesis of various dihydropyrido[2,3-*d*]pyrimidine-2,4-diones from 6-amino-1,3-dimethyl uracil, aromatic aldehyde and 1,3-dicarbonyl compounds using thiourea dioxide as an organocatalyst in water at 50 °C under nitrogen atmosphere. Here, the product is simply purified by filtration and the filtrate contains the thiourea dioxide, which can be reused up to several times (Scheme 1.29).[78]



Scheme 1.29

1.4. Sodium dithionite

Sodium dithionite is a white crystalline powder. The other name of sodium dithionite is sodium hydrosulfite. In 1956, Dunitz examined the crystal structure of sodium dithionite by using X-ray analysis. The crystals are monoclinic with space group *P2/c.* The dithionite ion is a combination of two sub units of SO_2^-, with long S–S bond (2.39 Å) and present in the eclipsed manner with 30 ° from parallel and it has C_{2v} symmetry (Figure 1.4).[79]

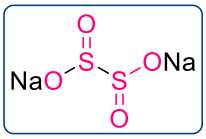
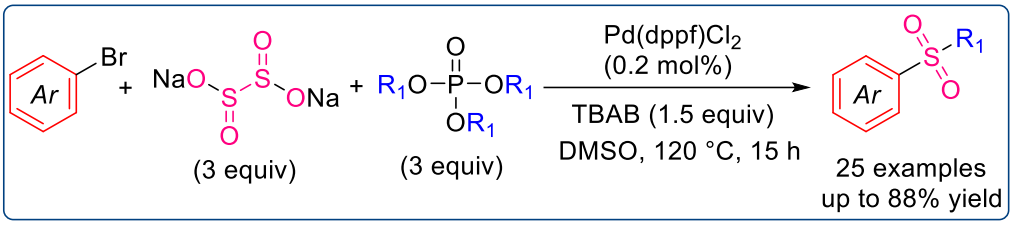


Figure 1.4

The reducing property of sodium dithionite has found wide applications. It is employed in the preparation of nickel sulfides from their nickel chlorides.[80] It is used to remove the residual lignin and the chromophores present in the kraft pulp.[81] Sodium dithionite in combination with ferrous sulfate is employed to reduce the Cr(VI), which is present in the ground water.[82] Also, it is employed in the recovery of Cu(II) from their complexes from waste water.[83] Sodium dithionite is utilized to precipitate out the selenium[84] and the silver[85] in elemental form. Little amount of sodium dithionite enhances the stability of 5-hydroxymethylfurfural and inhibit its side reactions in the Knoevenagel condensations and Cannizzaro reactions and also affording the good yields.[86] In addition to above general uses of sodium dithionite, it found more applications in the synthetic chemistry as a sulfone surrogate and a single electron reductant and some of them are discussed below.

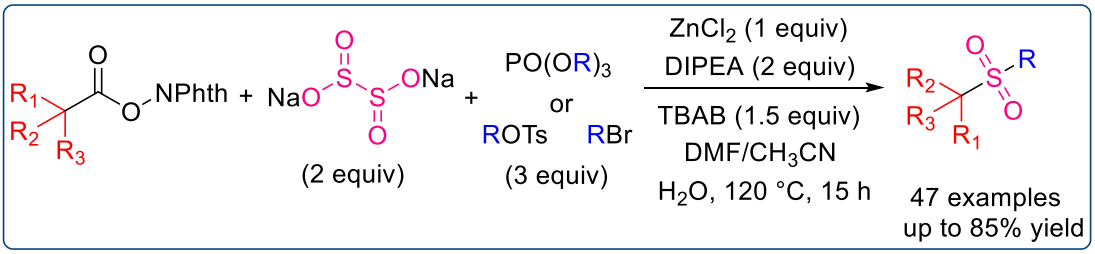
Jiang and co-workers developed a protocol for the synthesis of aryl-alkyl sulfones from aryl bromides and trialkyl phosphate using sodium dithionite in the presence of $Pd(dppf)Cl_2$ and

TBAB in DMSO at 120 °C for 15 h. This protocol allows the synthesis of wide range of aryl-alkyl sulfones with moderate to good yields. Here, sodium dithionite acts as a sulfur dioxide surrogate (Scheme 1.30).[65]



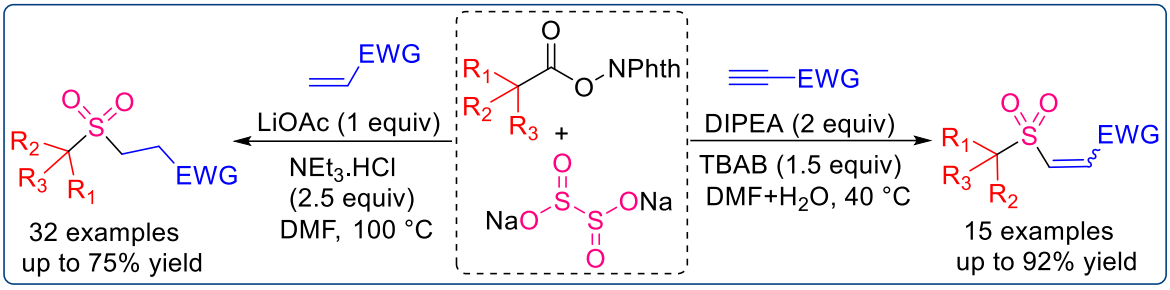
Scheme 1.30

Jiang and co-workers developed an efficient protocol for the synthesis of tertiary sulfones using *N*-hydroxyphthalimide ester (as a source of 3° alkyl radical source) and electrophiles such as alkyl bromides/alkyl tosylates/trialkyl phosphates by employing sodium dithionite as a single electron transfer reagent and also as a sulfone source in the presence of $ZnCl_2$, DIPEA and TBAB in a mixture of DMF, CH_3CN and H_2O at 120 °C for 15 h. Mechanistic studies reveled that the decarboxylation from *N*-hydroxyphthalimide ester is the rate-determining step (Scheme 1.31).[87]



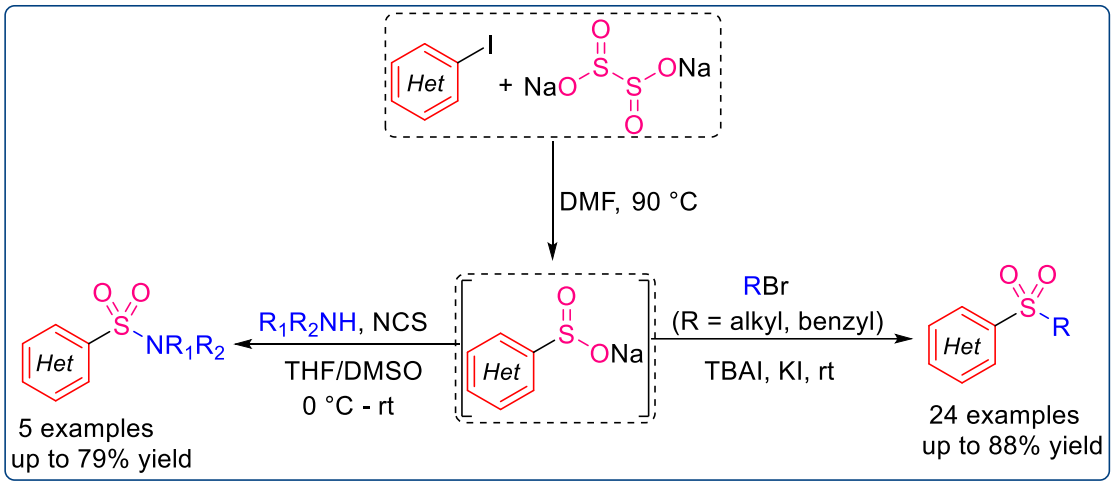
Scheme 1.31

Li et al. reported a decarboxylative cross-coupling protocol for the synthesis of alkenyl sulfones and alkyl sulfones with good yields. The alkenyl sulfones resulted with the mixture of *Z* and *E* from the *N*-hydroxyphthalimide ester, sodium dithionite and Michael acceptor (alkyne) in the presence of DIPEA and TBAB in a mixture of DMF and H_2O at 40 °C. In a similar way, the alkyl sulfones are also prepared from *N*-hydroxyphthalimide ester, sodium dithionite and electron deficient alkene in DMF at 100 °C using LiOAc and triethylammonium chloride. Here, sodium dithionite acts as a single electron reductant and as sulfone source (Scheme 1.32).[88]



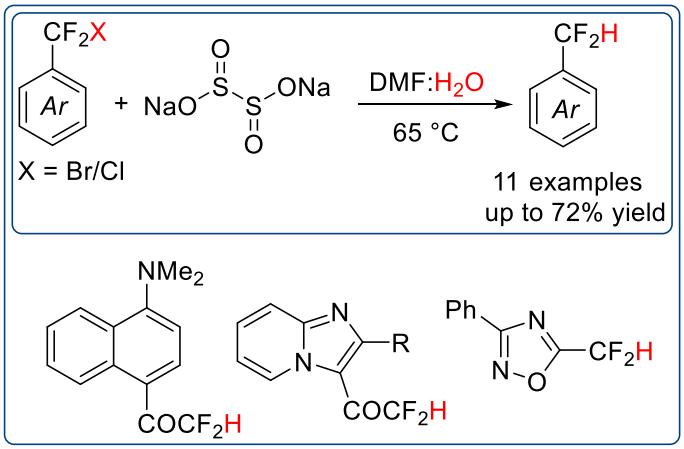
Scheme 1.32

Wu and co-workers described the synthesis of various heteroaryl sulfones or heteroaryl sulfonamides from heteroaryl iodides using sodium dithionite as a single electron reductant and a sulfone source with low to good yields. It is a one-pot two-step process, first step involves the formation of heteroaryl sulfinate in DMF at 90 °C. The second step is about the formation of i) heteroaryl sulfones, from the sulfinates using alkyl/benzyl bromide in the presence of TBAI and KI at room temperature, and ii) heteroaryl sulfonamides, from heteroaryl sulfinates using amine and *N*-chlorosuccinimide in a mixture of THF and DMSO at 0 °C to room temperature (Scheme 1.33).[89]



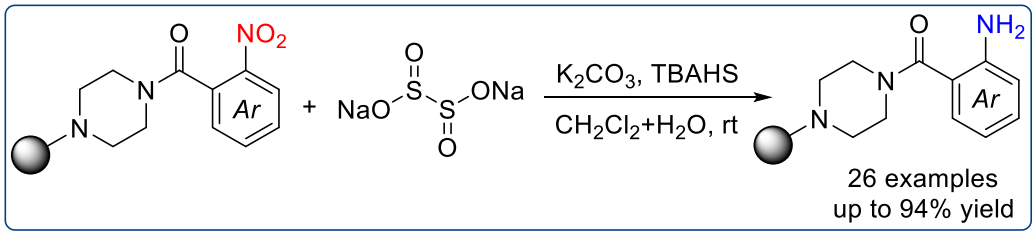
Scheme 1.33

Ait-Mohand and co-workers introduced a protocol for the synthesis of difluoromethylated aromatics and heteroaromatic compounds from their respective chlorinated or brominated compounds using sodium dithionite as a single electron transfer reductant in a mixture of DMF and water at 65 °C under nitrogen atmosphere. In this protocol, they also tested with the other reducing agents such as rongalite and tetrakis(dimethylamino)ethylene and got the comparable results as sodium dithionite (Scheme 1.34).[90]



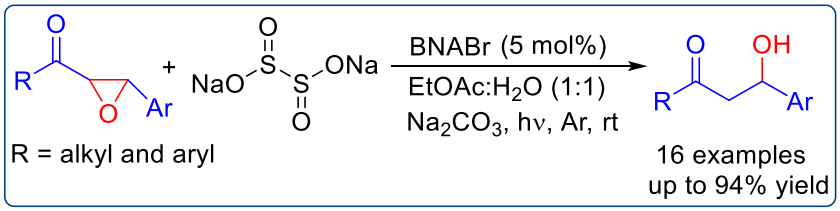
Scheme 1.34

Kaplanek et al. reported a reduction protocol for the synthesis of amines from aromatic nitro compounds, which are attached to wang and ring resins using sodium dithionite as a reducing agent in the presence of potassium carbonate and TBAHS (tetrabutylammonium hydrogen sulfate, a phase transfer catalyst) in CH_2Cl_2+H_2O at room temperature. Later, the resin is removed by using 1:1 ratio of TFA and CH_2Cl_2 at room temperature for 1 h (Scheme 1.35).[91]



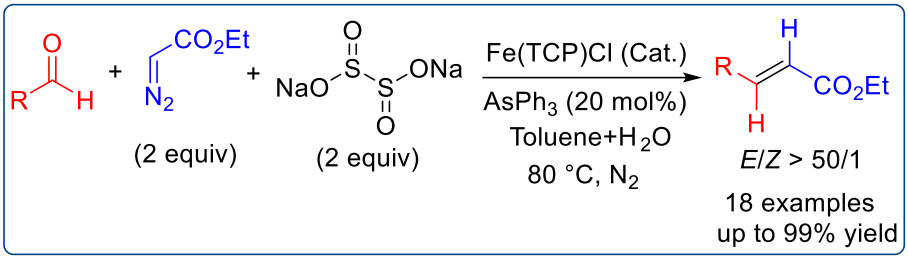
Scheme 1.35

Wu and co-workers described a protocol for the hydrogenation of *α,β*-epoxy ketones to produce *β*-hydroxy ketones in 80-94% yields using 5 mol% of 1-benzyl-1,4-dihydronicotinamide (BNAH) as a catalyst, which is generated *in situ via* reduction of BNABr using sodium dithionite in the presence of sodium carbonate in EtOAc+H_2O under room light for 24-48 h or 450 W Hg lamp for 2-3 h at room temperature in argon atmosphere (Scheme 1.36).[92]



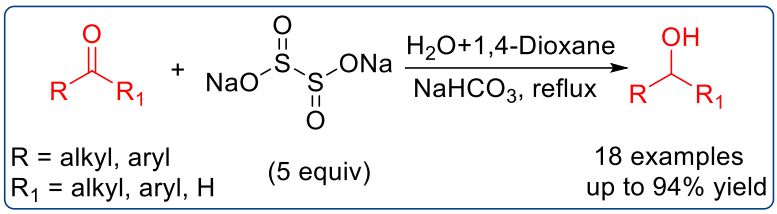
Scheme 1.36

Tang and co-workers developed a protocol for the synthesis of *α,β*-unsaturated esters from aldehydes, diazoacetates and sodium dithionite using catalytic amount of iron(tetra(*p*-chlorophenyl)porphyrinato) chloride Fe(TCP)Cl and $AsPh_3$ in a mixture of toluene and water at 80 °C under nitrogen atmosphere. This protocol involves the Wittig type olefination, here the sodium dithionite used as a reducing agent to regenerate $AsPh_3$ from $AsPh_3$=O, which is generated *in situ* during the reaction. This protocol offers the *E*-isomer stereoselectively compared to *Z*-isomer (Scheme 1.37).[93]



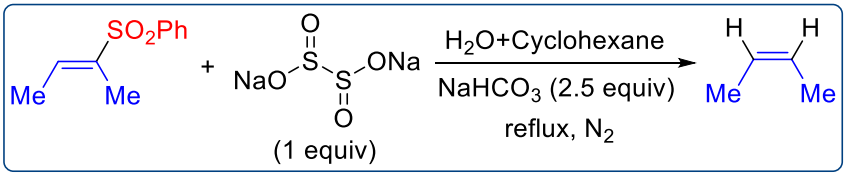
Scheme 1.37

Kellogg and co-workers developed a methodology for the synthesis of aliphatic and aromatic 1° and 2° alcohols from their respective carbonyl compounds utilizing sodium dithionite as a hydride-free reducing agent in aq. 1,4-dioxane in the presence of sodium bicarbonate under reflux condition. In this protocol, *α*-hydroxy sulfinates are the expected intermediates *via* radical mechanism (Scheme 1.38).[94]



Scheme 1.38

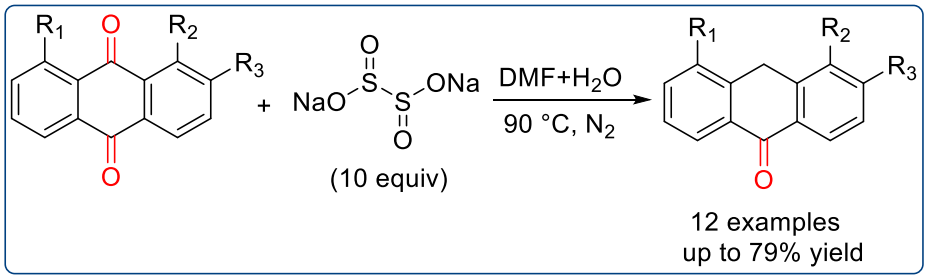
Julia and co-workers introduced a protocol for the hydrogenolysis of vinylic sulfones to the respective olefins using sodium dithionite in the presence of sodium bicarbonate in a mixture of cyclohexane and water under nitrogen atmosphere. In this protocol, sulfinate anion from sodium



Scheme 1.39

dithionite attacks on the *β*-position of vinylic sulfones to produce 1,2-bissulfones, further which undergoes elimination to produce olefins with retention of stereochemistry (Scheme 1.39). [95]

Muller and co-workers developed a protocol for the synthesis of *peri*-substituted anthracenones by the reduction of *peri*-substituted anthracenediones using sodium dithionite in DMF and H_2O at 90 °C under nitrogen atmosphere. It does not undergo overoxidation and stops at the anthracenone stage. In this protocol, sodium dithionite selectively reduces the carbonyl group which is flanked by the peri substituents and forms the 4,5-disubstituted 9(10*H*)-anthracenones (Scheme 1.40).[96]



Scheme 1.40

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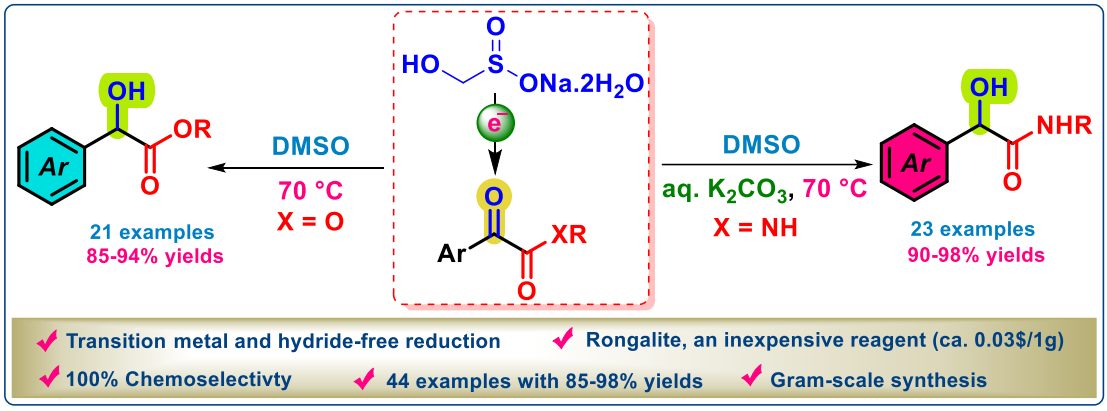
CHAPTER-II

Transition Metal and Hydride-Free Chemoselective Reduction of *α*-Keto Esters and *α*-Keto Amides Using Rongalite



2.1. Introduction

The chemoselective reduction of ketone to an alcohol in the presence of other reducible functionalities is a ubiquitous process and it helps in the synthesis of complex molecules.[1] Particularly, the chemoselective reduction of *α*-keto esters and *α*-keto amides captured the interest of chemists, because the anticipated products i.e., *α*-hydroxy esters and *α*-hydroxy amides are the important pharmacophores and exhibit broad spectrum of biological activities. The pharmacological properties of *α*-hydroxy amides include i) central nervous system depressants,[2] ii) anticonvulsants,[3] iii) bradykinin B1 antagonists,[4] iv) nuclear retinoic acid receptor (RARγ) agonists (BMS 270394),[5] v) γ-secretase inhibitors (LY411575),[6] vi) antibiotics (cefamandole)[7] and vii) calcium channel blockers (diltiazem).[8]

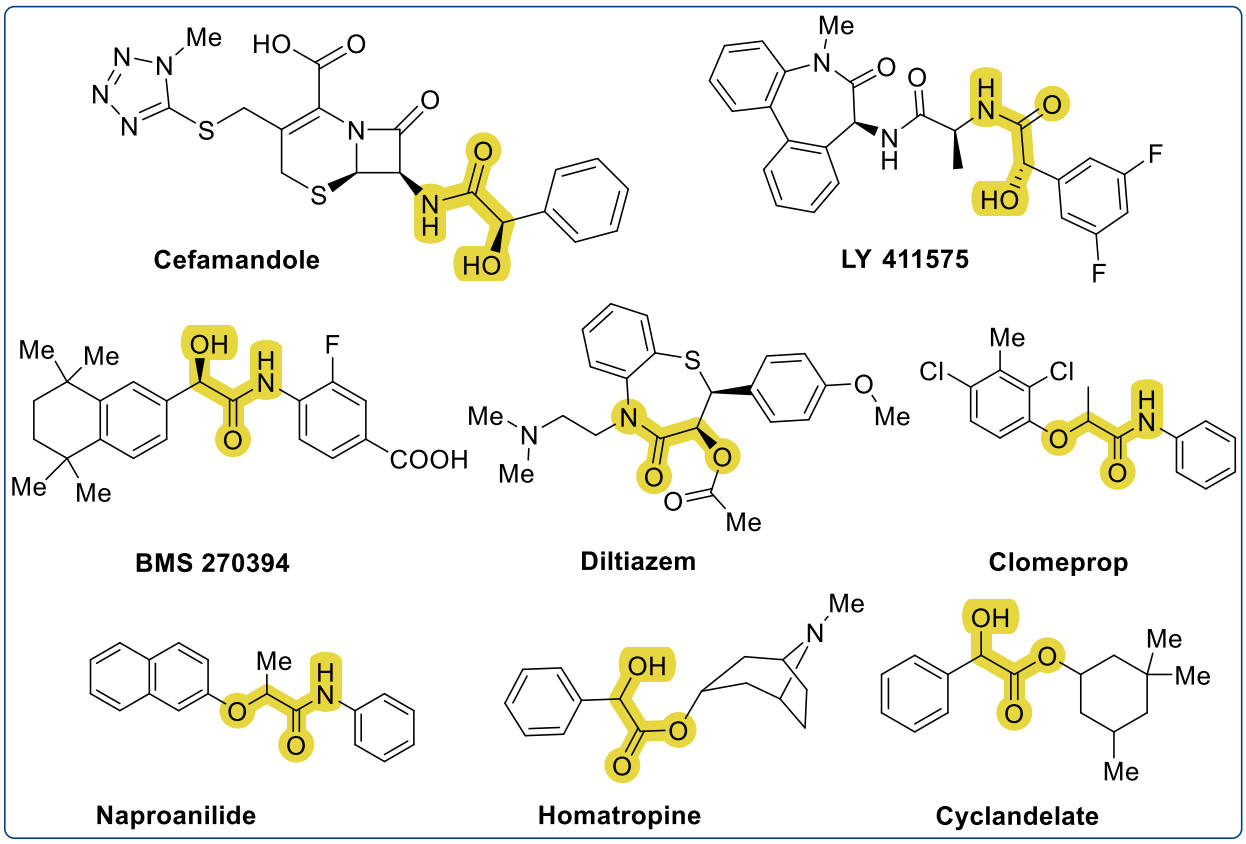


Figure 2.1. Some of the biologically active *α*-hydroxy amides and *α*-hydroxy esters

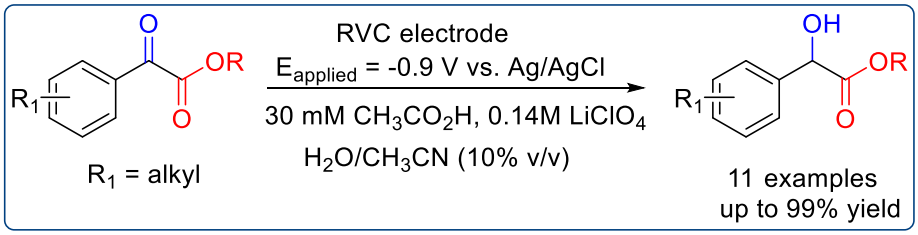
Also, the *α*-hydroxy esters are important building blocks in many commercial drugs such as homatropine,[9] which is used in eye drops to reduce the pain in patients after photorefractive keratectomy and the drug cyclandelate,[10] a vasodilator which is used in peripheral circulatory diseases. In addition, these are used as selective herbicides for weed control in rice fields[11]

(Figure 2.1). Moreover, due to variable coordinating capabilities of *α*-hydroxy esters and amides, which are employed as ligands in the metal catalyzed enantioselective synthesis.[12]

In addition to biological activities, *α*-hydroxy esters and *α*-hydroxy amides are the valuable synthetic precursors to get useful molecules such as cefamandole, an antibiotic drug,[13] halogenated esters by nucleophilic substitution,[14] nitro compounds *via* cross-dehydrogenative coupling,[15] passerini adducts *via* isocyanide-free approach and 3-phenyloxindoles,[16] polymers,[17] alcohols,[18] *α*-amino acid amides,[19] and tosylated products,[20] which are easily converted to *α*-amino acid derivatives. Thus, this chemoselective reduction is attracted the chemists all over the world to develop commercially viable methods.

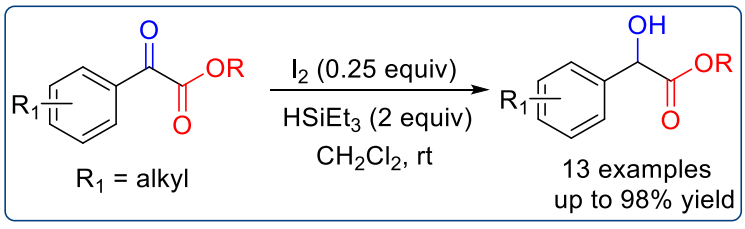
2.1.1. Previous reports for synthesis of *α*-hydroxy esters and *α*-hydroxy amides

Herbert and co-workers developed a protocol for the chemoselective electrochemical hydrogenation of keto group of *α*-keto esters using glassy carbon electrodes with bronsted acid like acetic acid in a mixture of 10% v/v of H_2O and CH_3CN. This protocol is free of redox mediators, hydrogen gas and expensive electrode materials (Scheme 2.1).[21]



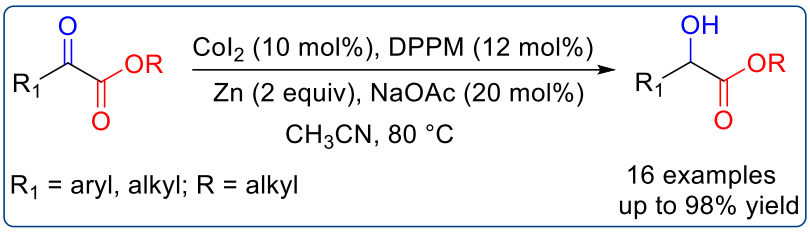
Scheme 2.1

Xiao et al. introduced a transition metal-free protocol for the production of *α*-hydroxy esters using a reduction system like molecular iodine with triethylsilane (I_2-$HSiEt_3$) in dichloromethane (CH_2Cl_2) at room temperature. Also, this methodology is useful to synthesize a vasodilator drug, i.e., cyclandelate as a mixture of diastereomers (Scheme 2.2).[22]



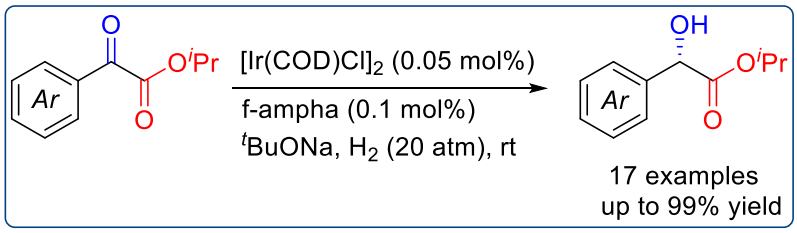
Scheme 2.2

Gao et al. developed a cobalt catalyzed transfer hydrogenation protocol for the synthesis of *α*-hydroxy esters from *α*-keto esters using H_2O as hydrogen source and Zn as a reducing agent in the presence of 1,1-bis(diphenylphosphino)methane (DPPM) ligand and sodium acetate in CH_3CN at 80 °C. This methodology offers excellent yields with wide substrate scope (Scheme 2.3).[23]



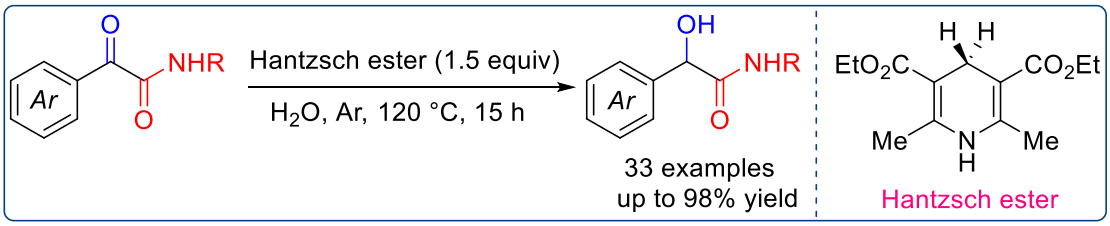
Scheme 2.3

Zhang and co-workers reported an iridium catalyzed asymmetric hydrogenation protocol for the synthesis of chiral *α*-hydroxy esters (up to 97% ee) using sodium *tert*-butoxide as base in isopropyl alcohol solvent at ambient temperature under 20 atm H_2. This protocol offers the synthesis of (*S*)-isomer selectively, which is attributed to the less steric repulsion (Scheme 2.4).[24]



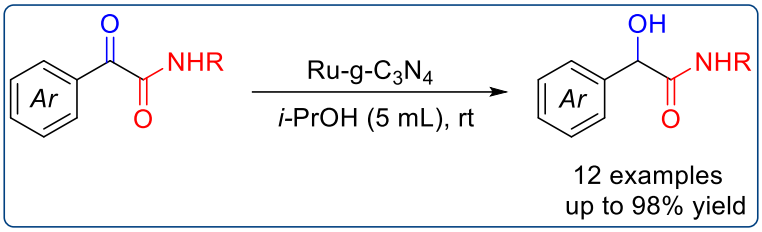
Scheme 2.4

Fang et al. reported "on-water" concept for the chemoselective synthesis of *α*-hydroxy amides from *α*-keto amides using Hantzsch ester as hydride source under argon atmosphere in H_2O at 120 °C for 15 h. This protocol is completely free of catalysts and additives, allows the synthesis of *α*-hydroxy amides in high yields (Scheme 2.5).[25]



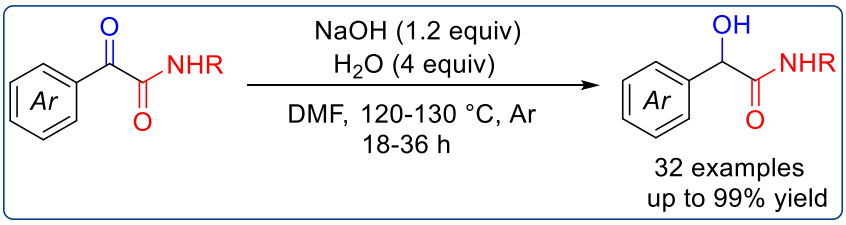
Scheme 2.5

Bhanage and co-workers developed a recyclable heterogeneous catalyst, which consists of ruthenium incorporated on the graphite sheet of carbon nitride (Ru-g-C_3N_4). This catalytic system is employed in the transfer hydrogenation of α-keto amides to produce the α-hydroxy amides using isopropyl alcohol as a hydrogen source and as reaction medium at room temperature (Scheme 2.6).[26]



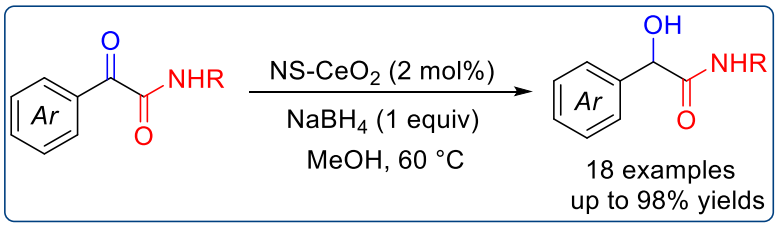
Scheme 2.6

Wu and co-workers reported a reduction system consists of DMF, NaOH and H_2O. The *in situ* generated sodium formate chemoselectively reduces the α-keto amides to α-hydroxy amides. Here, DMF acts as a hydrogen source and as a reaction medium. This protocol has good substrate scope with good to excellent yields, but requires longer reaction times and high reaction temperatures (Scheme 2.7).[27]



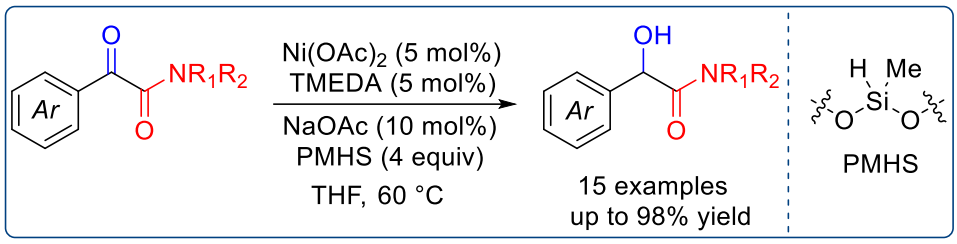
Scheme 2.7

Bhanage and co-workers developed a heterogeneous, recyclable and shape specific nanosphere cerium(IV) oxide (NS-CeO_2) catalyst and hired it in the chemoselective reduction of α-keto amides to synthesize α-hydroxy amides using sodium borohydride as reducing agent in methanol medium at 60 °C. It offers good to quantitative yields with low catalyst loading (Scheme 2.8).[28]



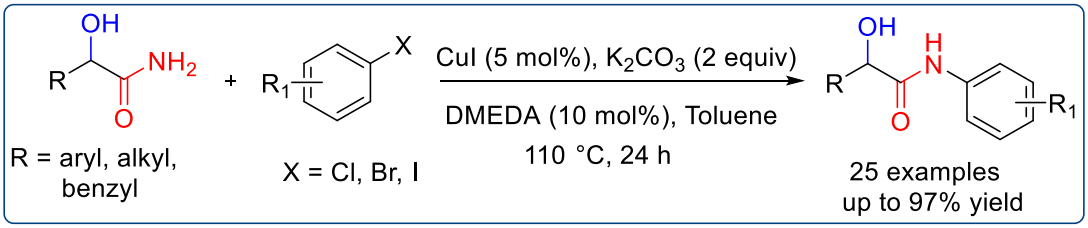
Scheme 2.8

Sekar and his group demonstrated a Ni-TMEDA catalyzed protocol for the synthesis of *α*-hydroxy amides from *α*-keto amides using polymethylhydrosiloxane (PMHS) as hydride source in the presence of sodium acetate in THF solvent at 60 °C. In this method, selective and complete reduction of *α*-keto amides was achieved by using different hydrosilanes (Scheme 2.9).[29]



Scheme 2.9

Zeng and co-workers synthesized *α*-hydroxycarboxylic acid anilides through a copper catalyzed C–N coupling of *α*-hydroxy amides with aryl halides in the presence of potassium carbonate and *N*,*N*-dimethylethylenediamine (DMEDA) ligand in toluene at 110 °C for 24 h. Also, this protocol selectively produced *N*-arylation without undergoing *O*-arylation (Scheme 2.10).[30]

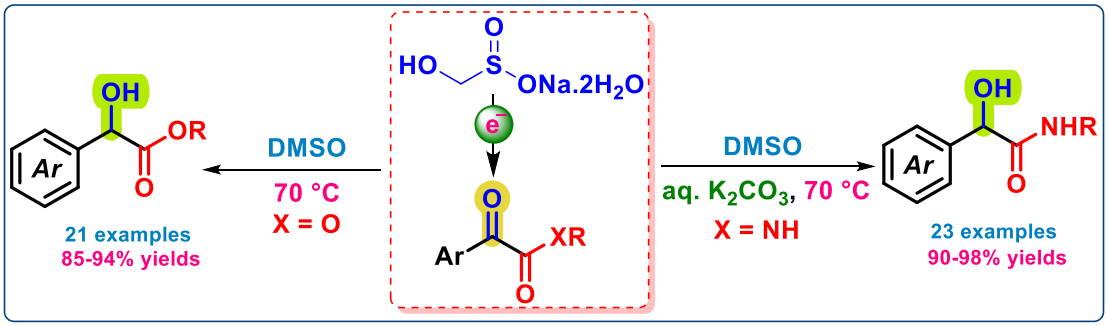


Scheme 2.10

Based on the literature study on *α*-hydroxy esters and *α*-hydroxy amides, we found that several reports were there on the chemoselective reduction of *α*-keto esters and *α*-keto amides and it is one of the most popular methods for their synthesis. Although, immense research work was done on chemoselective reduction, but most of the methods employed transition metals as catalysts with hazardous and expensive hydrosilanes as hydride sources. These protocols require high reaction temperatures, longer reaction times and producing huge amounts of silanol based by-products. To circumvent all the problems associated with literature methods, we aim to develop a transition metal and hydride-free protocol for this chemoselective reduction.

2.2. Present study

In light of the importance of *α*-hydroxy esters and *α*-hydroxy amides in the synthetic chemistry and the challenges associated for their preparation, we have developed an efficient protocol using rongalite as a reducing agent for the chemoselective reduction of *α*-keto esters and *α*-keto amides. Here, rongalite functions as a hydride-free reducing agent and it is an inexpensive, commercially available chemical (*ca*. 0.03$/1g). This transition metal and hydride-free protocol offers the synthesis of wide range of *α*-hydroxy esters and *α*-hydroxy amides with 85-98% yields. It tolerates the other reducible functionalities such as halides, ketones, alkenes, amides, and nitriles. This protocol is applicable to gram-scale synthesis and also prepared a vasodilator drug i.e., cyclandelate in gram-scale with 79% yield (Scheme 2.11).



Scheme 2.11. Chemoselective reduction of *α*-keto esters and *α*-keto amides using rongalite

2.2.1. Results and discussion

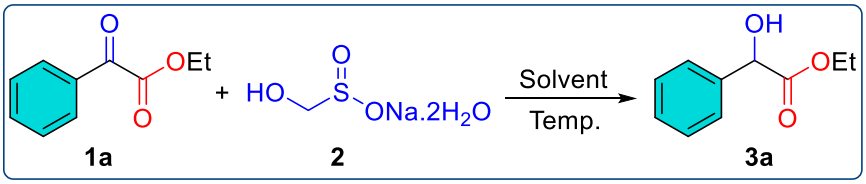
In our initial studies, a test reaction was conducted between ethyl 2-oxo-2-phenylacetate **1a** (1 mmol) as a model substrate and rongalite **2** (2 mmol) in EtOH+H_2O to obtain the desired product, ethyl 2-hydroxy-2-phenylacetate **3a** and only the key points are summarized in Table 2.1. At room temperature only 5% yield of **3a** was observed (Table 2.1, entry 1). To our delight, the yield of **3a** was dramatically increased to 82%, when the reaction was conducted at 70 °C (Table 2.1, entry 2). The structure of **3a** was confirmed by ^{1}H, ^{13}C NMR and HRMS spectral data.

Later, screening was continued in polar protic solvents such as H_2O, aq. MeOH and aq. *i*-PrOH resulting in low yields (Table 2.1, entries 3-5). Further, the polar aprotic solvents such as aq. acetone, aq. CH_3CN and DMF also followed the same trend of polar protic solvents (Table 2.1, entries 6-8). Fortunately, DMSO gave the **3a** in 93% yield within 10 min (Table 2.1, entry 9). Notably, there was a drop in the yield of **3a**, when loading of rongalite was decreased (Table 2.1,

entry 10). Additionally, variants in temperature and equiv of rongalite did not improve the yield of **3a** (Table 2.1, entries 11-13). In order to check the importance of rongalite, we have performed the same reaction with other sulfur containing reducing agents such as thiourea dioxide and sodium dithionite and found to be unreactive with *α*-keto esters. (Table 2.1, entries 14-15).

With the optimized reaction conditions in hand (Table 2.1, entry 9), then we have turned our attention to the testing of the scope of the reaction with diversely substituted *α*-keto esters (Table 2.2). Electron-donating groups such as methyl- and methoxy-substituted *α*-keto esters reacted smoothly with rongalite to furnish **3b-3d** in 89-92% yields (Table 2.2). This method can also tolerate halogen (–F, –Cl, and –Br) derivatives and afforded the corresponding *α*-hydroxy esters

Table 2.1. Optimization of reaction conditions for chemoselective reduction of *α*-keto esters[a]

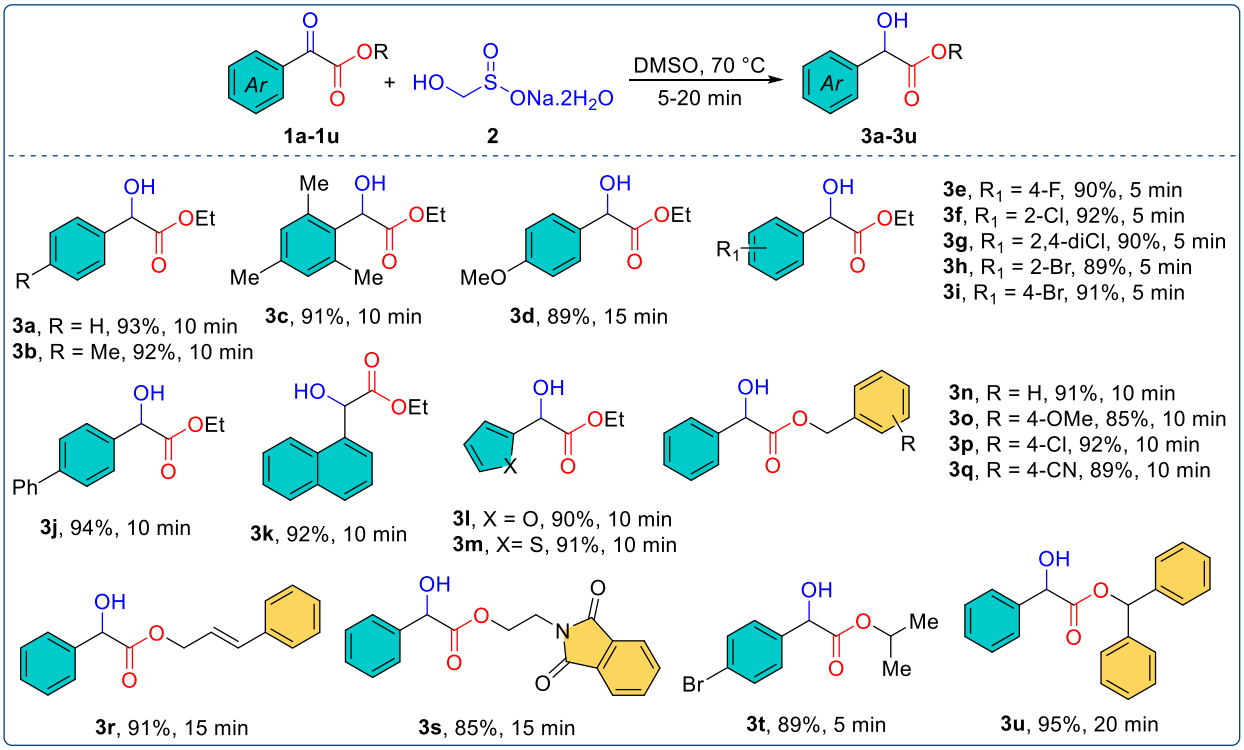


S. No	Solvent (8:2 v/v)	Reagent	Temp. (°C)	Time (min)	Yield (%)[b]
1	EtOH+H_2O	Rongalite	rt	24 h	5
2	EtOH+H_2O	Rongalite	70	20	82
3	H_2O+*β*-CD	Rongalite	70	24 h	trace
4	MeOH+H_2O	Rongalite	65	20	70
5	*i*-PrOH+H_2O	Rongalite	70	20	71
6	Acetone+H_2O	Rongalite	60	8 h	41
7	CH_3CN+H_2O	Rongalite	70	20	60
8	DMF	Rongalite	70	20	71
9	**DMSO**	**Rongalite**	**70**	**10**	**93**
10	DMSO	Rongalite	70	30	75[c]
11	DMSO	Rongalite	70	10	93[d]
12	DMSO	Rongalite	80	10	93
13	DMSO	Rongalite	60	15	91
14	DMSO	Thiourea dioxide	70	8 h	n.r.
15	DMSO	Sodium dithionite	70	10 h	n.r.

[a]Reaction conditions: ethyl 2-oxo-2-phenylacetate **1a** (1 mmol) and reagent **2** (2 mmol) in different solvent mixtures at variable temperatures. [b]Yield of isolated product. [c]1.5 equiv of rongalite was used. [d]2.5 equiv of rongalite was used. n.r. = no reaction.

3e-3i in 89-92% yields (Table 2.2). Biphenyl, naphthyl, and heteroaromatic α-keto esters were also effortlessly involved in the reaction to afford the reduced products **3j-3m** in 90-94% yields (Table 2.2). α-Keto benzyl esters, which have various substitutions on the benzyl group, also well participated in the reaction and delivered **3n-3q** in 85-92% yields (Table 2.2). Interestingly, cinnamyl and phthalimide α-keto esters offered the respective reduced products **3r** and **3s** in 91% and 85% yields, respectively with functional groups being intact (Table 2.2). This methodology is also applicable to α-keto esters that were formed by the secondary alcohols such as isopropyl alcohol and benzhydrol, furnished **3t** and **3u** in 89% and 95% yields, respectively (Table 2.2).

Table 2.2. Substrate scope of the chemoselective reduction of α-keto esters by rongalite[a,b]

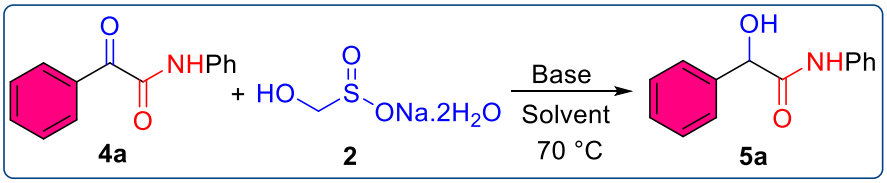


[a]Reaction conditions: α-keto ester **1** (1 mmol) and rongalite **2** (2 mmol) in 2 mL of DMSO at 70 °C. [b]Yield of isolated products.

To check the generality and scope of the protocol, we have extended our optimized method to α-keto amides to produce α-hydroxy amides, owing their applications in the synthetic and medicinal chemistry. 2-Oxo-*N*,2-diphenylacetamide **4a** (1mmol) was treated with rongalite **2** (2 mmol) under optimized reaction conditions, and the formation of 2-hydroxy-*N*,2-diphenylacetamide **5a** in 62% yield was observed, which is lower compared to esters (Table 2.3, entry 1). After that, the reaction was conducted with K_2CO_3, but this did not improve the product

yield (Table 2.3, entry 2). Later, we conducted the reaction with other solvents such as CH_3CN and EtOH (with water to dissolve rongalite) in basic conditions and observed that aq. EtOH gave 76% yield in 2h (Table 2.3, entries 3 and 4). Further, we conducted the reaction in DMSO+H_2O (8:2, v/v) with K_2CO_3; surprisingly, the reaction was completed within 15 min and resulted the **5a** in 96% yield (Table 2.3, entry 5).

Table 2.3. Optimization of reaction conditions for chemoselective reduction of *α*-keto amides[a]



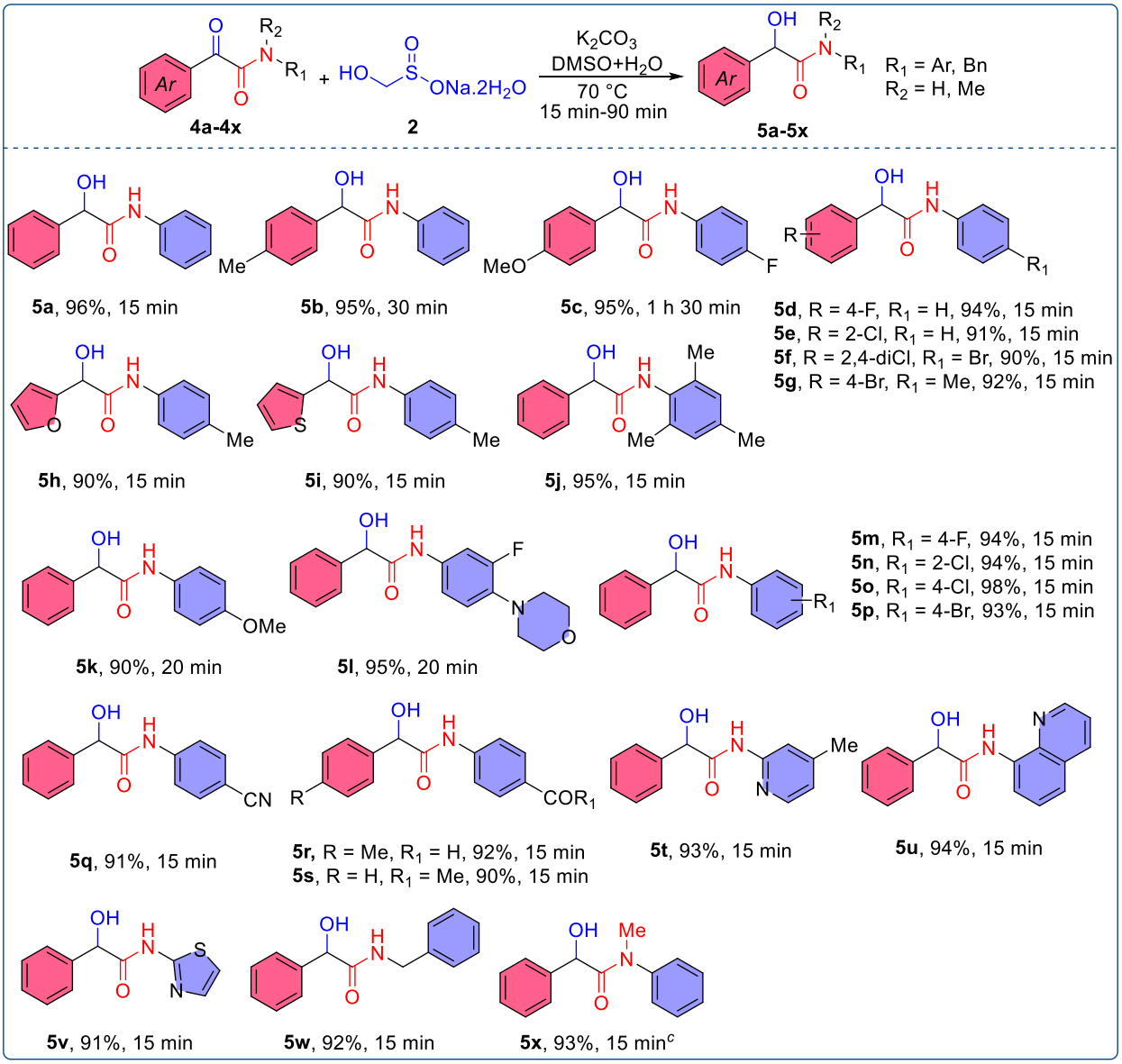
S. No	Solvent	Base (equiv)	Time (min)	Yield (%)[b]
1	DMSO	--	16 h	62
2	DMSO	K_2CO_3	1 h	60
3	CH_3CN+H_2O (8:2 v/v)	K_2CO_3	8 h	40
4	EtOH+H_2O (8:2 v/v)	K_2CO_3	2 h	76
5	**DMSO+H_2O (8:2 v/v)**	**K_2CO_3**	**15**	**96**
6	DMSO+H_2O (8:2 v/v)	--	24 h	50
7	DMSO+H_2O (6:4 v/v)	K_2CO_3	30	92
8	DMSO+H_2O (1:1 v/v)	K_2CO_3	50	90
9	DMSO+H_2O (8:2 v/v)	Cs_2CO_3	15	91
10	DMSO+H_2O (8:2 v/v)	DBU	15	85
11	DMSO+H_2O (8:2 v/v)	DMAP	15	81
12	DMSO+H_2O (8:2 v/v)	K_2CO_3	40	89[c]
13	DMSO+H_2O (8:2 v/v)	K_2CO_3	60	65[d]

[a]Reaction conditions: 2-oxo-*N*,2-diphenylacetamide **4a** (1 mmol), rongalite **2** (2 mmol, 2 equiv) and base (1.5 equiv) in 2 mL of solvent at 70 °C. [b]Yield of isolated product. [c]1.2 equiv of K_2CO_3 was used. [d]1.5 equiv of rongalite was used.

Also, reaction was tested with aq. DMSO without a base to know the role of the base in the aqueous condition and found an inferior result (Table 2.3, entry 6), which indicates that the aq. basic condition was required to produce **5a** in good yield. Further, the ratio of the solvent mixture was also examined and it was observed that the increasing amount of H_2O resulted in longer reaction times (Table 2.3, entries 7 and 8). Later, screening was continued with other bases such as Cs_2CO_3, DBU, and 4-DMAP and low yields were observed (Table 2.3, entries 9-11). Further, the change in the loadings of the base and rongalite also resulted in low yields

(Table 2.3, entries 12 and 13). Therefore, the optimized reaction conditions are 2-oxo-*N*,2-diphenylacetamide **4a** (1 mmol), rongalite **2** (2 mmol), and K_2CO_3 (1.5 mmol) in DMSO+H_2O (8:2, v/v) at 70 °C (Table 2.3, entry 5).

Table 2.4. Substrate scope of the chemoselective reduction of α-keto amides by rongalite[a,b]

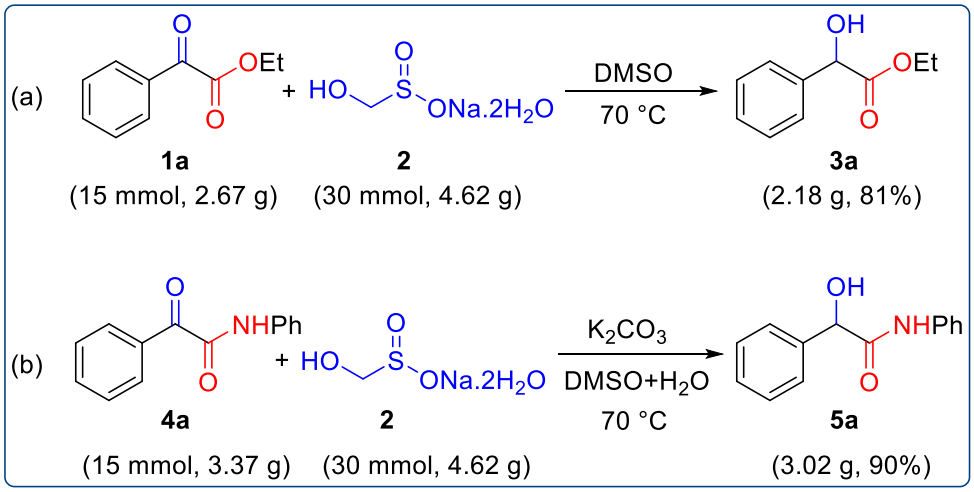


[a]Reaction conditions: α-keto amide **4** (1 mmol), rongalite **2** (2 mmol) and K_2CO_3 (1.5 mmol) in 2 mL of DMSO+H_2O (8:2 v/v) at 70 °C. [b]Yield of isolated products. [c]α-Keto amide **4x** (1 mmol) and rongalite **2** (2 mmol) in DMSO (2 mL) at 70 °C.

With the optimized reaction conditions for α-keto amides in hand (Table 2.3, entry 5), to check the generality of this chemoselective reduction, various α-keto amides were used, and the findings were discussed in Table 2.4. Electron-donating groups such as methyl- and methoxy-

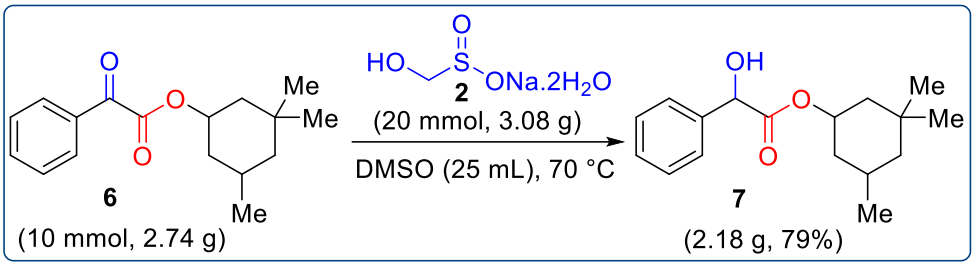
substituted *α*-keto amides underwent reaction smoothly with rongalite to furnish **5b**, **5c**, **5j**, and **5k** in 90-95% yields (Table 2.4). This method tolerated halogen derivatives (–F, –Cl, and –Br) and afforded the reduced products **5d-5g** and **5l-5p** in 90-98% yields (Table 2.4). Electron-withdrawing groups such as cyano-, formyl-, and acetyl-containing *α*-keto amides were effortlessly involved in the reaction to give **5q-5s** in 90-92% yields (Table 2.4). Also, heteroaromatic *α*-keto amides delivered the corresponding *α*-hydroxy amides **5h**, **5i**, and **5t-5v** in 90-94% yields (Table 2.4). Additionally, this protocol was applicable to *α*-keto amides that were formed by benzyl amine and secondary aniline, which readily gave reduced products **5w** and **5x** in 92-93% yields (Table 2.4).

Finally, we have evaluated the synthetic potential of our methodology for gram-scale synthesis, which are more useful in the industry. Ethyl 2-oxo-2-phenylacetate **1a** (2.67 g, 15 mmol) and rongalite **2** (4.62 g, 30 mmol) were added in DMSO (15 mL) at 70 °C, resulted the ethyl 2-hydroxy-2-phenylacetate **3a** in 81% yield (scheme 2.12a). Similarly, we have prepared 2-hydroxy-*N*,2-diphenylacetamide **5a** in 90% yield using 2-oxo-*N*,2-diphenylacetamide **4a** (3.37 g, 15 mmol), rongalite **2** (4.62 g, 30 mmol) and K_2CO_3 (22.5 mmol) in DMSO+H_2O (8:2 v/v, 15 mL) at 70 °C (Scheme 2.12b).

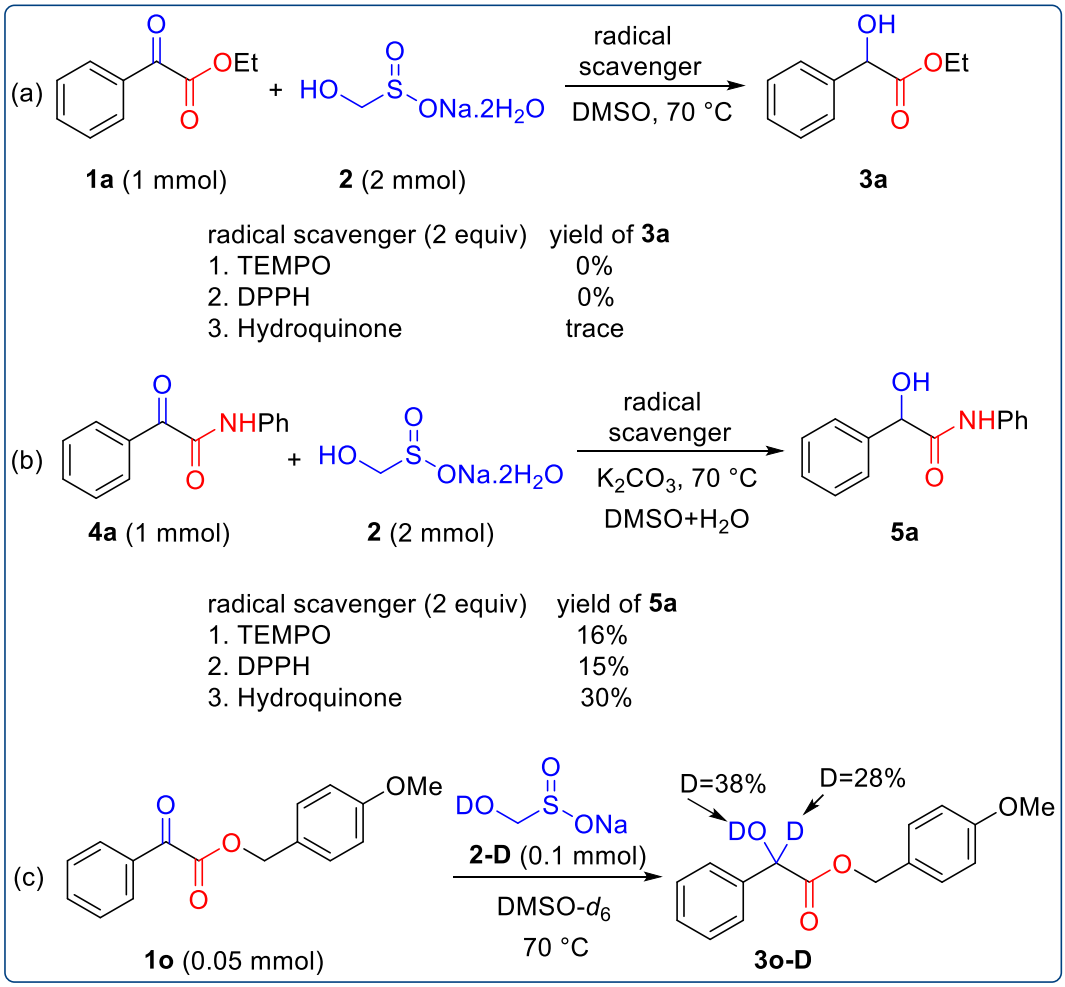


Scheme 2.12. Gram-scale synthesis

Also, we have synthesized "cyclandelate", a vasodilator drug **7**, which is used to treat heart and blood-vessel diseases and reduces high blood pressure, using 3,3,5-trimethylcyclohexyl 2-oxo-2-phenylacetate **6** (2.74 g, 10 mmol) and rongalite **2** (3.08 g, 20 mmol) in DMSO (25 mL) at 70 °C in 79% yield (Scheme 2.13).



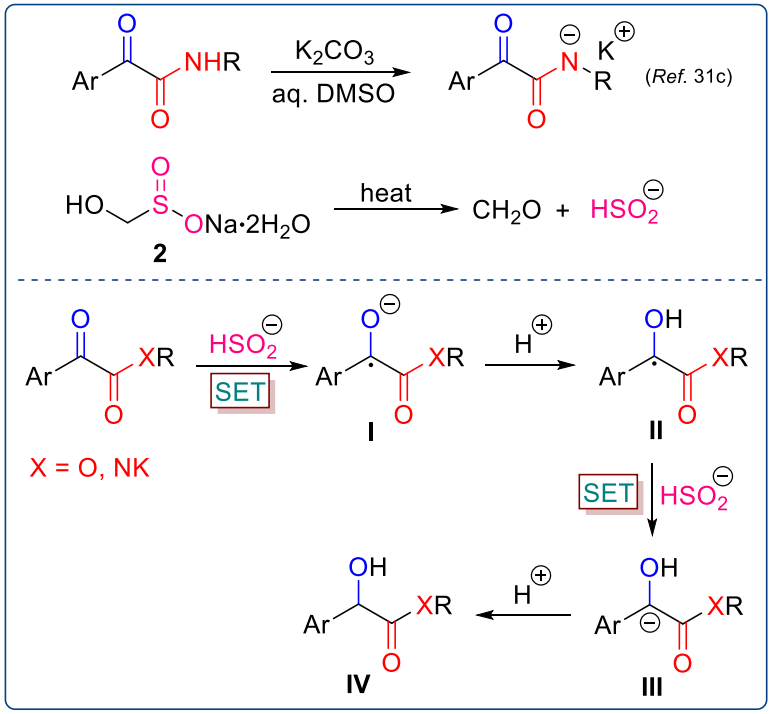
Scheme 2.13. Application of protocol for the synthesis of cyclandelate



Scheme 2.14. Control experiments

To gain mechanistic insight into these chemoselective reductions, we have conducted some control experiments with radical scavengers such as TEMPO, DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate), and hydroquinone (Scheme 2.14). Firstly, control experiments were conducted on *α*-keto ester by taking ethyl 2-oxo-2-phenylacetate **1a** (1 mmol), rongalite **2** (2 mmol), and TEMPO/DPPH/hydroquinone (2 equiv) in DMSO (2 mL) at 70 °C. No progress of

the reaction was observed to provide ethyl 2-hydroxy-2-phenylacetate **3a** in the case of TEMPO and DPPH, and only trace amounts of **3a** was observed in the case of hydroquinone (Scheme 2.14a). The above results clearly indicate that the reduction of *α*-keto esters by rongalite is undergoing a radical mechanism. Similarly, same control experiments were conducted on *α*-keto amide using 2-oxo-*N*,2-diphenylacetamide **4a** (1 mmol), rongalite **2** (2 mmol), K_2CO_3 (1.5 mmol), and TEMPO/DPPH/hydroquinone (2 equiv) in 2 mL of DMSO+H_2O (8:2, v/v) at 70 °C (Scheme 2.14b). The product, i.e., 2-hydroxy-*N*,2-diphenylacetamide **5a**, was formed in 15-30% yield, which indicated that the reduction of *α*-keto amides by rongalite also follows through a radical mechanism. Additionally, the TEMPO adduct with *α*-keto amide was detected in HRMS analysis (see, Figure 2.2). Further, to know the proton source in the hydroxy products, we have conducted a reaction between *α*-keto ester **1o** (0.05 mmol) and anhydrous deuterated rongalite **2-D** (0.1 mmol) in DMSO-d_6 at 70 °C and observed the incorporation of 28% and 38% deuterium into −CH and −OH groups of *α*-hydroxy ester, respectively, which is indicating that the rongalite is also acting as proton source (Scheme 2.14c, for details see, Figure 2.3 - Figure 2.4).



Scheme 2.15. Plausible reaction mechanism

Based on the control experiments and previous literature reports,[31] a plausible mechanism is proposed in Scheme 2.15. Initially, the reductant rongalite dissociates itself into formaldehyde

and HSO_2^-. Later on, a single-electron transfer (SET) takes place from HSO_2^- to *α*-keto ester/amide to form ketyl radical anion intermediate **I**, which further converts into ketyl radical **II** by protonation. Subsequently, another single electron transfer occurs at ketyl radical **II** from HSO_2^- to generate intermediate **III**, which finally yields the title compound *α*-hydroxy ester/amide **IV** by abstraction of proton.

2.3. Evidence in support of the mechanism

2.3.1. TEMPO adduct with *α*-keto amide

We have conducted an experiment on *α*-keto amide using 2-oxo-*N*,2-diphenylacetamide **4a** (1 mmol, 1 equiv), rongalite **2** (2 mmol, 2 equiv), K_2CO_3 (1.5 mmol, 1.5 equiv) and TEMPO (2.0 mmol, 2.0 equiv) in 2 mL of DMSO+H_2O (8:2 v/v) at 70 °C (Scheme 2.16).

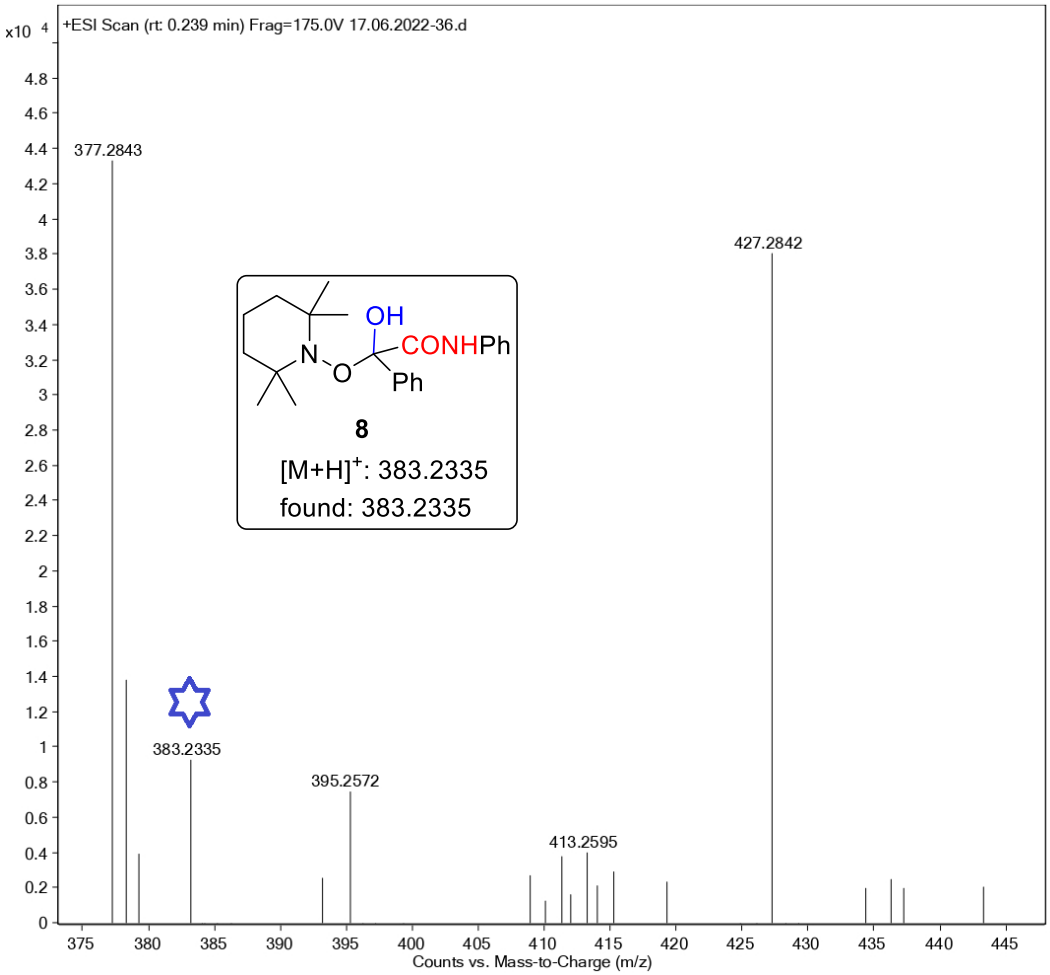
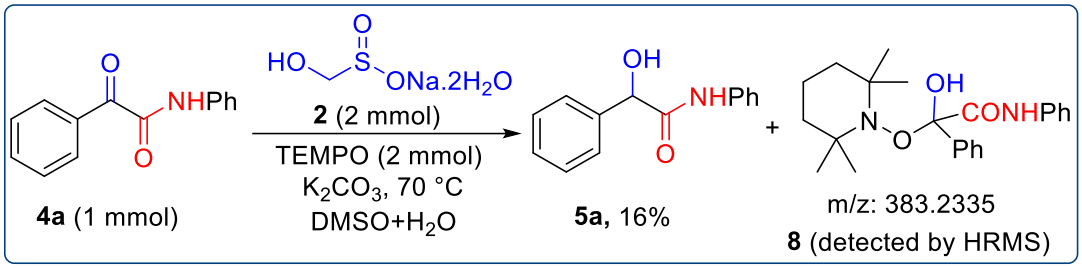


Figure 2.2. HRMS of reaction mixture of 2-oxo-*N*,2-diphenylacetamide **4a** (1 mmol), rongalite **2** (2 mmol), K_2CO_3 (1.5 mmol) and TEMPO (2 equiv) in 2 mL of DMSO+H_2O (8:2 v/v) at 70 °C.

The product i.e., 2-hydroxy-*N*,2-diphenylacetamide **5a** was formed in 16% yield and we detected the TEMPO adduct **8** with *α*-keto amide in the HRMS, which is indicating that the reduction of *α*-keto amides by rongalite is following through radical mechanism (Figure 2.2).



Scheme 2.16

2.3.2. Deuterium labeling studies

An oven dried 10 mL reaction flask was charged with *α*-keto ester **1o** (0.05 mmol), anhydrous deuterated rongalite **2-D** (0.1 mmol) and DMSO-d_6 (1 mL) and allowed the mixture to stir at 70 °C using oil bath for 10 min under N_2 atmosphere (Scheme 2.14c). The crude mixture was recorded for ^{1}H NMR and results were shown in Figure 2.3.

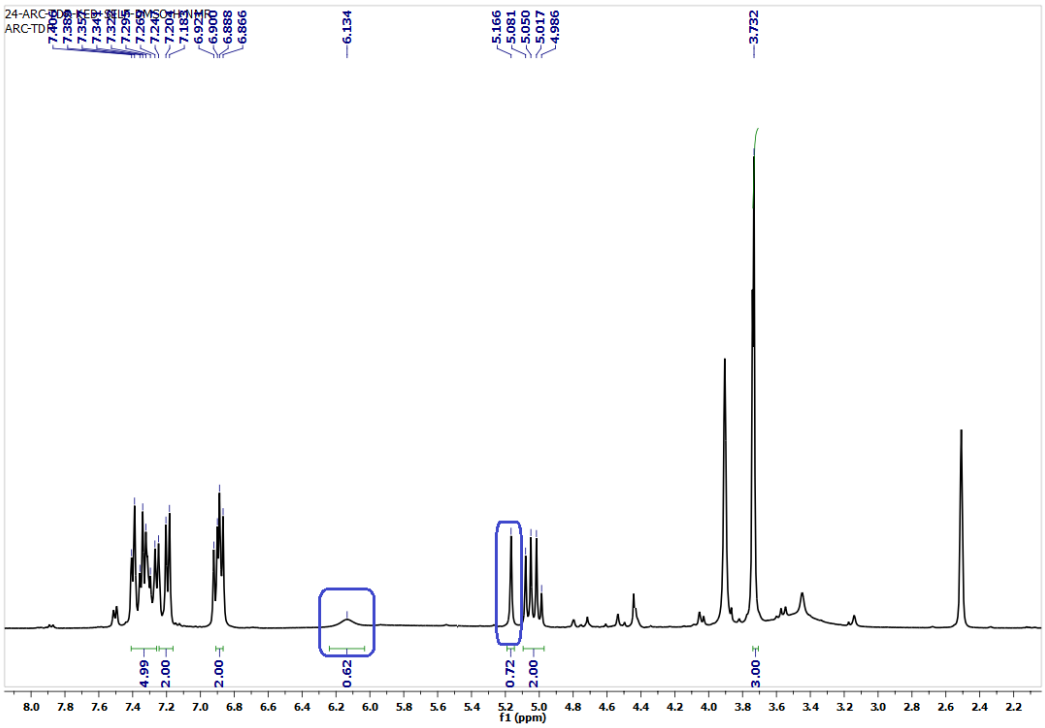


Figure 2.3. ^{1}H NMR (400 MHz, DMSO-d_6) spectrum of reaction mixture of *α*-keto ester **1o** (0.05 mmol) and deuterated rongalite **2-D** (0.1 mmol) in DMSO-d_6 at 70 °C.

Similarly, we have recorded the ^{1}H NMR spectrum of reaction mixture of *α*-keto ester **1o** (0.05 mmol) and anhydrous rongalite **2** (2 equiv) in DMSO-d_6 (1 mL) at 70 °C after 10 min (Figure 2.4). Based on ^{1}H NMR, we have found that 28% and 38% of deuterium was incorporated into –CH and –OH groups of the *α*-hydroxy ester **3o**, respectively. This result suggested that the rongalite is also acting as proton source.

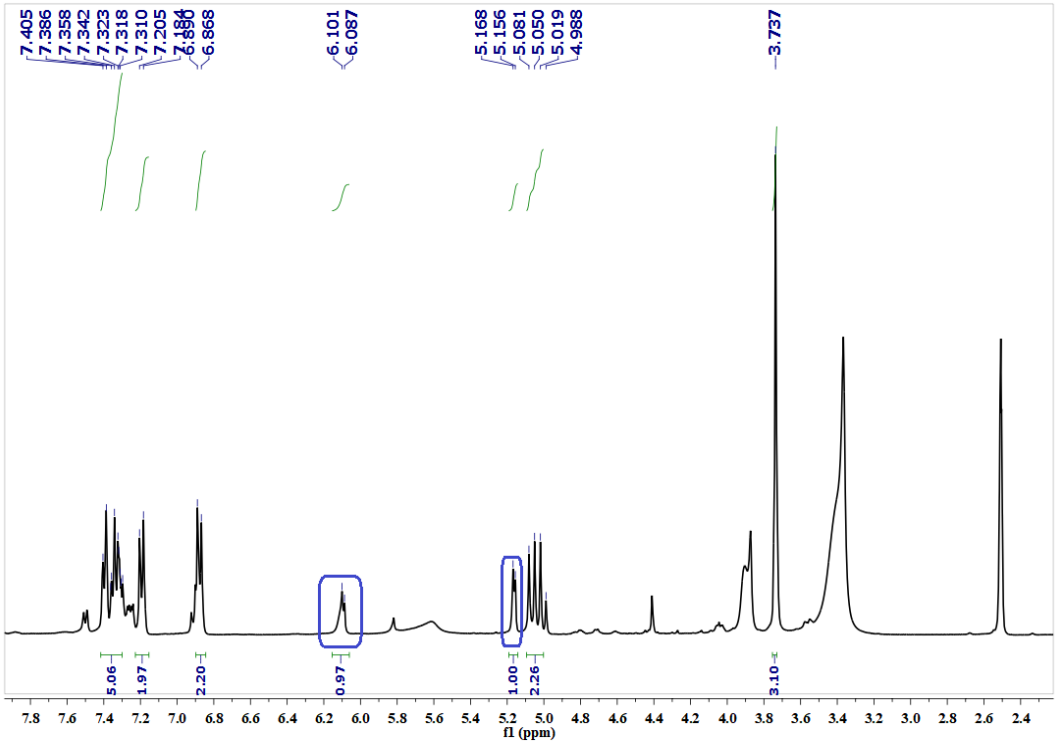


Figure 2.4. ^{1}H NMR (400 MHz, DMSO-d_6) spectrum of reaction mixture of *α*-keto ester **1o** (0.05 mmol) and anhydrous rongalite **2** (0.1 mmol) in DMSO-d_6 at 70 °C.

2.4. Conclusion

In conclusion, we have developed a transition metal and hydride-free protocol for the chemoselective reduction of *α*-keto esters and *α*-keto amides to produce diversely substituted *α*-hydroxy esters and *α*-hydroxy amides with 85-98% yields using rongalite. Rongalite is an inexpensive industrial product (1g, 0.03$) and found to be a potential radical source of hydride-free reducing agent. This protocol overcomes all the constraints associated with the existing methods such as hazardous by-products, long reaction times, elevated temperatures and chemoselectivity problems. Also, we applied our protocol to synthesize cyclandelate, a vasodilator drug in gram-scale with 79% yield.

2.5. Experimental section

2.5.1. General information

All chemicals and solvents were purchased from Alfa Aesar, Spectrochem, SRL, Finar and used as received. Thin layer chromatography was performed on 200 µm aluminum-foil backed silica gel plates and the column chromatography was performed using 100-200 mesh silica gel (Merk). Bruker Avance 400 MHz spectrometer was used to record ^{1}H NMR spectra and used $CDCl_3$ and DMSO-d_6 as solvents and TMS as an internal standard. The multiplicities were described using the following acronyms: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Coupling constants *J*, were reported in Hertz unit (Hz). Bruker Avance 100/125 MHz spectrometer was used to record $^{13}C\{^{1}H\}$ NMR spectra, and they were fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to the center line of a triplet at 77.16 ppm of chloroform-*d* (a multiplet at 39.52 ppm of DMSO-d_6). A Stuart SMP30 apparatus was used to determine the melting points and are uncorrected. FT-IR spectra were recorded on a Perkin Elmer spectrometer. HRMS were analyzed with Agilent Q-TOF 6230.

2.5.2. General procedure for the synthesis of *α*-keto acids[32]

An oven dried 25 mL reaction flask was charged with appropriate acetophenone (10 mmol), selenium dioxide (20 mmol, 2 equiv) and pyridine (70 mmol, 7 equiv), stirred at 100 °C in an oil bath and the reaction was monitored by TLC using hexanes and ethyl acetate as an eluent. After disappearance of the acetophenone on TLC, reaction was stopped and filtered with EtOAc. To this 11N HCl was added and organic compound was extracted with EtOAc (3 x 25 mL). Organic layers were washed with brine and with fresh water. The organic layers were dried on Na_2SO_4 and evaporated to give *α*-keto acids, which were used directly in the next step without further purification.

2.5.3. General procedure for the synthesis of *α*-keto esters (1a-1m, 1t)[33]

An oven dried 25 mL reaction flask was charged with appropriate *α*-keto acid (5 mmol), EtOH/*i*-PrOH (10 mL) and catalytic amount of H_2SO_4 (1 mL). The reaction mixture was stirred under reflux in an oil bath and the reaction was monitored by TLC using hexanes and ethyl acetate as an eluent. After completion of reaction, EtOH/*i*-PrOH was evaporated under vacuum and organic compound is extracted with ethyl acetate (3 x 20 mL). The organic layers were dried on Na_2SO_4

and evaporated to give a residue that was purified on silica gel by column chromatography using hexanes and ethyl acetate as an eluent.

2.5.4. General procedure for the synthesis of *α*-keto esters (1n-1s, 1u)[34]

An oven dried 25 mL reaction flask was charged with benzoylformic acid (5 mmol), appropriate alcohol (6 mmol, 1.2 equiv) and benzene (5 mL). The reaction mixture was stirred under reflux in an oil bath and the reaction was monitored by TLC using hexanes and ethyl acetate as an eluent. After completion of reaction, benzene was evaporated under vacuum and the residue was purified on silica gel by column chromatography using hexanes and ethyl acetate as an eluent.

2.5.5. General procedure for the synthesis of *α*-keto amides (4a-4x)[35]

An oven dried 25 mL reaction flask was charged with appropriate *α*-keto acid (5 mmol) and DCM (10 mL) and kept at 0-5 °C, to this NEt_3 (10 mmol, 2 equiv) was added and with a gap of five minutes, thionyl chloride (10 mmol, 2 equiv) was added in dropwise. Later, appropriate aniline/amine (5 mmol, 1 equiv) was added in portions (if anilne is liquid, disolved in DCM and added in dropwise). Now, allow the reaction mixture to room temperature and continue to stir. Reaction was monitored by TLC using hexanes and ethyl acetate as an eluent. After completion of reaction, the excess $SOCl_2$ was removed under vacuum and the organic compound is extracted with ethyl acetate (3 x 25 mL). The organic layers were dried on Na_2SO_4 and evaporated to give *α*-keto amides, which were purified by column chromatography.

2.5.6. General procedure (A) for the synthesis of *α*-hydroxy esters (3a-3u)

An oven dried 10 mL reaction flask was charged with appropriate *α*-keto ester **1** (1 mmol), rongalite **2** (2 mmol) and DMSO (2 mL), stirred at 70 °C for the appropriate time (5-20 min). The reaction was monitored by TLC using hexanes and ethyl acetate as an eluent. After the completion of reaction, water was added to the reaction mixture and the organic compound was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried on Na_2SO_4 and evaporated to give a residue that was purified on silica gel by column chromatography using hexanes and ethyl acetate as an eluent.

2.5.7. General procedure (B) for synthesis of *α*-hydroxy amides (5a-5x)

An oven dried 10 mL reaction flask was charged with appropriate *α*-keto amide **4** (1 mmol), rongalite **2** (2 mmol), K_2CO_3 (1.5 mmol) and DMSO+H_2O (2 mL, 8:2 v/v), stirred at 70 °C for

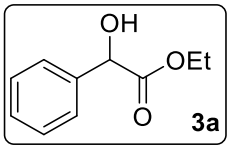
the appropriate time (15 min - 1 h 30 min). The reaction was monitored by TLC using hexanes and ethyl acetate as an eluent. After the completion of reaction, water was added to the reaction mixture and the organic compound was extracted with ethyl acetate (3 x 10 mL). The organic layers were dried on Na_2SO_4 and evaporated to give a residue that was purified on silica gel by column chromatography using hexanes and ethyl acetate as an eluent.

2.5.8. Preparation of deuterated rongalite

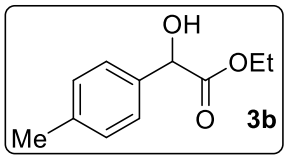
An oven dried 10 mL reaction flask was charged with anhydrous rongalite **2** (0.3 g) and methanol-d_4 (3 mL), the resulting mixture was stirred for 2 h at room temperature. After that the methanol-d_4 was evaporated and dried under vacuum to get the deuterated rongalite **2-D**.

2.6. Characterization data of products 3a-3u, 5a-5x & 7

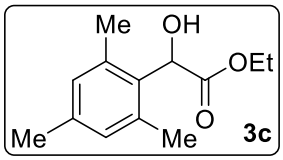
ethyl 2-hydroxy-2-phenylacetate (3a). Colorless liquid; Yield (167 mg, 93%); The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3456, 3064, 2983, 1737, 1211, 733; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.41 (d, J = 7.6 Hz, 2H), 7.36 (t, J = 7.6 Hz, 2H), 7.30 (t, J = 7.2 Hz, 1H), 6.03 (d, J = 5.2 Hz, 1H), 5.12 (d, J = 5.6 Hz, 1H), 4.15 – 4.01 (m, 2H), 1.13 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ (ppm): 173.0, 140.2, 128.7, 128.3, 127.1, 72.9, 60.9, 14.7, 14.5; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{10}H_{12}NaO_3$ 203.0684; found 203.0680.



ethyl 2-hydroxy-2-(*p*-tolyl)acetate (3b).[36] White solid; Yield (178 mg, 92%); mp 76-77 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3458, 3091, 2954, 1738, 1215, 791; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.22 - 7.09 (AB quartet, J = 8.0 Hz, 4H), 5.04 (s, 1H), 4.21 – 4.05 (m, 2H), 3.32 (s, 1H), 2.27 (s, 3H), 1.15 (d, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 173.9, 138.2, 135.5, 129.3, 126.5, 72.8, 62.2, 21.2, 14.0.

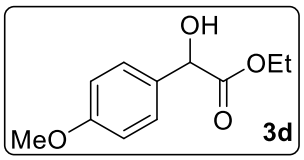


ethyl 2-hydroxy-2-mesitylacetate (3c). White crystalline solid; Yield (202 mg, 91%); mp 54-55 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3450, 3092, 2945, 1736, 1218, 802; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.83 (s, 2H), 5.52 (s,

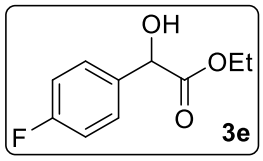


1H), 4.32 – 4.15 (m, 2H), 3.28 (s, 1H), 2.32 (s, 6H), 2.25 (s, 3H), 1.22 (d, J = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 174.9, 137.8, 137.2, 131.5, 129.8, 69.1, 62.2, 20.9, 19.9, 14.1; HRMS (ESI) *m/z:* $[M+Na]^+$ calcd for $C_{13}H_{18}NaO_3$ 245.1154; found 245.1146.

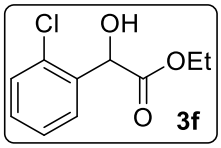
ethyl 2-hydroxy-2-(4-methoxyphenyl)acetate (3d). White solid; Yield (187 mg, 89%); mp 51-52 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3455, 2982, 1735, 1713, 1250, 837; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.25 - 6.80 (AB quartet, J = 8.6 Hz, 4H), 5.03 (s, 1H), 4.21 – 4.07 (m, 2H), 3.73 (s, 3H), 3.14 (s, 1H), 1.15 (t, J = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 173.9, 159.7, 130.7, 127.8, 114.0, 72.5, 62.1, 55.3, 14.1; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{11}H_{14}NaO_4$ 233.0790; found 233.0785.



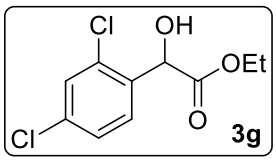
ethyl 2-(4-fluorophenyl)-2-hydroxyacetate (3e). White solid; Yield (178 mg, 90%); mp 71-72 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3441, 3095, 2982, 1732, 1387, 1324; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.36 – 7.30 (m, 2H), 7.01 – 6.94 (m, 2H), 5.06 (s, 1H), 4.22 – 4.08 (m, 2H), 3.43 (s, 1H), 1.15 (t, J = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 173.5, 162.7 (d, $^{1}J_{C\text{-}F}$ = 245.2 Hz), 134.2 (d, $^{4}J_{C\text{-}F}$ = 3.2 Hz), 128.3 (d, $^{3}J_{C\text{-}F}$ = 8.3 Hz), 115.5 (d, $^{2}J_{C\text{-}F}$ = 21.6 Hz), 72.2, 62.4, 14.0; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{10}H_{11}FNaO_3$ 221.0590; found 221.0585.



ethyl 2-(2-chlorophenyl)-2-hydroxyacetate (3f).[37] Colorless liquid; Yield (197 mg, 92%); The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3451, 3091, 2925, 1732, 1191, 790; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.34 – 7.30 (m, 2H), 7.21 – 7.18 (m, 2H), 5.47 (s, 1H), 4.22 – 4.10 (m, 2H), 3.44 (s, 1H), 1.15 (t, J = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 173.2, 136.2, 133.6, 129.9, 129.7, 128.8, 127.1, 70.4, 62.4, 13.9.

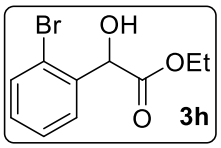


ethyl 2-(2,4-dichlorophenyl)-2-hydroxyacetate (3g).[38] White solid; Yield (224 mg, 90%); mp 54-55 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3457, 3095, 2937, 1738, 1218, 1188, 571; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.62 (d,



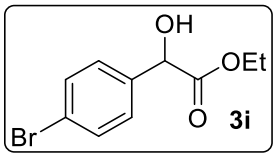
J = 2.0 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.47 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.45 (d, *J* = 6.0 Hz, 1H), 5.38 (d, *J* = 5.6 Hz, 1H), 4.14 – 4.07 (m, 2H), 1.14 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 171.6, 137.1, 133.7, 133.4, 130.5, 129.1, 128.0, 69.8, 61.3, 14.4.

ethyl 2-(2-bromophenyl)-2-hydroxyacetate (3h). Colorless liquid; Yield (231 mg, 89%); The



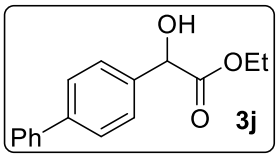
title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3440, 3090, 2952, 1735, 1121; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.50 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.31 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.25 (td, *J* = 7.2, 1.2 Hz, 1H), 7.14 – 7.08 (m, 1H), 5.49 (s, 1H), 4.22 – 4.10 (m, 2H), 3.35 (s, 1H), 1.15 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 173.2, 137.9, 133.2, 129.9, 128.8, 127.8, 123.6, 72.4, 62.5, 13.9; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{10}H_{11}BrNaO_3$ 280.9789; found 280.9783.

ethyl 2-(4-bromophenyl)-2-hydroxyacetate (3i). White solid; Yield (236 mg, 91%); mp 63-64



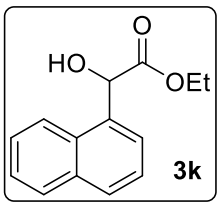
°C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3441, 3092, 2986, 1731, 1021, 523; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.42 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 5.04 (s, 1H), 4.23 – 4.07 (m, 2H), 3.42 (s, 1H), 1.16 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 173.2, 137.4, 131.7, 128.2, 122.4, 72.2, 62.5, 14.0; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{10}H_{11}BrNaO_3$ 280.9789; found 280.9777.

ethyl 2-([1,1'-biphenyl]-4-yl)-2-hydroxyacetate (3j).[21] White solid; Yield (241 mg, 94%); mp



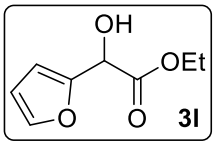
117-118 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3456, 3061, 2991, 1731, 1210, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.61 – 7.57 (m, 4H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.43 (t, *J* = 7.2 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 1H), 5.20 (d, *J* = 5.2 Hz, 1H), 4.32 – 4.16 (m, 2H), 3.53 (d, *J* = 5.6 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 172.6, 140.3, 139.6, 136.4, 127.8, 126.4, 126.3, 126.1, 125.9, 71.6, 61.3, 13.0.

ethyl 2-hydroxy-2-(naphthalen-1-yl)acetate (3k).[39] Colorless liquid; Yield (212 mg, 92%); The



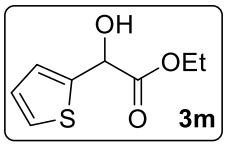
title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3456, 3064, 2983, 1737, 1211, 721; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.03 (d, J = 8.4 Hz, 1H), 7.71 – 7.63 (m, 2H), 7.38 – 7.22 (m, 4H), 5.63 (s, 1H), 4.07 – 3.92 (m, 2H), 3.84 (s, 1H), 0.93 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 172.9, 133.2, 132.9, 129.9, 128.2, 127.6, 125.3, 124.7, 124.6, 124.1, 122.8, 70.3, 60.9, 12.8.

ethyl 2-(furan-2-yl)-2-hydroxyacetate (3l). Colorless liquid; Yield (153 mg, 90%); The title



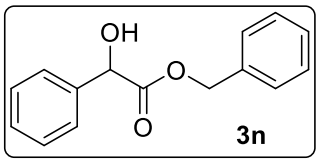
compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3444, 3097, 2984, 1740, 1370, 804; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.40 – 7.38 (m, 1H), 6.38 – 6.35 (m, 2H), 5.18 (d, J = 6.8 Hz, 1H), 4.32 – 4.25 (m, 2H), 3.38 (d, J = 6.8 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 171.5, 150.9, 142.9, 110.5, 108.6, 66.9, 62.5, 14.1; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_8H_{10}NaO_4$ 193.0477; found 193.0469.

ethyl 2-hydroxy-2-(thiophen-2-yl)acetate (3m). Colorless liquid; Yield (169 mg, 91%); The



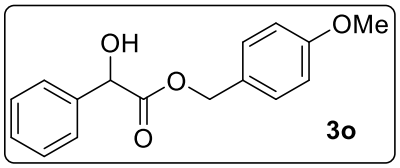
title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3452, 3097, 2982, 1736, 1664, 1227; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.21 (dd, J = 5.2, 1.2 Hz, 1H), 7.03 (d, J = 3.6 Hz, 1H), 6.91 (dd, J = 5.2, 3.6 Hz, 1H), 5.33 (s, 1H), 4.25 – 4.17 (m, 2H), 3.43 (s, 1H), 1.22 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 172.5, 141.6, 126.9, 125.7, 125.3, 69.1, 62.6, 14.1; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_8H_{10}NaO_3S$ 209.0248; found 209.0245.

benzyl 2-hydroxy-2-phenylacetate (3n). White crystalline solid; Yield (220 mg, 91%); mp 95-

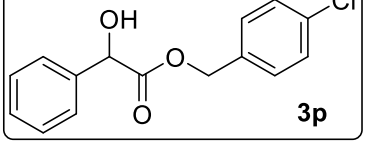


96 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3445, 3078, 2950, 1955, 1739, 1727, 1211, 724; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.43 – 7.18 (m, 8H), 7.17 – 7.04 (m, 2H), 5.18 – 5.03 (m, 3H), 3.28 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 173.5, 138.2, 135.0, 128.6, 128.6, 128.5, 128.5, 127.9, 126.6, 72.9, 67.7; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{15}H_{14}NaO_3$ 265.0841; found 265.0839.

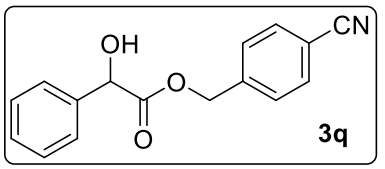
4-methoxybenzyl 2-hydroxy-2-phenylacetate (3o). White solid; Yield (231 mg, 85%); mp 66-67 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3377, 3047, 2951, 1712, 1384, 1086; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.42 – 7.26 (m, 5H), 7.19 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.08 (d, J = 5.2 Hz, 1H), 5.16 (d, J = 5.2 Hz, 1H), 5.06 (d, J = 12.0 Hz, 1H), 5.00 (d, J = 12.0 Hz, 1H), 3.73 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ (ppm): 172.9, 159.6, 140.0, 130.1, 128.7, 128.4, 128.3, 127.1, 114.2, 72.9, 66.1, 55.6; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{16}H_{16}NaO_4$ 295.0946; found 295.0941.



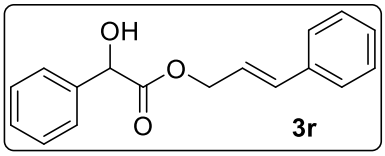
4-chlorobenzyl 2-hydroxy-2-phenylacetate (3p). White crystalline solid; Yield (254 mg, 92%); mp 133-134 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3377, 3047, 2954, 1715, 1384, 1086; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.34 – 7.26 (m, 5H), 7.20 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.5 Hz, 2H), 5.14 (s, 1H), 5.06 (t, J = 10.0 Hz, 2H), 3.31 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 173.4, 138.1, 134.4, 133.5, 129.3, 128.8, 128.7, 128.6, 126.6, 72.9, 66.8; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{15}H_{13}ClNaO_3$ 299.0451; found 299.0449.



4-cyanobenzyl 2-hydroxy-2-phenylacetate (3q). White solid; Yield (238 mg, 89%); mp 141-142 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3442, 3062, 2924, 2230, 1737, 1728, 896; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.49 (d, J = 8.4 Hz, 2H), 7.35 – 7.27 (m, 5H), 7.14 (d, J = 8.4 Hz, 2H), 5.20 – 5.11 (m, 3H), 3.33 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 173.3, 140.3, 137.9, 132.4, 128.8, 128.8, 127.9, 126.6, 118.4, 112.3, 73.0, 66.2; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{16}H_{13}NNaO_3$ 290.0793; found 290.0791.

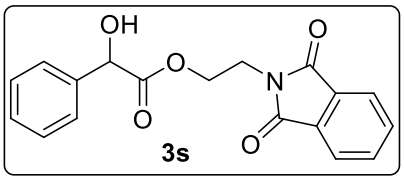


cinnamyl 2-hydroxy-2-phenylacetate (3r). White solid; Yield (244 mg, 91%); mp 68-69 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3449, 3031, 2980, 1731, 1493, 1200; ^{1}H NMR (400 MHz, $CDCl_3$) δ

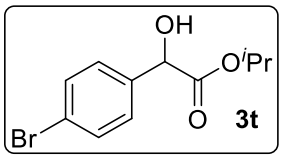


(ppm): 7.40 – 7.36 (m, 2H), 7.33 – 7.14 (m, 8H), 6.42 (dt, *J* = 15.6, 1.2 Hz, 1H), 6.11 (dt, *J* = 16.0, 6.4 Hz, 1H), 5.15 (s, 1H), 4.79 – 4.69 (m, 2H), 3.37 (s, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 173.5, 138.3, 135.9, 134.6, 128.7, 128.6, 128.6, 128.3, 126.7, 122.0, 73.0, 66.5; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{17}H_{16}NaO_3$ 291.0997; found 291.1000.

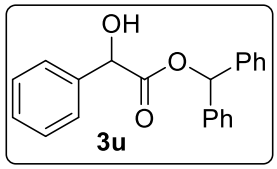
2-(1,3-dioxoisoindolin-2-yl)ethyl 2-hydroxy-2-phenylacetate (3s). White solid; Yield (276 mg, 85%); mp 89-90 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3470, 2959, 1774, 1742, 1712, 529; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.78 – 7.74 (m, 2H), 7.68 – 7.65 (m, 2H), 7.28 – 7.25 (m, 2H), 7.16 – 7.09 (m, 3H), 5.09 (s, 1H), 4.42 – 4.36 (m, 1H), 4.28 – 4.21 (m, 1H), 3.94 – 3.83 (m, 2H), 3.31 (s, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 173.3, 167.9, 137.8, 134.1, 131.8, 128.4, 128.3, 126.5, 123.5, 72.9, 63.0, 36.6; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{18}H_{15}NNaO_5$ 348.0848; found 348.0843.



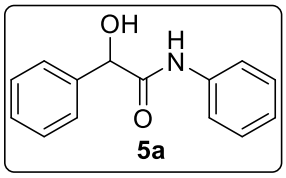
isopropyl 2-(4-bromophenyl)-2-hydroxyacetate (3t). White crystalline solid; Yield (243 mg, 89%); mp 72-73 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3444, 3091, 2989, 1740, 1108, 513; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.40 - 7.24 (AB quartet, *J* = 8.4 Hz, 4H), 5.04 – 4.94 (m, 2H), 3.44 (s, 1H), 1.21 (d, *J* = 6.4 Hz, 3H), 1.04 (d, *J* = 6.4 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 172.7, 137.6, 131.6, 128.1, 122.3, 72.3, 70.5, 21.7, 21.4; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{11}H_{13}BrNaO_3$ 294.9946; found 294.9937.



benzhydryl 2-hydroxy-2-phenylacetate (3u).[40] White solid; Yield (302 mg, 95%); mp 115-116 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3443, 3095, 2982, 1735, 1265, 1172; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35 – 7.20 (m, 10H), 7.11 – 7.04 (m, 3H), 6.83 (d, *J* = 6.8 Hz, 2H), 6.80 (s, 1H), 5.20 (s, 1H), 3.39 (s, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 172.8, 139.3, 139.2, 138.1, 128.7, 128.6, 128.6, 128.4, 128.3, 127.9, 127.4, 126.8, 126.3, 78.8, 73.2.

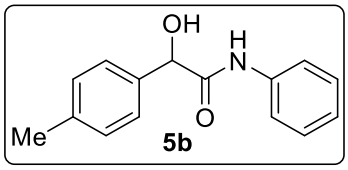


2-hydroxy-*N*,2-diphenylacetamide (5a).[28] White solid; Yield (218 mg, 96%); mp 150-151 °C;



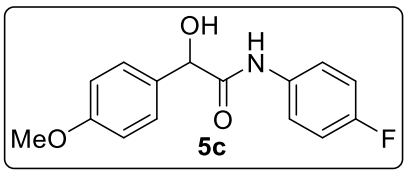
The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3444, 3064, 2973, 1642, 1563, 880; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.90 (s, 1H), 7.70 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 7.2 Hz, 2H), 7.36 (t, J = 7.2 Hz, 2H), 7.29 (t, J = 7.2 Hz, 3H), 7.05 (t, J = 7.6 Hz, 1H), 6.43 (d, J = 4.8 Hz, 1H), 5.11 (d, J = 4.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 171.6, 141.3, 138.9, 129.1, 128.6, 128.1, 127.0, 124.0, 120.2, 74.5.

2-hydroxy-*N*-phenyl-2-(*p*-tolyl)acetamide (5b).[28] White crystalline solid; Yield (229 mg,



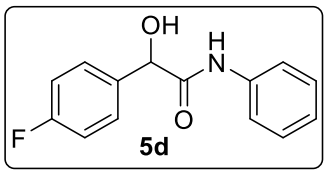
95%); mp 145-146 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3373, 3092, 2973, 1642, 1557, 1076; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.90 (s, 1H), 7.73 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.34 (t, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.10 (t, J = 7.2 Hz, 1H), 6.39 (d, J = 4.8 Hz, 1H), 5.10 (d, J = 4.4 Hz, 1H), 2.33 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 171.8, 138.9, 138.4, 137.2, 129.1, 129.1, 126.9, 123.9, 120.1, 74.3, 21.2.

***N*-(4-fluorophenyl)-2-hydroxy-2-(4-methoxyphenyl)acetamide (5c)**. White crystalline solid;



Yield (261 mg, 95%); mp 156-157 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3351, 3012, 2842, 1659, 1273, 832; ^1H NMR (400 MHz, $CDCL_3$+DMSO-d_6) δ (ppm): 9.03 (s, 1H), 7.54 – 7.48 (m, 2H), 7.36 (d, J = 8.8 Hz, 2H), 6.91 (t, J = 8.8 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 5.87 (s, 1H), 5.04 (s, 1H), 3.71 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCL_3$+DMSO-d_6) δ (ppm): 171.1, 159.5, 159.1 (d, $^1J_{C\text{-}F}$ = 241.3 Hz), 133.9, 132.5, 128.0, 121.3 (d, $^3J_{C\text{-}F}$ = 7.8 Hz), 115.4 (d, $^2J_{C\text{-}F}$ = 22.3 Hz), 113.8, 73.8, 55.3; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{15}H_{14}FNNaO_3$ 298.0855; found 298.0849.

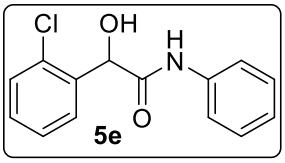
2-(4-fluorophenyl)-2-hydroxy-*N*-phenylacetamide (5d).[28] White crystalline solid; Yield (230



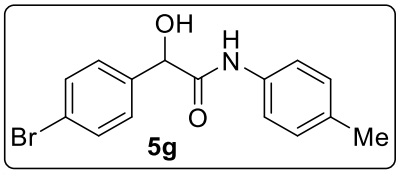
mg, 94%); mp 115-116 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3301, 3095, 1656, 1512, 1231, 1061; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.91 (s, 1H), 7.72 – 7.67 (m, 2H), 7.59 – 7.53 (m, 2H), 7.32 – 7.27 (m, 2H), 7.19 (t, J =

9.2 Hz, 2H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.49 (d, *J* = 4.8 Hz, 1H), 5.13 (d, *J* = 4.4 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 171.5, 162.1 (d, $^{1}J_{C\text{-}F}$ = 241.8 Hz), 138.9, 137.5 (d, $^{3}J_{C\text{-}F}$ = 11.2 Hz), 129.1 (d, $^{4}J_{C\text{-}F}$ = 4.6 Hz), 128.9, 124.1, 120.2, 115.4 (d, $^{2}J_{C\text{-}F}$ = 21.2 Hz), 73.7.

2-(2-chlorophenyl)-2-hydroxy-*N*-phenylacetamide (5e).[30] White crystalline solid; Yield (238 mg, 91%); mp 158-159 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3300, 3179, 3091, 2915, 1656, 1061; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.02 (s, 1H), 7.75 – 7.70 (m, 2H), 7.58 (dd, *J* = 7.6, 2.4 Hz, 1H), 7.48 – 7.42 (m, 1H), 7.39 – 7.29 (m, 4H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.65 (d, *J* = 5.2 Hz, 1H), 5.49 (d, *J* = 5.2 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 170.5, 139.2, 138.9, 133.1, 129.9, 129.7, 129.6, 129.1, 127.7, 124.1, 120.3, 71.6.

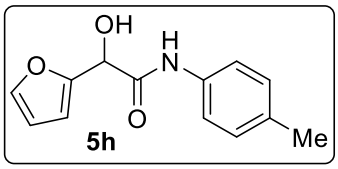


***N*-(4-bromophenyl)-2-(2,4-dichlorophenyl)-2-hydroxyacetamide (5f)**. White crystalline solid; Yield (338 mg, 90%); mp 155-156 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3433, 3061, 2977, 1641, 1556, 1077; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.22 (s, 1H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.66 – 7.53 (m, 2H), 7.52 – 7.45 (m, 3H), 6.76 (d, *J* = 5.2 Hz, 1H), 5.45 (d, *J* = 5.2 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 170.3, 138.3, 138.2, 133.9, 133.6, 131.9, 130.9, 129.1, 127.9, 122.3, 115.9, 71.3; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{11}BrCl_2NO_2$ 373.9350; found 373.9323.

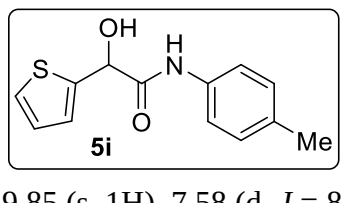


2-(4-bromophenyl)-2-hydroxy-*N*-(*p*-tolyl)acetamide (5g). Off-white crystalline solid; Yield (294 mg, 92%); mp 166-167 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3412, 3062, 2978, 1640, 1557, 1077; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.83 (s, 1H), 7.56 (d, *J* = 8.4 Hz, 4H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.49 (d, *J* = 4.8 Hz, 1H), 5.09 (d, *J* = 4.8 Hz, 1H), 2.24 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 170.9, 140.8, 136.4, 133.0, 131.4, 129.5, 129.2, 121.2, 120.2, 73.7, 20.9; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{15}BrNO_2$ 320.0286; found 320.0280.

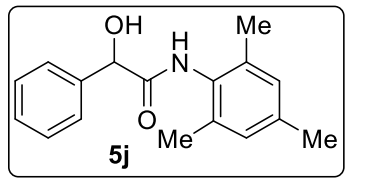
2-(furan-2-yl)-2-hydroxy-*N*-(*p*-tolyl)acetamide (5h). White crystalline solid; Yield (208 mg, 90%); mp 163-164 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3286, 3036, 1651, 1602, 1232, 507; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.83 (s, 1H), 7.64 – 7.56 (m, 3H), 7.11 (d, J = 8.4 Hz, 2H), 6.44 (d, J = 5.6 Hz, 1H), 6.44 – 6.37 (m, 2H), 5.13 (d, J = 5.6 Hz, 1H), 2.25 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 169.1, 153.8, 143.0, 136.3, 133.1, 129.5, 120.2, 110.9, 108.4, 68.5, 20.9; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{13}H_{13}NNaO_3$ 254.0793; found 254.0792.



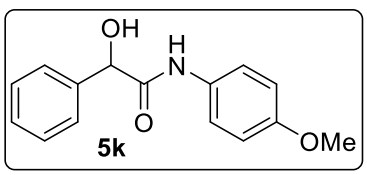
2-hydroxy-2-(thiophen-2-yl)-*N*-(*p*-tolyl)acetamide (5i). White solid; Yield (222 mg, 90%); mp 172-173 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3344, 3090, 2925, 1651, 1233, 819; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.85 (s, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 5.2 Hz, 1H), 7.15 – 7.07 (m, 3H), 6.99 (dd, J = 5.2, 4.0 Hz, 1H), 6.69 (d, J = 5.2 Hz, 1H), 5.34 (d, J = 4.8 Hz, 1H), 2.24 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 170.4, 144.6, 136.3, 133.2, 129.5, 127.0, 125.9, 125.3, 120.3, 70.6, 20.9; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{13}H_{13}NNaO_2S$ 270.0565; found 270.0561.



2-hydroxy-*N*-mesityl-2-phenylacetamide (5j). Off-white crystalline solid; Yield (256 mg, 95%); mp 126-127 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3329, 3036, 2917, 1659, 1440, 1065, 697; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.26 (s, 1H), 7.53 (d, J = 7.2 Hz, 2H), 7.36 (t, J = 7.2 Hz, 2H), 7.28 (t, J = 7.2 Hz, 1H), 6.82 (s, 2H), 6.29 (d, J = 4.4 Hz, 1H), 5.09 (d, J = 4.4 Hz, 1H), 2.19 (s, 3H), 1.96 (s, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 171.5, 141.8, 135.8, 135.5, 132.5, 128.6, 128.4, 127.9, 127.0, 74.4, 20.9, 18.3; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{17}H_{19}NNaO_2$ 292.1313; found 292.1317.

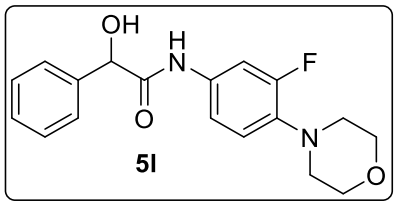


2-hydroxy-*N*-(4-methoxyphenyl)-2-phenylacetamide (5k).[27] White crystalline solid; Yield (231 mg, 90%); mp 152-153 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3349, 3095, 2942, 1659, 1271, 762; ^{1}H NMR (400

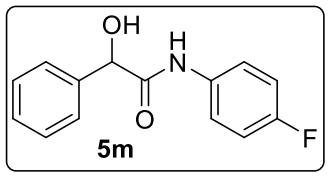


MHz, DMSO-d_6) δ (ppm): 9.82 (s, 1H), 7.64 (d, J = 9.2 Hz, 2H), 7.55 (d, J = 7.2 Hz, 2H), 7.39 (t, J = 7.2 Hz, 2H), 7.33 (t, J = 7.6 Hz, 1H), 6.90 (d, J = 8.8 Hz, 2H), 6.42 (d, J = 4.4 Hz, 1H), 5.12 (d, J = 4.8 Hz, 1H), 3.75 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 171.1, 155.9, 141.5, 132.1, 128.5, 128.0, 127.0, 121.7, 114.2, 74.4, 55.6.

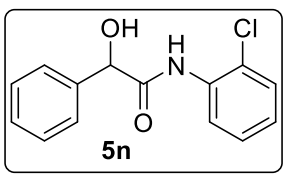
***N*-(3-fluoro-4-morpholinophenyl)-2-hydroxy-2-phenylacetamide (5l)**. Off-white solid; Yield (314 mg, 95%); mp 176-177 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3299, 3091, 2829, 1659, 1652, 1304, 1251; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.98 (s, 1H), 7.63 (dd, J = 14.8, 2.0 Hz, 1H), 7.50 (d, J = 7.6 Hz, 2H), 7.43 (d, J = 8.8 Hz, 1H), 7.35 (t, J = 6.8 Hz, 2H), 7.29 (t, J = 6.8 Hz, 1H), 6.97 (t, J = 9.2 Hz, 1H), 6.46 (d, J = 4.4 Hz, 1H), 5.08 (d, J = 4.8 Hz, 1H), 3.715 (t, J = 4.4 Hz, 4H), 2.93 (t, J = 4.4 Hz, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 171.6, 154.8 (d, $^1J_{C\text{-}F}$ = 241.4 Hz), 141.2, 135.9 (d, $^2J_{C\text{-}F}$ = 14 Hz), 134.1 (d, $^3J_{C\text{-}F}$ = 10.6 Hz), 128.6, 128.1, 127.0, 119.4 (d, $^3J_{C\text{-}F}$ = 3.9 Hz), 116.3 (d, $^4J_{C\text{-}F}$ = 2.7 Hz), 108.4 (d, $^2J_{C\text{-}F}$ = 25.5 Hz), 74.4, 66.6, 51.2 (d, $^4J_{C\text{-}F}$ = 2.4 Hz); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{20}FN_2O_3$ 331.1458; found 331.1449.



***N*-(4-fluorophenyl)-2-hydroxy-2-phenylacetamide (5m)**. White solid; Yield (230 mg, 94%); mp 162-163 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3303, 3100, 1656, 1513, 1236, 1064, 504; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.00 (s, 1H), 7.77 – 7.70 (m, 2H), 7.52 (d, J = 7.6 Hz, 2H), 7.36 (t, J = 7.2 Hz, 2H), 7.29 (t, J = 7.2 Hz, 1H), 7.13 (t, J = 8.8 Hz, 2H), 6.45 (d, J = 4.8 Hz, 1H), 5.10 (d, J = 4.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 171.6, 158.6 (d, $^1J_{C\text{-}F}$ = 238.5 Hz), 141.3, 135.4 (d, $^4J_{C\text{-}F}$ = 2.2 Hz), 128.6, 128.1, 127.1, 121.9 (d, $^3J_{C\text{-}F}$ = 7.8 Hz), 115.6 (d, $^2J_{C\text{-}F}$ = 22 Hz), 74.5; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{12}FNNaO_2$ 268.0750; found 268.0747.

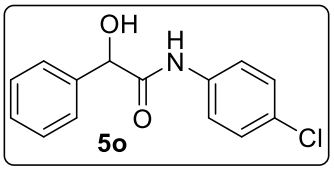


***N*-(2-chlorophenyl)-2-hydroxy-2-phenylacetamide (5n)**.[16] White solid; Yield (245 mg, 94%); mp 167-168 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3299, 3184, 3092, 2842, 1651, 1062; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.65 (s, 1H),



8.11 (d, *J* = 8.4 Hz, 1H), 7.52 (t, *J* = 8.4 Hz, 3H), 7.40 – 7.30 (m, 4H), 7.16 (t, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 4.4 Hz, 1H), 5.20 (d, *J* = 4.4 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 171.4, 140.8, 134.6, 129.8, 128.7, 128.3, 127.2, 125.9, 124.3, 122.7, 74.1.

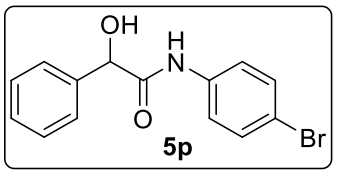
***N*-(4-chlorophenyl)-2-hydroxy-2-phenylacetamide (5o)**. White solid; Yield (256 mg, 98%);



5o

mp 164-165 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3317, 3157, 3092, 2842, 1650, 1060; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.08 (s, 1H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.53 – 7.45 (m, 4H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 6.47 (d, *J* = 4.4 Hz, 1H), 5.10 (d, *J* = 4.8 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d_6) δ (ppm): 171.9, 141.1, 138.4, 131.9, 128.6, 128.1, 127.0, 122.2, 115.7, 74.5; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{12}ClNNaO_2$ 284.0454; found 284.0448.

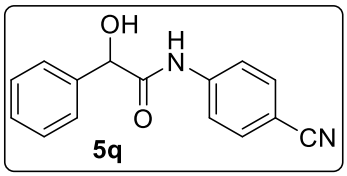
***N*-(4-bromophenyl)-2-hydroxy-2-phenylacetamide (5p)**.[27] Off-white crystalline solid; Yield



5p

(285 mg, 93%); mp 127-128 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3343, 3294, 3091, 2900, 1668, 751; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.65 (s, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.52 (t, *J* = 8.4 Hz, 3H), 7.41 – 7.30 (m, 4H), 7.16 (t, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 4.4 Hz, 1H), 5.20 (d, *J* = 4.4 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 171.9, 141.1, 138.4, 131.9, 128.6, 128.1, 127.0, 122.2, 115.7, 74.5.

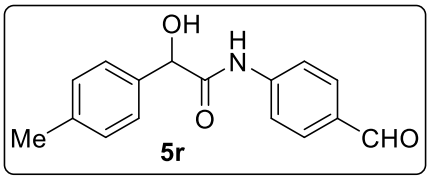
***N*-(4-cyanophenyl)-2-hydroxy-2-phenylacetamide (5q)**.[16] Off-white crystalline solid; Yield



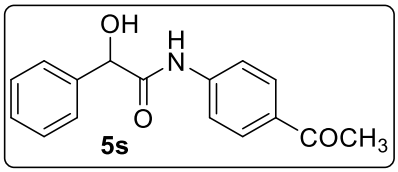
5q

(229 mg, 91%); mp 169-170 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3358, 3092, 2913, 2224, 1667, 1309; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.39 (s, 1H), 7.95 - 7.76 (AB quartet, *J* = 8.8 Hz, 4H), 7.52 (d, *J* = 7.2 Hz, 2H), 7.37 (t, *J* = 6.8 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 1H), 6.57 (d, *J* = 4.4 Hz, 1H), 5.16 (d, *J* = 4.4 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 172.6, 143.3, 140.8, 133.6, 128.7, 128.3, 127.1, 120.3, 119.5, 105.8, 74.6.

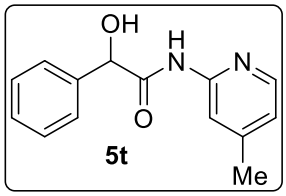
***N*-(4-formylphenyl)-2-hydroxy-2-(*p*-tolyl)acetamide (5r).** Off-white solid; Yield (247 mg, 92%); mp 164-165 °C; The title compound is prepared according to the general procedure (B) described as above (EtOAc:Hexanes = 25:75); FT-IR (KBr, cm^{-1}) 3434, 3092, 2976, 1692, 1562, 802; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.29 (s, 1H), 9.87 (s, 1H), 7.94 (d, J = 8.8 Hz, 2H), 7.84 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 6.43 (s, 1H), 5.11 (s, 1H), 2.28 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ (ppm): 192.1, 172.6, 144.6, 137.9, 137.4, 132.0, 131.1, 129.2, 127.0, 119.9, 74.4, 21.2; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{16}H_{15}NNaO_3$ 292.0950; found 292.0936.



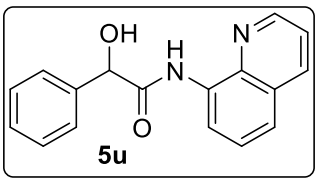
***N*-(4-acetylphenyl)-2-hydroxy-2-phenylacetamide (5s)**.[16] White solid; Yield (242 mg, 90%); mp 169-170 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3434, 3092, 2975, 1644, 1556, 815; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.29 (s, 1H), 7.98 – 7.89 (m, 4H), 7.57 (d, J = 7.2 Hz, 2H), 7.41 (t, J = 7.2 Hz, 2H), 7.34 (t, J = 7.2 Hz, 1H), 6.55 (d, J = 4.8 Hz, 1H), 5.20 (d, J = 4.8 Hz, 1H), 2.56 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ (ppm): 197.1, 172.3, 143.4, 140.9, 132.5, 129.8, 128.6, 128.2, 127.1, 119.5, 74.6, 26.9.



2-hydroxy-*N*-(4-methylpyridin-2-yl)-2-phenylacetamide (5t). White solid; Yield (225 mg, 93%); mp 142-143 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3410, 3056, 2978, 1685, 1647, 1552, 850; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.90 (s, 1H), 8.22 (d, J = 4.8 Hz, 1H), 7.93 (s, 1H), 7.55 (d, J = 7.2 Hz, 2H), 7.40 (t, J = 7.2 Hz, 2H), 7.34 (t, J = 7.2 Hz, 1H), 7.03 – 6.98 (m, 1H), 6.57 (d, J = 4.8 Hz, 1H), 5.26 (d, J = 4.8 Hz, 1H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ (ppm): 171.8, 151.5, 149.7, 148.3, 140.9, 128.6, 128.2, 127.0, 121.4, 114.0, 73.8, 21.3; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{15}N_2O_2$ 243.1134; found 243.1127.

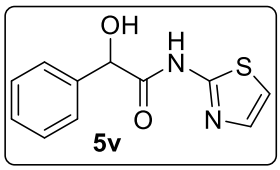


2-hydroxy-2-phenyl-*N*-(quinolin-8-yl)acetamide (5u). Off-white crystalline solid; Yield (261 mg, 94%); mp 136-137 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3419, 3071, 2980, 1641, 1554, 881; ^{1}H NMR (400 MHz, DMSO-d_6)

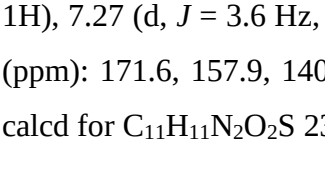


δ (ppm): 11.23 (s, 1H), 9.02 (dd, J = 4.4, 1.6 Hz, 1H), 8.70 (dd, J = 7.6, 1.2 Hz, 1H), 8.45 (dd, J = 8.4, 1.6 Hz, 1H), 7.73 – 7.67 (m, 2H), 7.63 – 7.55 (m, 3H), 7.41 (t, J = 7.2 Hz, 2H), 7.34 (t, J = 7.2 Hz, 1H), 7.08 (d, J = 4.4 Hz, 1H), 5.29 (d, J = 4.0 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 171.5, 149.7, 141.1, 138.5, 137.2, 134.1, 128.7, 128.3, 128.2, 127.5, 127.1, 122.8, 122.5, 115.9, 74.5; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{15}N_2O_2$ 279.1134; found 279.1131.

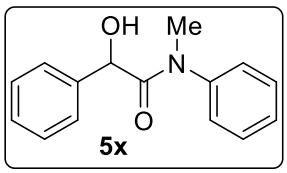
2-hydroxy-2-phenyl-*N*-(thiazol-2-yl)acetamide (5v). White solid; Yield (213 mg, 91%); mp 150-151 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3432, 3082, 2979, 1645, 1554, 1077; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.07 (s, 1H), 7.60 – 7.55 (m, 2H), 7.54 (d, J = 3.6 Hz, 1H), 7.41 (t, J = 7.2 Hz, 2H), 7.35 (t, J = 7.2 Hz, 1H), 7.27 (d, J = 3.6 Hz, 1H), 6.38 (s, 1H), 5.37 (s, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 171.6, 157.9, 140.4, 138.2, 128.7, 128.4, 127.1, 114.3, 73.4; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{11}N_2O_2S$ 235.0541; found 235.0538.



***N*-benzyl-2-hydroxy-2-phenylacetamide (5w)**.[41] White crystalline solid; Yield (222 mg, 92%); mp 110-111 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3278, 3083, 2976, 1619, 1295, 754; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.52 (t, J = 6.0 Hz, 1H), 7.43 (d, J = 7.6 Hz, 2H), 7.32 (t, J = 7.2 Hz, 2H), 7.29 – 7.24 (m, 3H), 7.23 – 7.18 (m, 3H), 6.19 (d, J = 4.8 Hz, 1H), 4.97 (d, J = 4.8 Hz, 1H), 4.33 – 4.23 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 172.7, 141.8, 140.0, 128.6, 128.4, 127.9, 127.6, 127.1, 127.0, 74.0, 42.2.

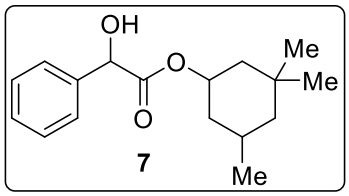


2-hydroxy-*N*-methyl-*N*,2-diphenylacetamide (5x). White crystalline solid; Yield (224 mg, 93%); mp 128-129 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3423, 3091, 2954, 1656, 1495, 707; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.49 – 7.38 (m, 3H), 7.30 – 6.90 (m, 7H), 5.59 (d, J = 6.4 Hz, 1H), 5.06 (s, 1H), 3.22 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 172.2, 143.1, 140.7, 129.9, 128.5, 128.3, 128.2,



128.1, 127.4, 70.6, 37.9; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{15}H_{15}NNaO_2$ 264.1000; found 264.0995.

3,3,5-trimethylcyclohexyl 2-hydroxy-2-phenylacetate (Cyclandelate) (7).[23] Colorless liquid;



7

Yield (212 mg, 90%); The cyclandelate is prepared according to the general procedure (A) as a mixture of diastereomers; FT-IR (KBr, cm^{-1}) 3458, 3091, 2994, 2954, 1738, 1215, 786; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.43 – 7.27 (m, 5H), 5.18 – 5.13 (m, 0.2 H), 5.12 – 5.07 (m, 1H), 4.99 – 4.90 (m, 0.8H), 3.67 (dd, J = 13.2, 5.6 Hz, 0.2H), 3.58 (d, J = 5.6 Hz, 0.8H), 2.05 – 1.98 (m, 0.4H), 1.81 – 1.61 (m, 2H), 1.51 – 1.41 (m, 0.6H), 1.35 – 1.25 (m, 2H), 0.95 – 0.82 (m, 9H), 0.77 – 0.67 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 173.4, 173.4, 173.3, 173.3, 138.8, 138.8, 138.5, 128.6, 128.5, 128.5, 128.4, 127.0, 126.7, 126.6, 126.5, 73.8, 73.7, 73.6, 73.4, 73.3, 73.1, 48.0, 47.5, 47.5, 43.9, 43.5, 41.4, 41.2, 40.3, 39.9, 38.5, 38.1, 34.0, 33.8, 33.1, 33.0, 32.5, 32.4, 27.4, 27.2, 27.1, 26.8, 25.6, 25.5, 23.4, 23.1, 22.5, 22.4, 22.3.

2.7. References

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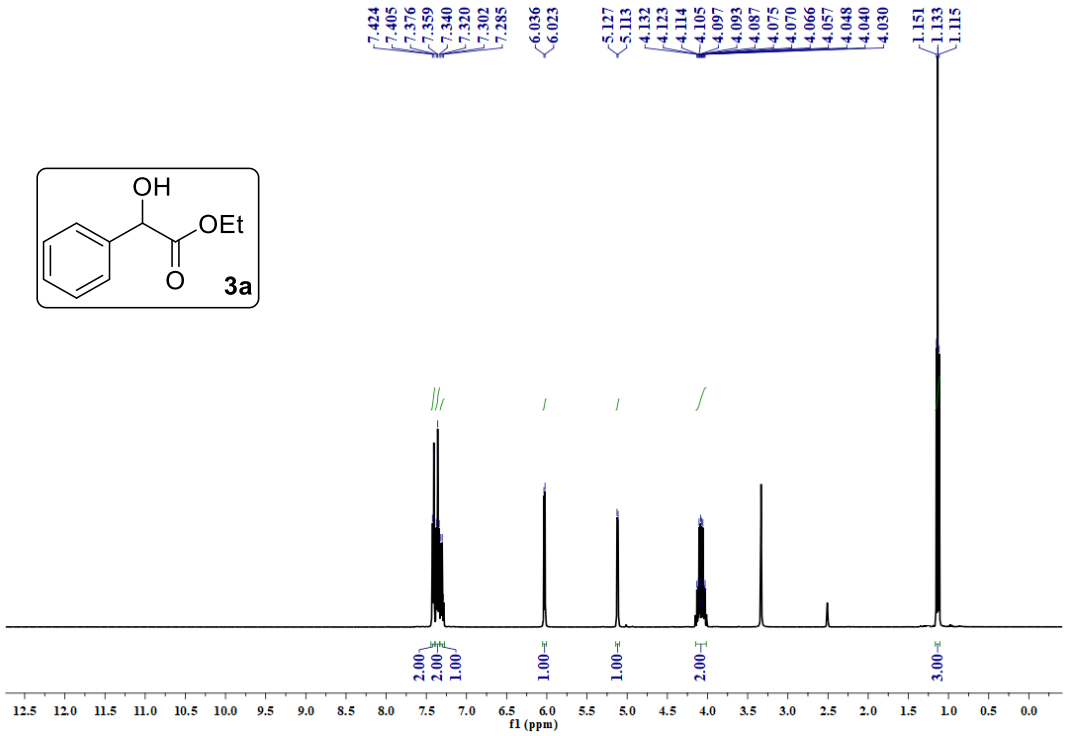
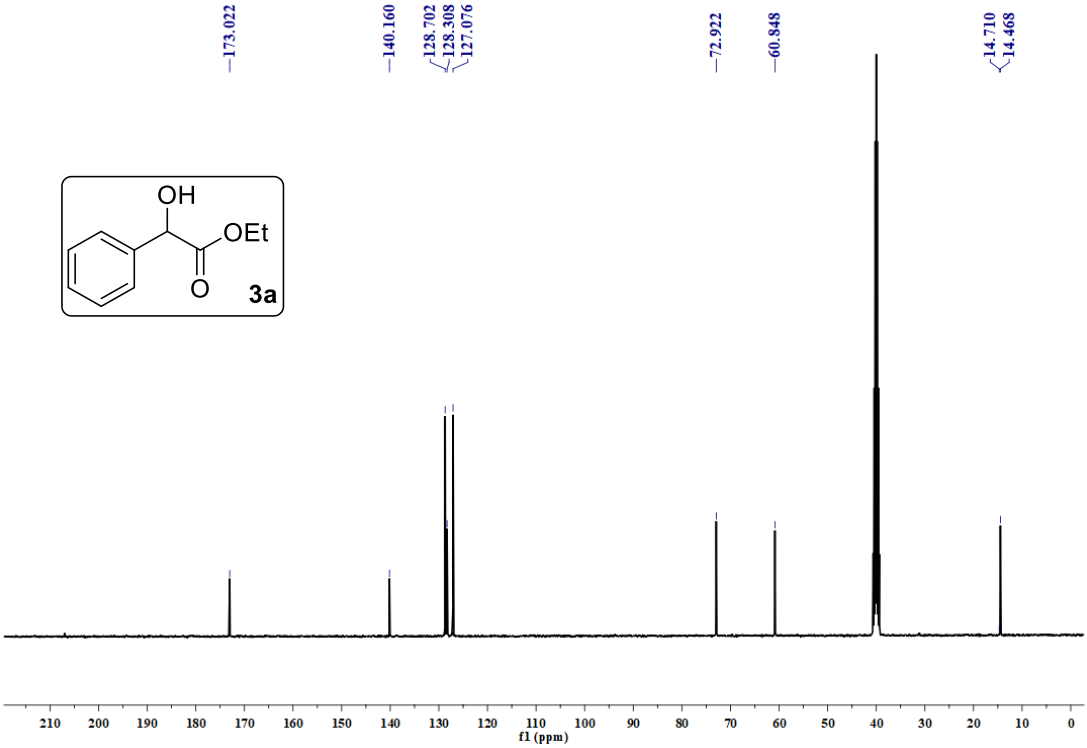
2.8. Selected HRMS and NMR (^{1}H & ^{13}C) spectra

^{1}H NMR (400 MHz, DMSO-d_6) spectrum of ethyl 2-hydroxy-2-phenylacetate (3a)



$^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) spectrum of ethyl 2-hydroxy-2-phenylacetate (3a)



HRMS of ethyl 2-hydroxy-2-phenylacetate (3a)

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User Name		**Inj Vol**	2	**InjPosition**	
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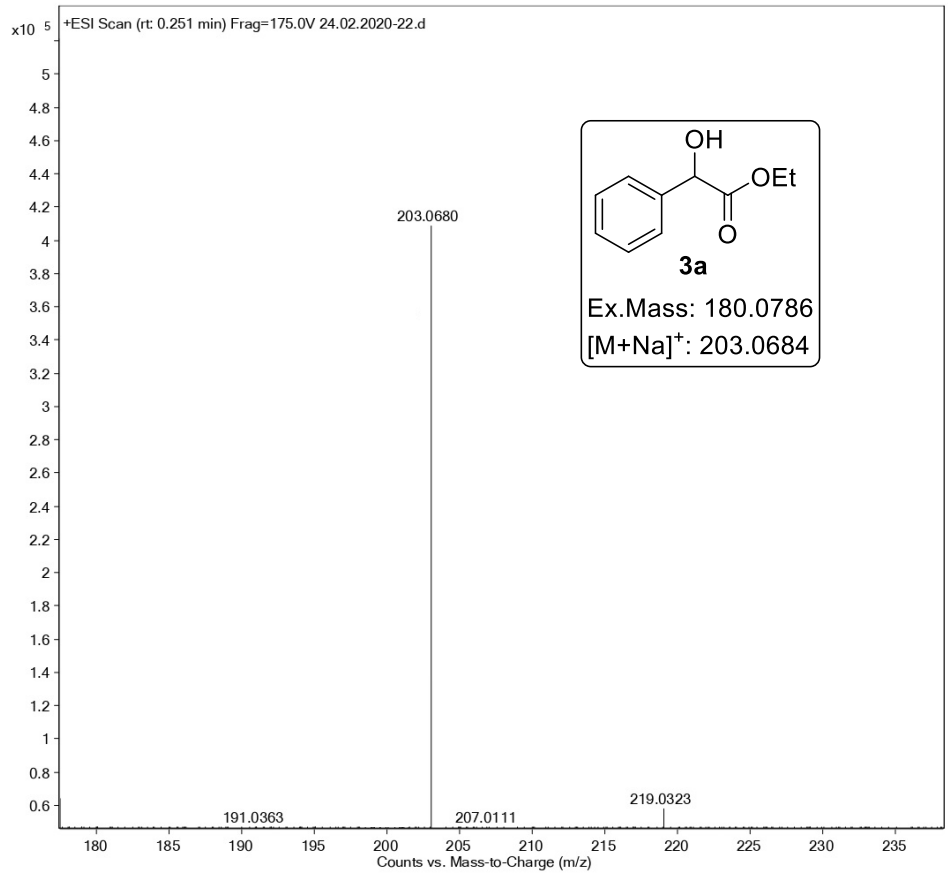
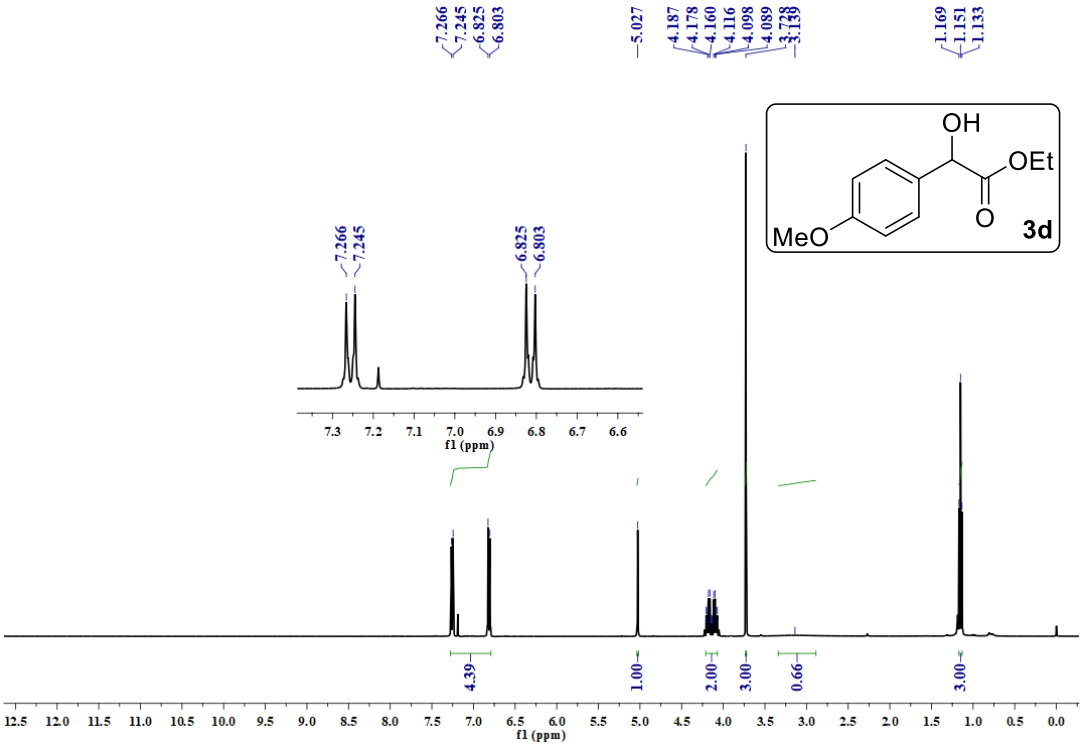
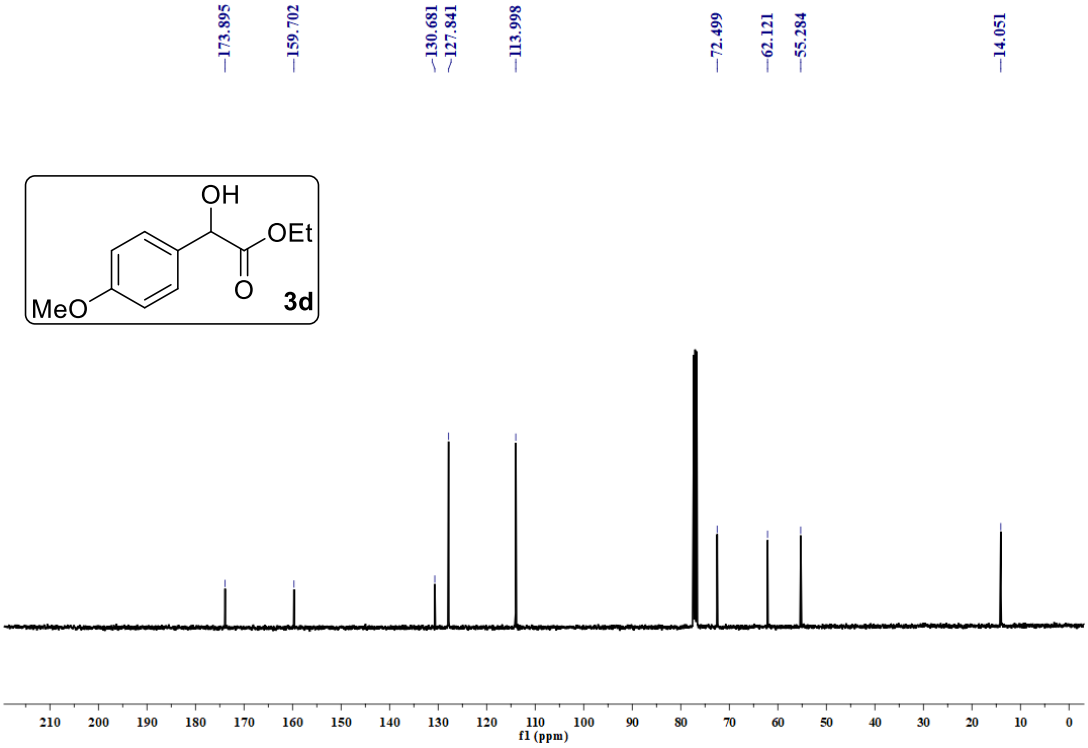


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of ethyl 2-hydroxy-2-(4-methoxyphenyl)acetate (3d)



^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of ethyl 2-hydroxy-2-(4-methoxyphenyl)acetate (3d)



HRMS of ethyl 2-hydroxy-2-(4-methoxyphenyl)acetate (3d)

Sample Name	KER 4	**Position**	P1-C7	**Instrument Name**	Instrument 1
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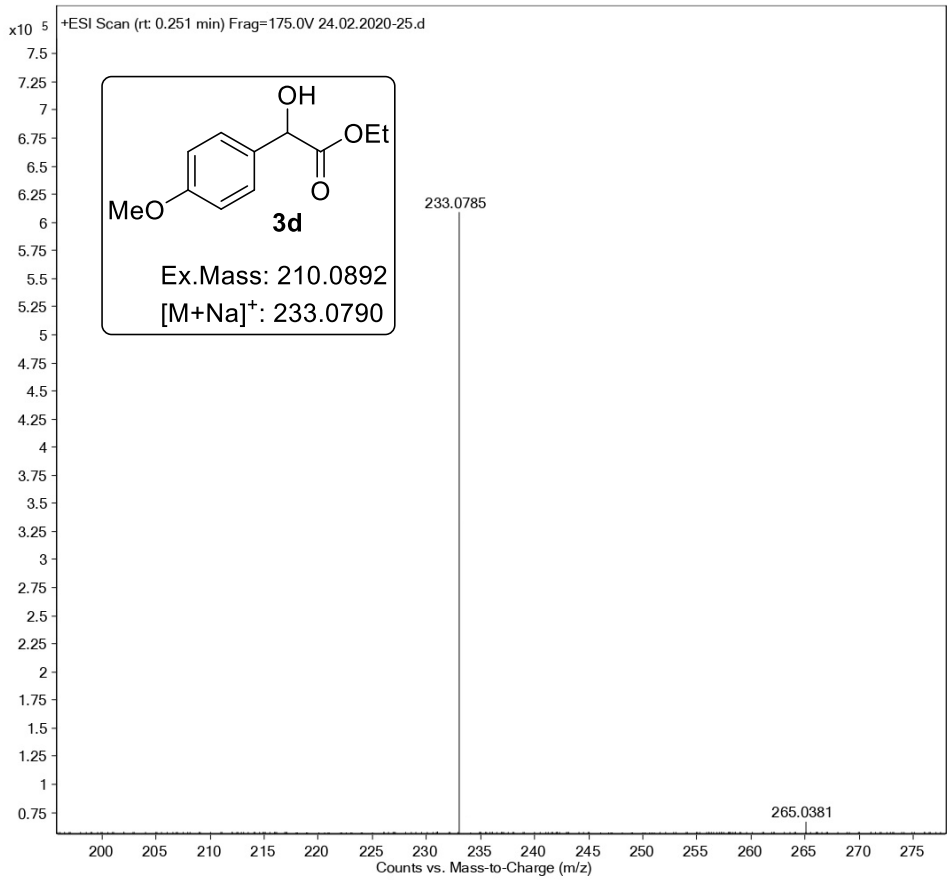
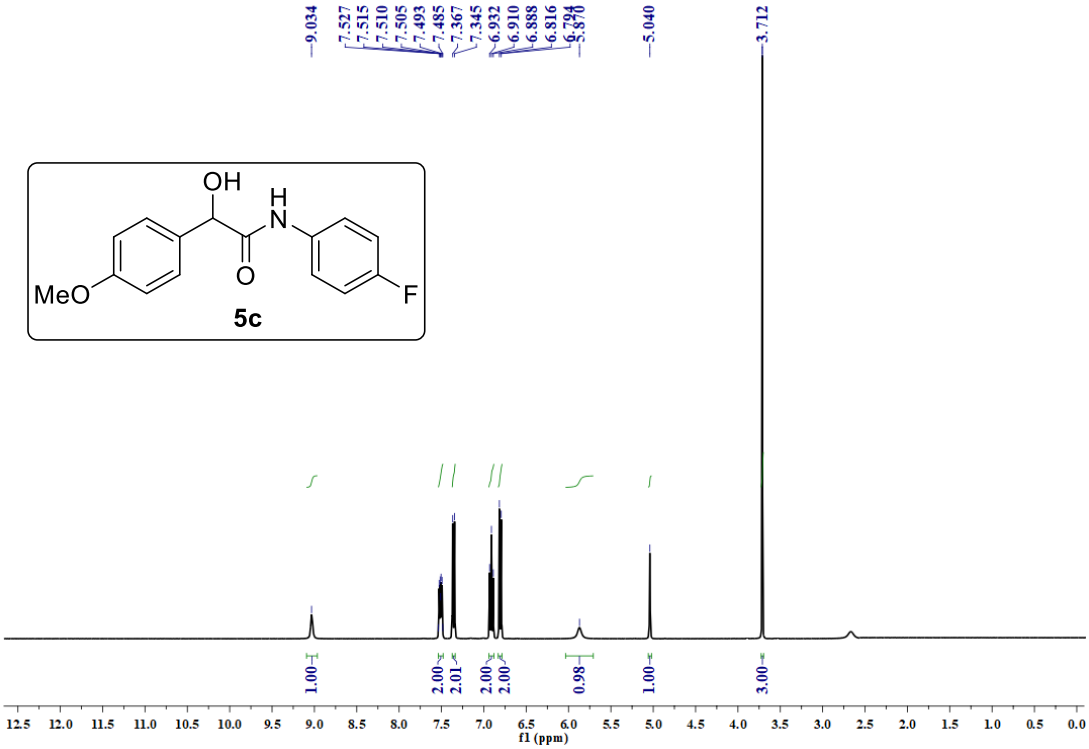
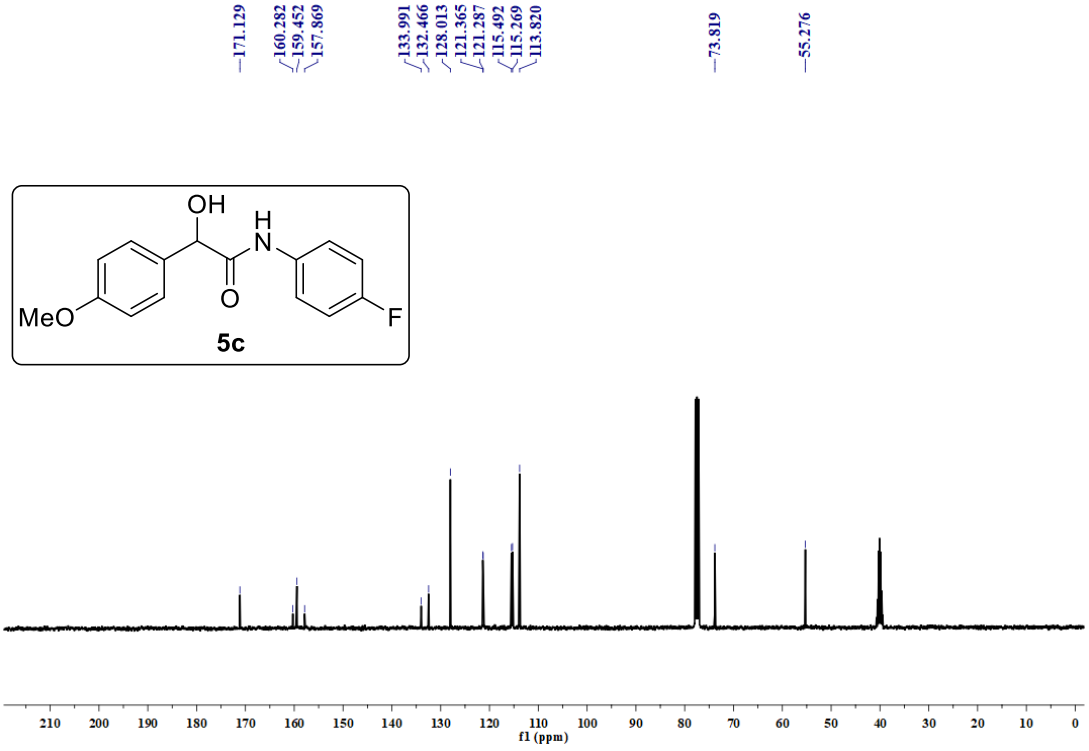


^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) spectrum of *N*-(4-fluorophenyl)-2-hydroxy-2-(4-methoxyphenyl)acetamide (5c)



^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$+DMSO-d_6) spectrum of *N*-(4-fluorophenyl)-2-hydroxy-2-(4-methoxyphenyl)acetamide (5c)



HRMS of *N*-(4-fluorophenyl)-2-hydroxy-2-(4-methoxyphenyl)acetamide (5c)

Sample Name	KAR 10	**Position**	P1-B8	**Instrument Name**	Instrument 1
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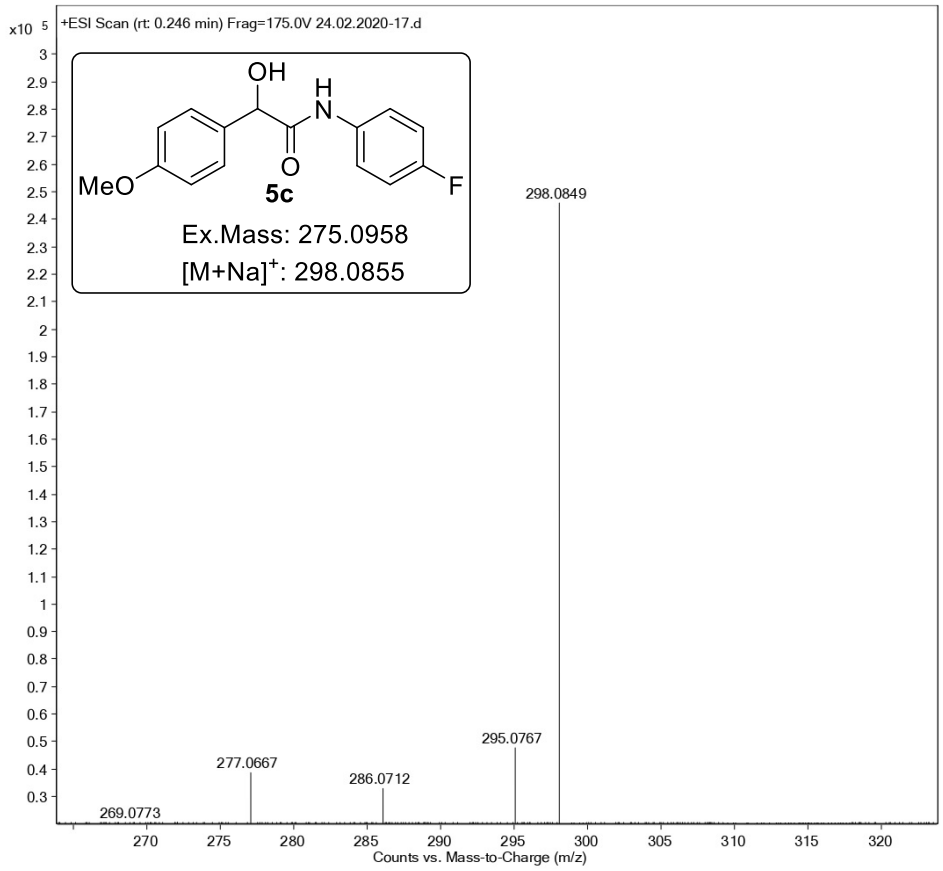
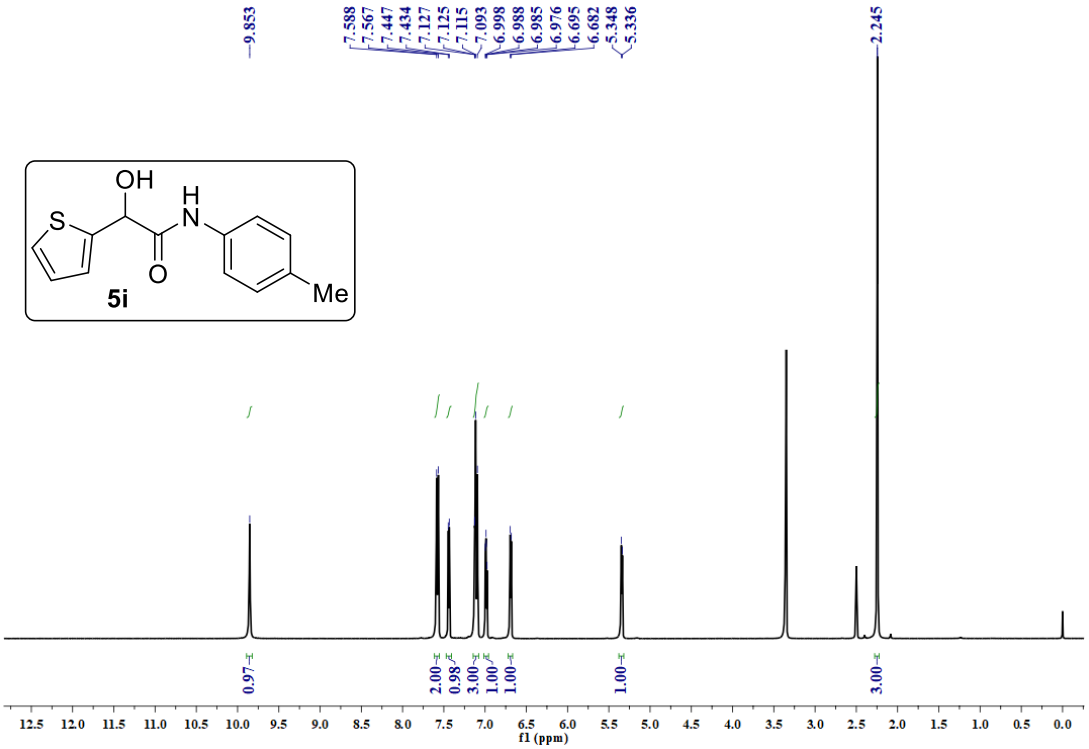
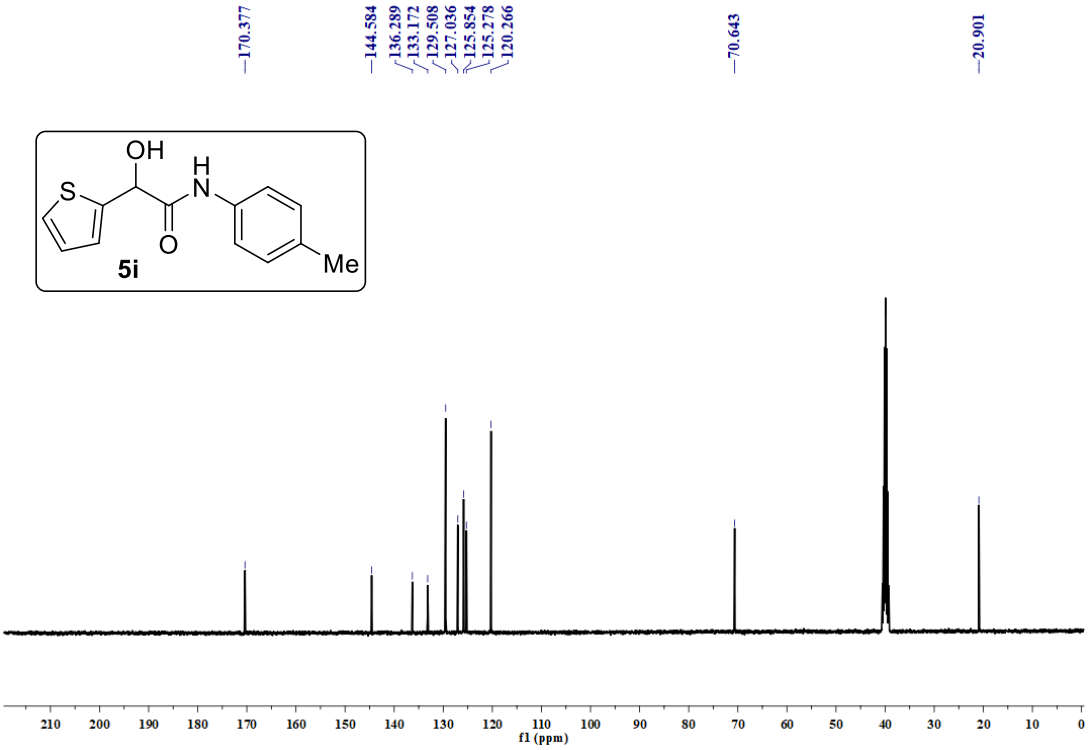


^{1}H NMR (400 MHz, DMSO-d_6) spectrum of 2-hydroxy-2-(thiophen-2-yl)-*N*-(*p*-tolyl)acetamide (5i)



^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) spectrum of 2-hydroxy-2-(thiophen-2-yl)-*N*-(*p*-tolyl)acetamide (5i)



HRMS of 2-hydroxy-2-(thiophen-2-yl)-*N*-(*p*-tolyl)acetamide (5i)

Sample Name	KAR-50	**Position**	P1-A1	**Instrument Name**	Instrument 1
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Sample Type	Sample	**IRM Calibration Status**	Success	**Data Filename**	3.03.2020.d
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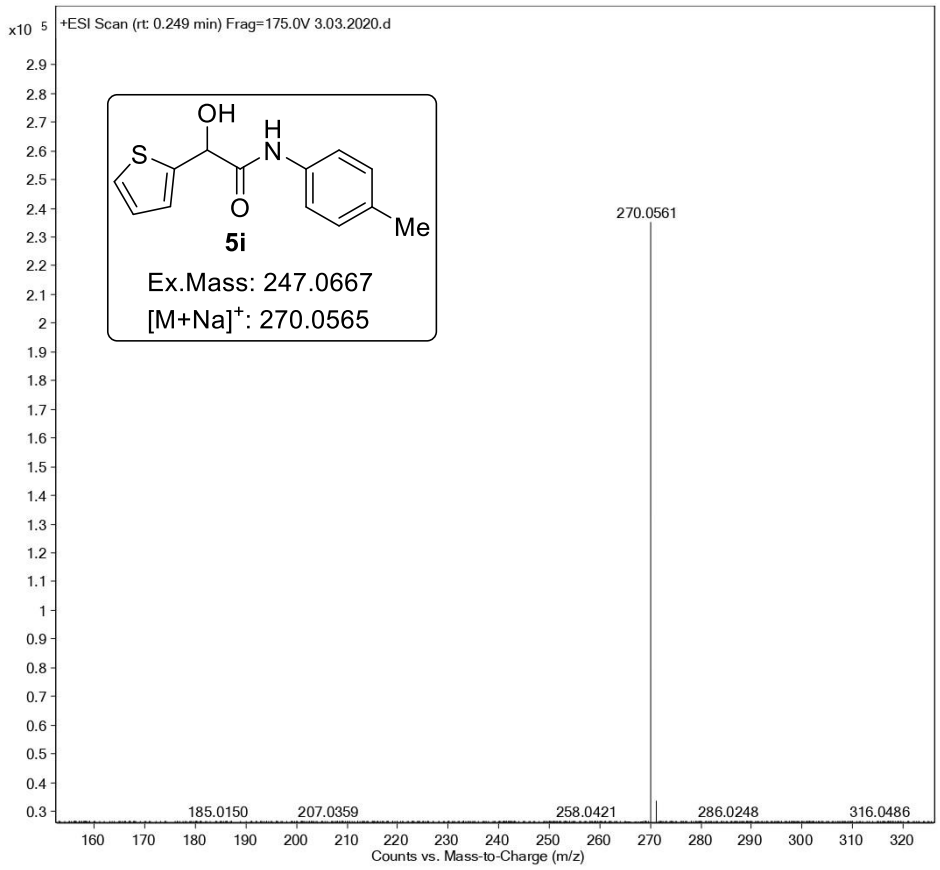
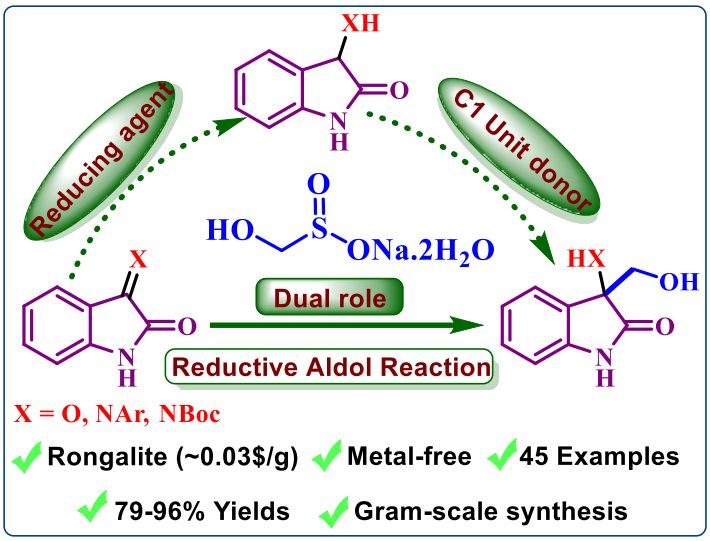


CHAPTER-III

Rongalite-Promoted Transition Metal and Hydride-Free Reductive Aldol Reaction: A Direct Access to 3,3´- Disubstituted Oxindoles



3.1. Introduction

Oxindole is a privileged structural motif in many natural products and bioactive compounds.[1] Among these, 3,3´-disubstituted oxindoles have attracted the chemists due to wide spectrum of biological activities.[2-5] In the realm of oxindoles, the skeleton with a hydroxy and amine-bearing quaternary centre at C3 position (3-hydroxy-2-oxindole and 3-amino-2-oxindole) has significantly intersected the biological space through its three-dimensional spatial arrangement.

Notably, these are the core structures of many pharmaceuticals such as i) convolutamydines A-B,[6] which are isolated from the Floridian bryozoan *Amathia convoluta*, used in the differention of HL-60 cells, ii) TMC-95A-B,[7] isolated from the fermentation broth of *Apiospora montagnei* Sacc. TC 1093, acts as novel 20S proteasome inhibitors and notably, TMC-95A is more effective compared to TMC-95B, iii) YK-4-279,[8] inhibits growth of Ewing's sarcoma, iv) SM-130686,[9] act as growth hormone secretagogues, v) NITD-609,[10] a synthetic antimalarial drug, developed at the Novartis institute for tropical diseases, and vi) AG-041R,[11] a stimulator of chondrogenesis and could be a therapeutic agent for cartilage disorders (Figure 3.1). Cancer is the second major

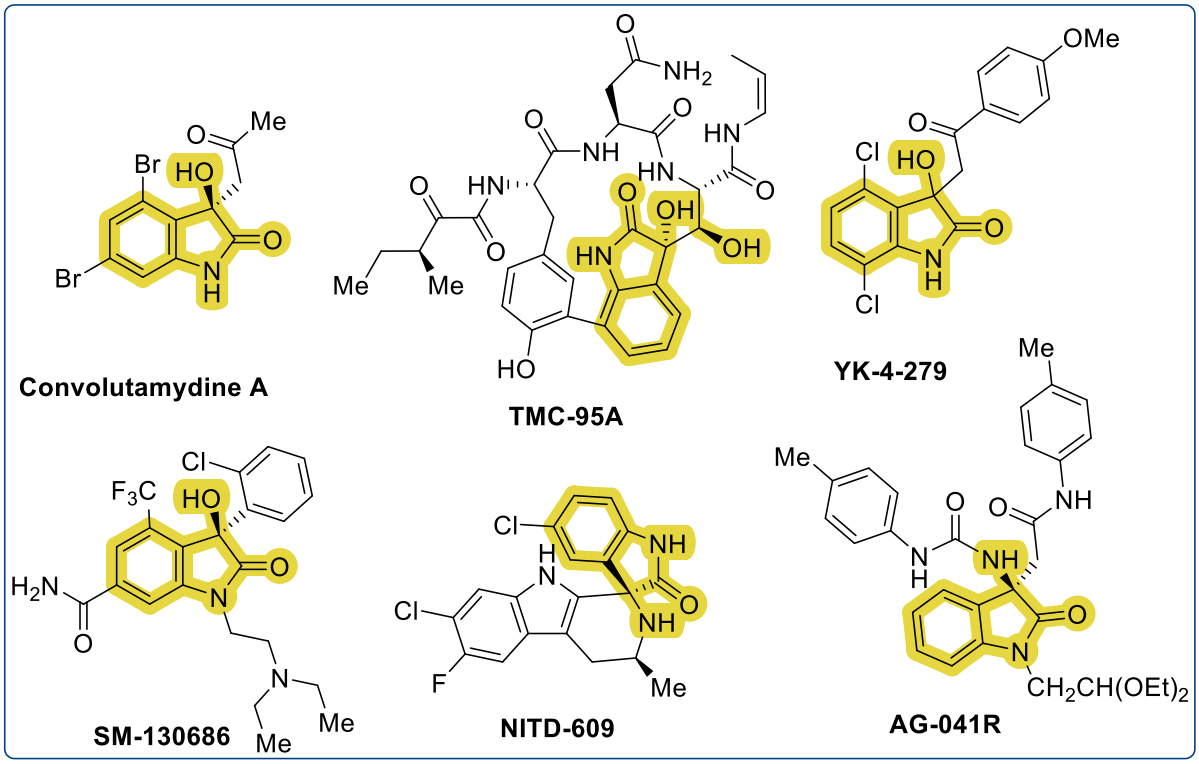
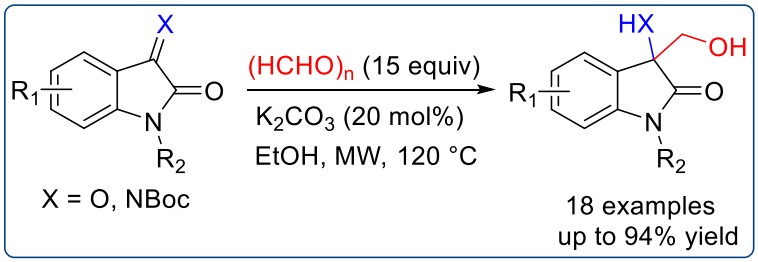


Figure 3.1. Natural and synthetic bioactive 3-hydroxy and 3-amino substituted 2-oxindoles

cause of mortality in the universe, even though superior treatments are available.[12] Recently, 3-amino-3-hydroxymethyloxindoles reported as anti-cancer agents *via in vitro* screening, and exhibits anti-proliferating effect against HCT-116, SJSA-1 and Jurkat cancer cell lines.[13] The biological importance of 3-hydroxy and 3-amino-2-oxindoles provides impetus to the development of new methodologies.[14-16] Limited methods are only available for synthesis of 3-hydroxy-3-hydroxymethyloxindoles and 3-amino-3-hydroxymethyloxindoles despite of their biological activity.

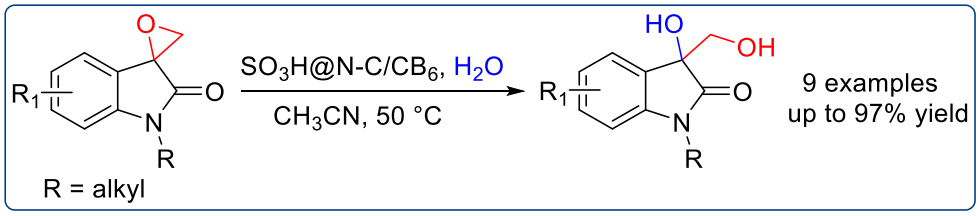
3.1.1. Previous reports for the synthesis of 3-hydroxy-3-hydroxymethyloxindoles and 3-amino-3-hydroxymethyloxindoles

Zhang and co-workers developed a protocol for the synthesis of 3-hydroxy-3-hydroxymethyloxindoles and 3-amino-3-hydroxymethyloxindoles using isatins and isatin-derived ketimines in the presence of K_2CO_3 by employing 15 equivalents of paraformaldehyde, (which acts as a reducing agent as well as a C1 unit donor) under microwave assisted heating at 120 °C (Scheme 3.1).[17]



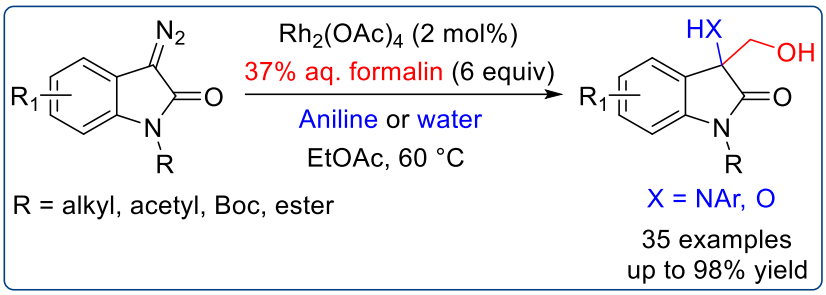
Scheme 3.1

Subramanian and co-workers reported a nitrogen rich and sulfonic acid functionalized heterogeneous carbon catalyst (SO_3H@N–C/CB_6) for the selective ring opening hydrolysis of spiro-epoxyoxindoles to achieve the 3-hydroxy-3-hydroxymethyloxindoles using water in acetonitrile (CH_3CN) at 50 °C for 24 h. This heterogeneous catalyst is thermally stable, recyclable, and no leaching was observed even after four cycles (Scheme 3.2).[18]



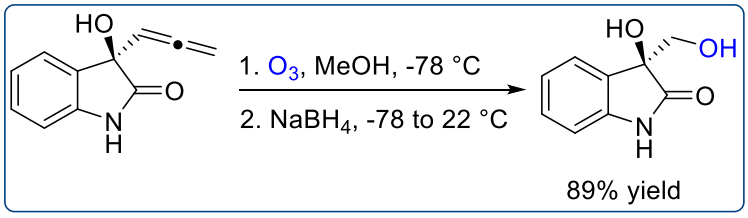
Scheme 3.2

Wang et al. described a Rh(II) catalyzed three-component protocol for the synthesis of 3-hydroxy-3-hydroxymethyloxindoles and 3-amino-3-hydroxymethyloxindoles from 3-diazooxindoles, aq. formalin and water or anilines in ethyl acetate solvent at 60 °C. Also, tested these products for anticancer activity *via in vitro* cytotoxicity screening (Scheme 3.3).[19]



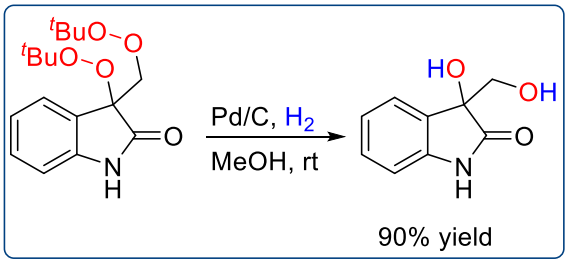
Scheme 3.3

Hoveyda and co-workers developed a two-step protocol for the enantioselective synthesis of 3-hydroxy-3-hydroxymethyloxindoles. In the first step, the oxidation of allene by ozone at -78 °C forms the corresponding aldehyde and in the second step, the formed aldehyde undergoes reduction with $NaBH_4$ to furnish the 3-hydroxy-3-hydroxymethyloxindoles (Scheme 3.4).[20]



Scheme 3.4

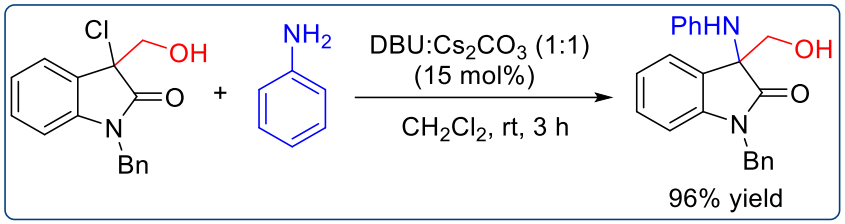
Pan and co-workers developed a protocol for the synthesis of diperoxyoxindoles. Later, they prepared the biologically active dihydroxyoxindole by hydrogenation using Pd/C and H_2 in methanol solvent at room temperature for 10 h (Scheme 3.5).[21]



Scheme 3.5

Kureshy and co-workers developed a regioselective hydrochlorination protocol for the synthesis of 3-chloro-3-hydroxymethyloxindoles. Later, they extended this protocol for the

synthesis of 3-amino-3-hydroxymethyloxindoles by employing aniline, and a mixture of DBU and Cs_2CO_3 in CH_2Cl_2 at ambient temperature for 3 h (Scheme 3.6).[22]

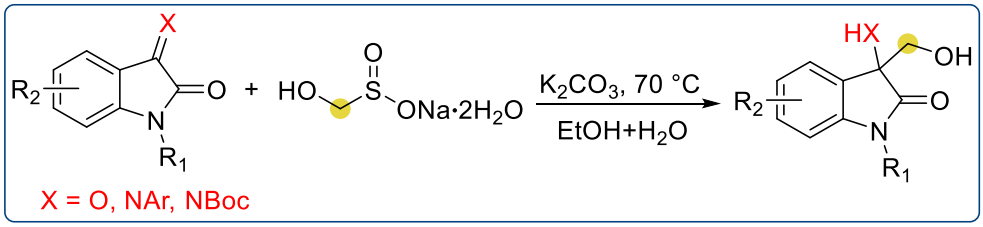


Scheme 3.6

The most common synthetic routes to 3-hydroxy(amino)-3-hydroxymethyloxindoles are (i) the C3-fuctionalization of activated oxindoles, includes the catalyst-induced ring opening of spiro-epoxyoxindoles and the $Rh_2(OAc)_4$-catalyzed MCR reaction on 3-diazooxindoles, but these approaches suffer from the use of expensive catalysts, and (ii) the direct functionalization at C3-position of isatins using paraformaldehyde as C1 source under microwave irradiation at 120 °C, but this protocol employing 15 equiv of paraformaldehyde, which found to be a potential carcinogenic agent and has limited substrate scope. To overcome all the limitations of existed methods, we planned to develop an environmentally benign method to produce 3-hydroxy-3-hydroxymethyloxindoles and 3-amino-3-hydroxymethyloxindoles using rongalite.

3.2. Present study

Based on the significance of the pharmacological properties of 3-hydroxy(amino)-3-hydroxymethyloxindoles and to overcome the obstacles for their preparation, we have developed a transition metal and hydride-free reductive aldol reaction from isatin-derivatives using rongalite, which is an inexpensive reagent. Here, rongalite plays the dual role of hydride-free



Scheme 3.7. Synthesis of 3-hydroxy(amino)-3-hydroxymethyloxindoles

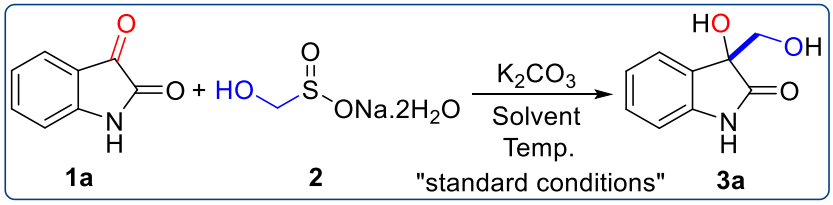
reducing agent and C1 unit donor. This method is about one-pot reduction followed by aldol reaction and offers the synthesis of wide range of 3-hydroxy-3-hydroxymethyloxindoles and

3-amino-3-hydroxymethyloxindoles in 79-96% yields. This methodology is also applicable to gram-scale synthesis (Scheme 3.7).

3.2.1. Results and discussion

In our initial studies, isatin **1a** was reacted with rongalite **2** in the presence of K_2CO_3 to obtain 3-hydroxy-3-(hydroxymethyl)indolin-2-one **3a** and only the key facts are reported (Table 3.1).

Table 3.1. Optimization of the reaction conditions[a]



Entry	Solvent (8:2 v/v)	Variation from the standard conditions (equiv) i.e., rongalite (2) & K_2CO_3 (2)	Temp (°C)	Time (h)	Yield (%)[b]
1	CH_3CN+H_2O	None	rt	15	10
2	CH_3CN+H_2O	None	70	0.5	70
3	H_2O+*β*-CD	None	70	1	50
4	Acetone+H_2O	None	50	1	35
5	THF+H_2O	None	70	1	40
6	DMF+H_2O	None	70	0.5	70
7	DMSO+H_2O	None	70	0.3	75
8	MeOH+H_2O	None	60	0.5	75
9	**EtOH+H_2O**	**None**	**70**	**0.3**	**92**
10	*i*-PrOH+H_2O	None	70	0.5	70
11	EtOH+H_2O	Na_2CO_3 instead of K_2CO_3	70	0.5	78
12	EtOH+H_2O	KOH instead of K_2CO_3	70	0.5	65
13	EtOH+H_2O	NaOH instead of K_2CO_3	70	0.5	68
14	EtOH+H_2O	DBU instead of K_2CO_3	70	0.5	70
15	EtOH+H_2O	NEt_3 instead of K_2CO_3	70	0.5	66
16	EtOH+H_2O	None	60	1	85
17	EtOH+H_2O	rongalite (1.5) instead of (2)	70	2	50
18	EtOH+H_2O	K_2CO_3 (1.5) instead of (2)	70	1	75
19	EtOH+H_2O	paraformaldehyde (3) instead of rongalite	70	5	n.d.
20	EtOH+H_2O	formalin (5) instead of rongalite	70	5	n.d.

[a]Reaction conditions: isatin **1a** (1 mmol), reagent and base in different solvent mixtures at different temperatures. [b]Yield of the isolated product. rt = room temperature. n.d. = not detected.

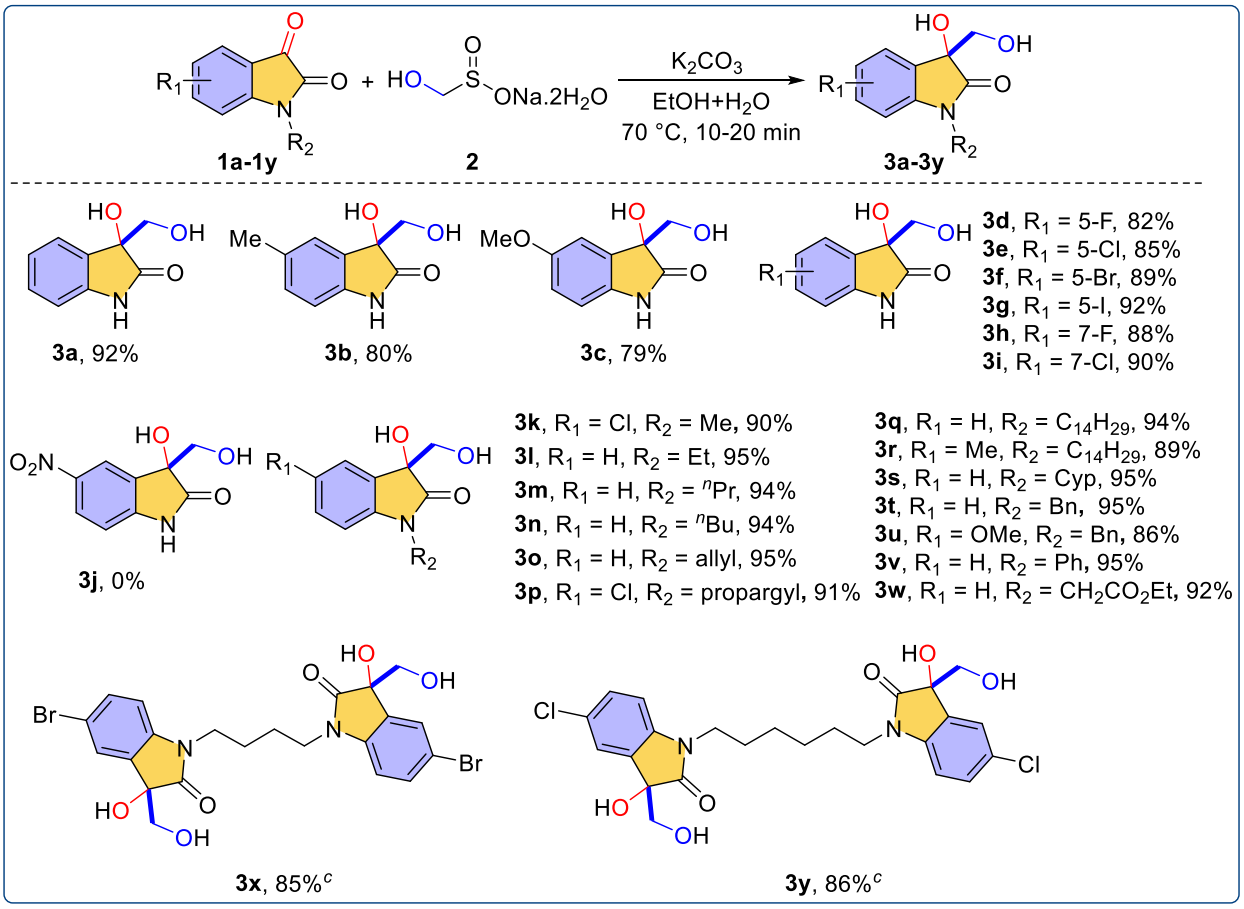
The reaction of isatin **1a** (1 mmol) with rongalite **2** (2 mmol) and K_2CO_3 (2 mmol) in CH_3CN+H_2O at ambient temperature resulted in the formation of **3a** in 10% yield (Table 3.1, entry 1). The structure of **3a** was identified using ^{1}H, ^{13}C NMR and HRMS spectral data. To our delight, the yield of **3a** was dramatically improved to 70% when the temperature was increased to 70 °C (Table 3.1, entry 2). Inspired by these preliminary results, further screenings were carried out with different solvent systems and bases to improve the product yield. Reactions were conducted in polar aprotic solvents, i.e., acetone, THF, DMF, and DMSO, and the product **3a** was obtained in 35-75% yields (Table 3.1, entries 4-7). Among the tested polar protic solvents, ethanol was found to be superior and gave the target compound in 92% yield (Table 3.1, entries 8-10). Then, we screened the reaction using different organic and inorganic bases and obtained inferior results (Table 3.1, entries 11-15). Additionally, change in the loadings of rongalite, base and temperature did not improve the yields of the product (Table 3.1, entries 16-18). Surprisingly, formaldehyde sources such as formalin and paraformaldehyde did not form the desired product (Table 3.1, entries 19 and 20). Thus, the optimal reaction conditions are: isatin **1a** (1.0 mmol), rongalite **2** (2.0 mmol) and K_2CO_3 (2.0 mmol) in 2 mL of $EtOH+H_2O$ (8:2 v/v) at 70 °C for 20 min (Table 3.1, entry 9).

With the optimized reaction conditions in hand, we turned our attention to evaluate the scope and limitations of the reaction with various isatin substrates (Table 3.2). The electron-donating groups on the benzene ring such as methyl and methoxy isatins underwent the reaction smoothly with rongalite to furnish **3b** and **3c** in 80% and 79% yields, respectively (Table 3.2). Also, this method tolerated various isatin halogen derivatives (–F, –Cl, –Br, and –I) and afforded dihydroxylated products **3d-3i** in 82-92% yields (Table 3.2). 5-Nitroisatin **1j** did not offer the dihydroxylated product even at high temperatures for long durations. We observed that *N*-substituted isatins are superior to *N*-unsubstituted isatins in terms of product yields and reaction time. *N*-alkyl, *N*-allyl, *N*-propargyl, *N*-benzyl and *N*-arylated isatins readily reacted with rongalite to form vicinal diols in 86-95% yields (Table 3.2, **3k-3v**). Interestingly, rongalite is more chemoselectively added to the carbonyl group of isatin when compared to the carbonyl group of the ester to give 3-hydroxy-3-(hydroxymethyl)indolin-2-one in 92% yield (Table 3.2, **3w**). The dimers of isatins linked by the alkyl chain (1,4- and 1,6-) through nitrogen atoms are

also efficiently involved in the reaction to produce the corresponding products **3x** and **3y** in 85% and 86% yields, respectively (Table 3.2).

To demonstrate the generality of this methodology, we also explored the substrate scope of isatin Schiff bases so as to obtain the desired products, i.e. 3-(hydroxymethyl)-3-(phenylamino)indolin-2-ones, which show potential anti-cancer activity.[13] The isatin Schiff bases were prepared from isatins and anilines by the reported method.[23] We tested the scope of the optimized conditions and the results were presented in Table 3.3.

Table 3.2. Scope of isatins[a,b]

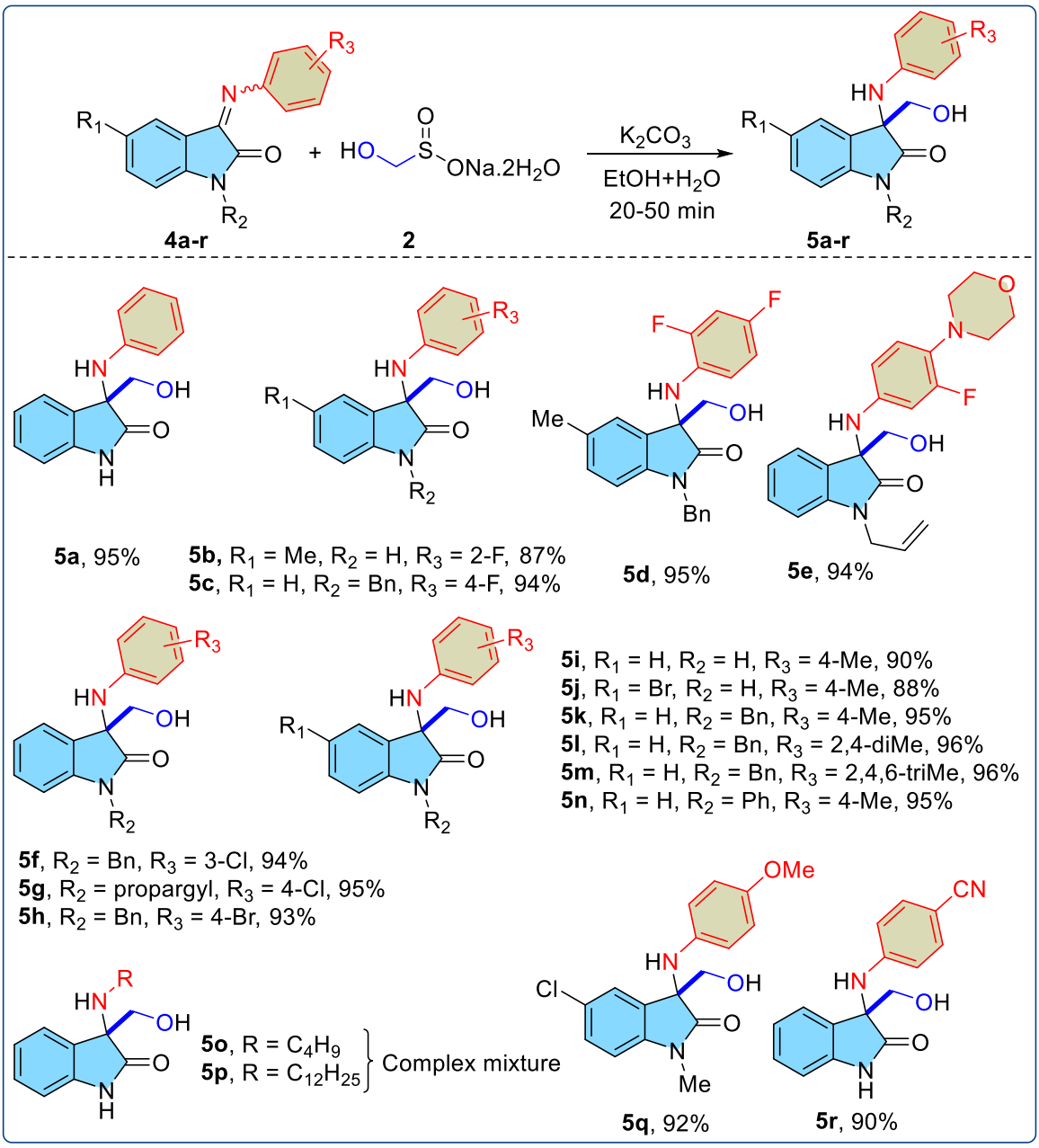


[a]Reaction conditions: isatin **1** (1 mmol), rongalite **2** (2 mmol) and K_2CO_3 (2 mmol) in 2 mL of EtOH+H_2O at 70 °C. [b]Yield of the isolated product. [c]4 equiv of rongalite and K_2CO_3 were used.

All the synthesized isatin Schiff bases **4a-4r** readily reacted with rongalite to form the corresponding 3-(hydroxymethyl)-3-(phenylamino)indolin-2-ones **5a-5r** in good to excellent yields within 50 min. During the course of the study, we observed that isatins are more reactive with rongalite than with isatin Schiff bases. Notably, isatin Schiff bases containing both electron-

donating groups (–Me and –OMe) and electron-withdrawing group (–CN) on the aniline moiety did not affect the product yields (Table 3.3, **5i-5m**, **5q** and **5r**). The *N*-phenyl isatin Schiff base also afforded the corresponding oxindole **5n** in 95% yield (Table 3.3).

Table 3.3. Scope of isatin Schiff bases[a,b]

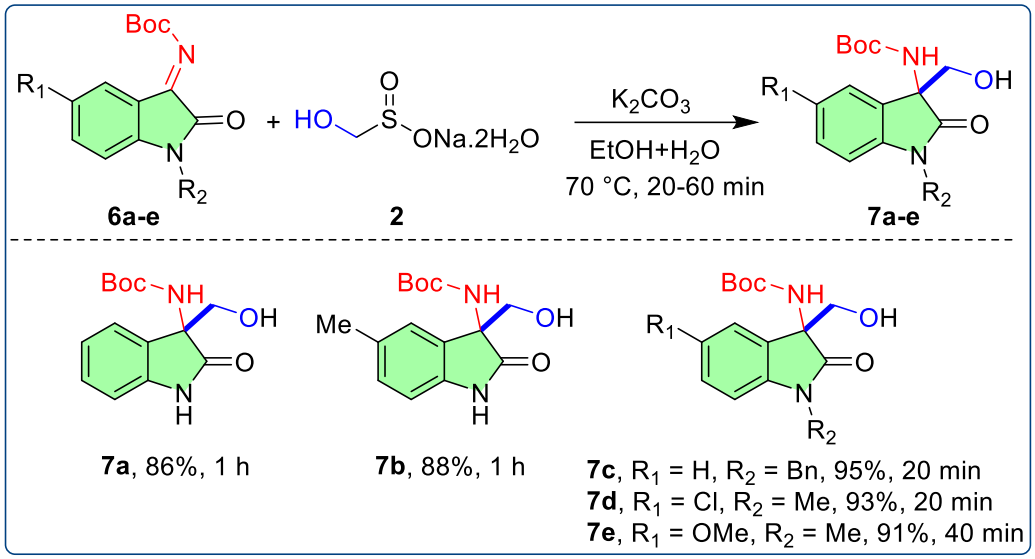


[a]Reaction conditions: isatin Schiff base **4** (1 mmol), rongalite **2** (2 mmol) and K_2CO_3 (2 mmol) in 2 mL of EtOH+H_2O at 70 °C. [b] Yield of isolated product.

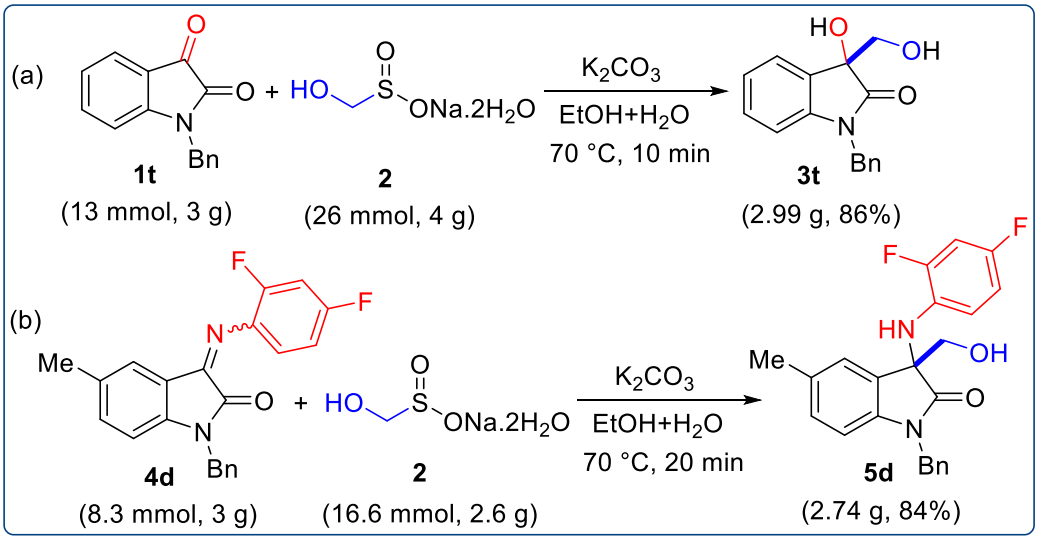
Next, we extended our methodology to isatin-derived ketimines and the results are shown in Table 3.4. To our delight, unprotected isatin-derived ketimines reacted smoothly under the

optimized conditions to furnish *tert*-butyl (3-(hydroxymethyl)-2-oxoindolin-3-yl)carbamates **7a** and **7b** in 86% and 88% yields, respectively, which is not possible with other reported methods (Table 3.4).[17] Similarly, the *N*-protected substrates, i.e., *N*-benzyl and *N*-methyl isatin-derived ketimines, readily participated in the reaction under the optimized reaction conditions to form the corresponding products **7c**-**7e** in 91-95% yields (Table 3.4).

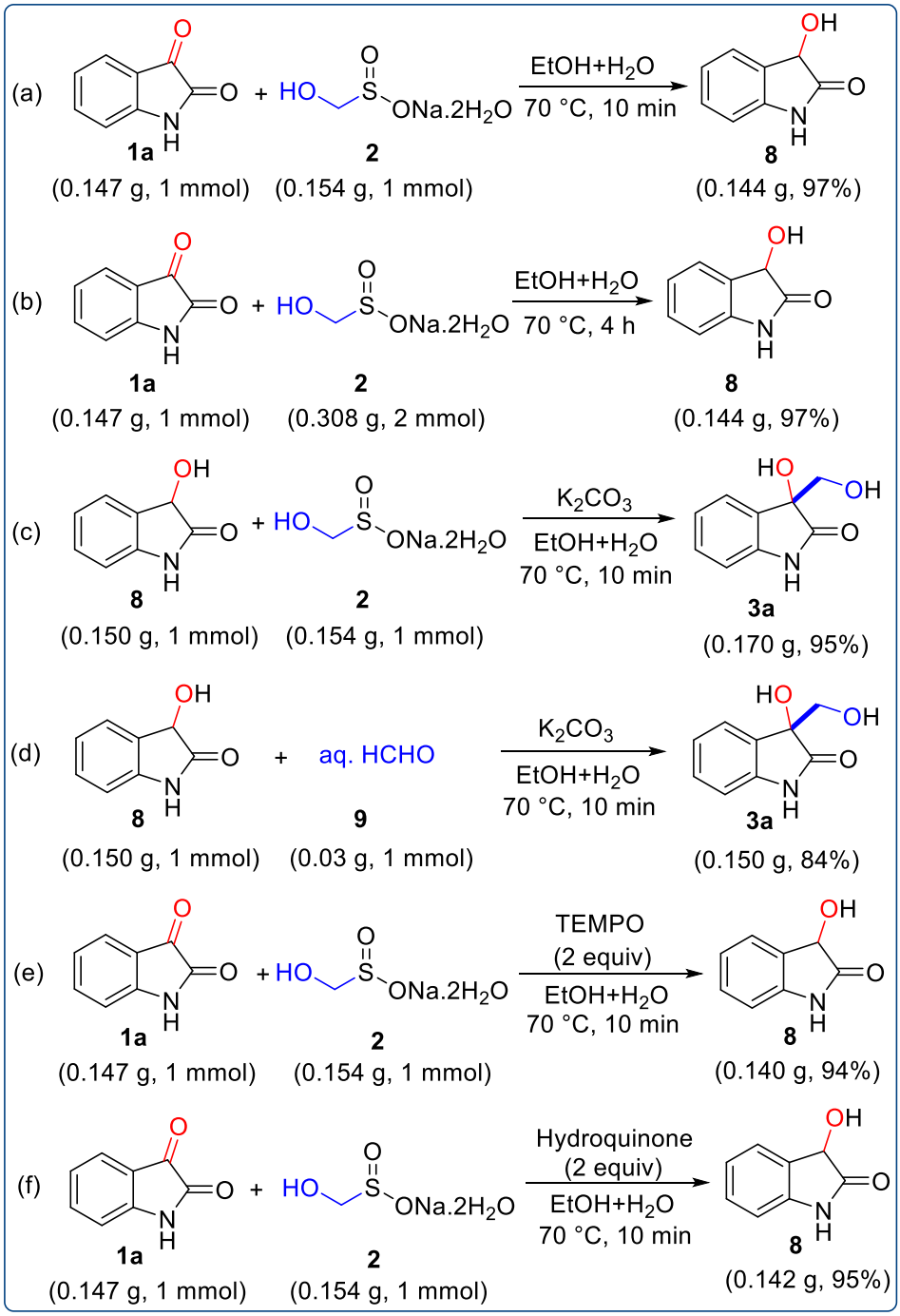
Table 3.4. Scope of isatin-derived ketimines[a b]



[a]Reaction conditions: isatin-derived ketimines **6** (1 mmol), rongalite **2** (2 mmol) and K_2CO_3 (2 mmol) in 2 mL of EtOH+H_2O at 70 °C. [b]Yield of isolated product.



Scheme 3.8. Gram-scale reactions: a) on isatins b) isatin Schiff bases.



Scheme 3.9. Control experiments

Finally, we evaluated the synthetic potential of our method on a gram scale reaction using 1-benzylindoline-2,3-dione **1t** (3 g, 13 mmol), rongalite **2** (4 g, 26 mmol) and K_2CO_3 (3.6 g, 26 mmol) in EtOH+H_2O (20 mL) at 70 °C, which gave 1-benzyl-3-hydroxy-3-(hydroxymethyl)indolin-2-one **3t** in 88% yield within 10 min (Scheme 3.8a). We also

synthesized the biologically active compound **5d** with IC_{50} = 3.14 mM against the SJSA-1 cell line on a gram scale in 84% yield (Scheme 3.8b).

In order to unveil the reaction mechanism, we carried out several control experiments to determine the role of rongalite and the base (Scheme 3.9). A reaction between isatin **1a** (1.0 mmol) and rongalite **2** (1.0 mmol) in EtOH+H_2O at 70 °C in the absence of a base resulted in the formation of 3-hydroxyindolin-2-one **8** with 97% yield within 10 min (Scheme 3.9a). This intermediate is stable even after increasing the quantity of rongalite and the reaction time (Scheme 3.9b) and was isolated and characterized by ^1H and ^{13}C NMR. Later, the intermediate product 3-hydroxyindolin-2-one **8** was treated again with rongalite **2** (1.0 mmol) in the presence of K_2CO_3 at 70 °C and the product **3a** was obtained within 10 min with 95% yield (Scheme 3.9c). Furthermore, 3-hydroxyindolin-2-one **8** was treated with aq. formaldehyde **9** instead of rongalite in the presence of K_2CO_3 at 70 °C and the formation of product **3a** was observed in 84% yield (Scheme 3.9d), which revealed that rongalite plays a dual role as a reducing agent and an *in situ* formaldehyde source.

Finally, we have conducted a few more control experiments with radical scavengers such as TEMPO and hydroquinone to determine the reaction pathway and found no impact on the reaction outcome. These results eliminate the possibility of the radical pathway (Schemes 3.9e and 3.9f). Notably, reductive dimerization of isatins was observed during the photoredox-catalysis *via* the radical mechanism, but we did not observe any reductive dimerization products.[24] These results revealed that initially, rongalite converts isatin to 3-hydroxy oxindole **8** *via* hydride-free reduction, which further reacts with another mole of rongalite to obtain aldol product **3a** with the help of K_2CO_3.

Furthermore, to gain more insights into the mechanism of the reductive aldol reaction, we performed some ^1H NMR experiments. Isatin **1a** (50 mg, 0.35 mmol) was treated with rongalite **2** (2 equiv) in 1 mL of DMSO-d_6 at 70 °C and after 5 min, K_2CO_3 (2 equiv) was added. A 10 µL aliquot of the reaction mixture was transferred to an NMR tube and diluted with DMSO-d_6 (0.5 mL) and the ^1H NMR spectrum was recorded. The ^1H NMR spectra of all the aliquots are shown in Figure 3.2. Characterization data of the identified compounds are as follows. When the reaction mixture was analyzed at 5 min, peaks at δ 10.23, 6.17 and 4.83 ppm were observed, which correspond to the intermediate, i.e., 3-hydroxyindolin-2-one **8**. The ^1H NMR spectrum of

the aliquot (10 min) showed peaks at δ 10.14 ppm representing the NH proton, 5.87 ppm representing the OH proton (C3, quaternary carbon) and 3.62 ppm representing the CH_2 protons of the final product, i.e., 3-hydroxy-3-(hydroxymethyl)indolin-2-one **3a**. Notably, decrease in the intensity of the peak at δ 10.23 ppm and an increase in the intensity of the peak at δ 10.14 were observed during the course of the reaction. Finally, the peak at 10.23 ppm disappeared after 20 min. Similarly, the intensity of the peak at δ 6.17 ppm initially increased (5-10 min) and later decreased (from 10-20 min). Also, the intensity of the peak at δ 3.62 ppm increased between 5-20 min. Continuous monitoring of this reaction by ^{1}H NMR showed that the reaction was

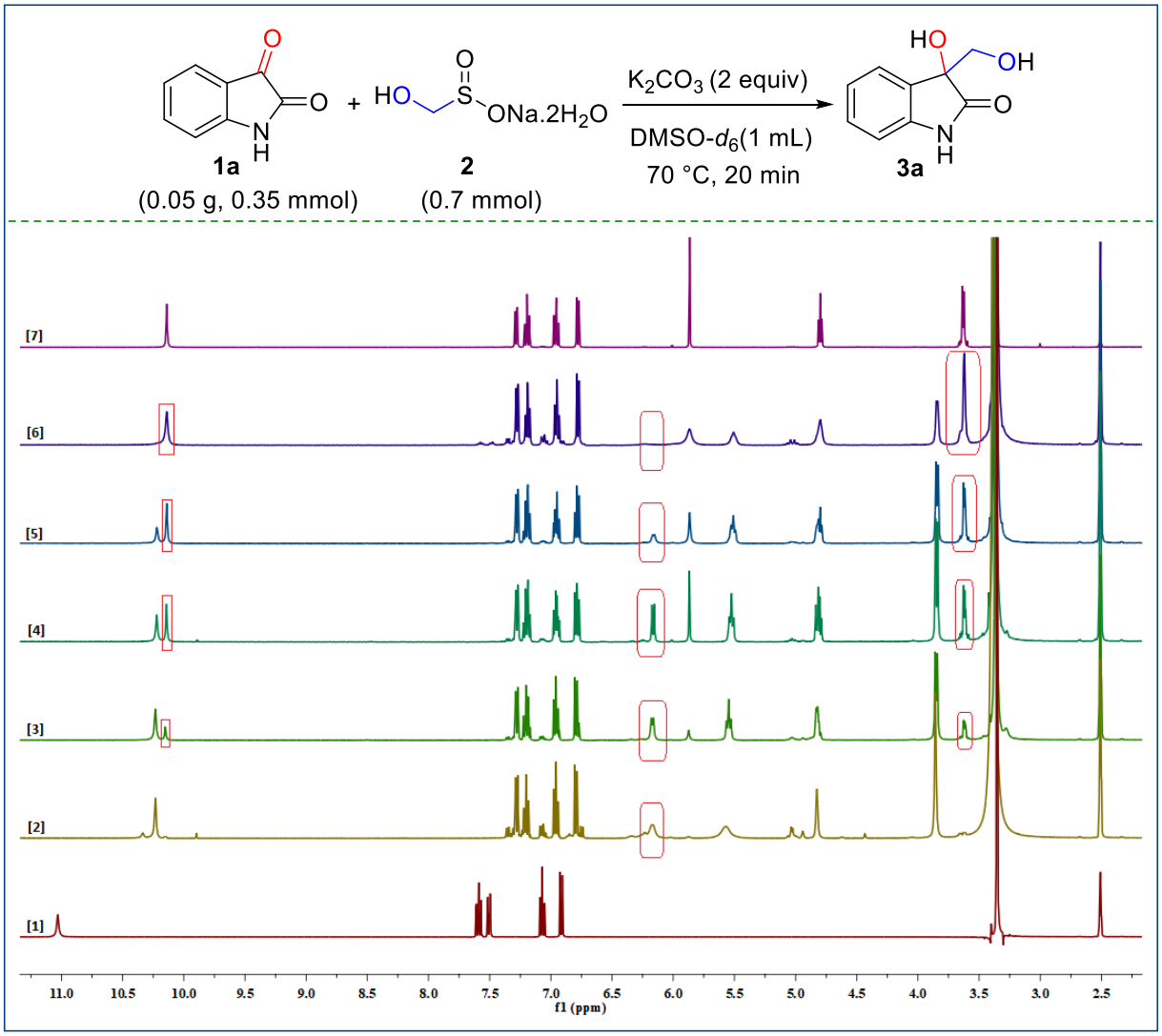


Figure 3.2. 400 MHz ^{1}H NMR spectra of aliquots taken at noted times. All spectra were recorded by diluting an aliquot of the reaction mixture in DMSO-d_6. Panel 1. Isatin; panel 2. Isatin and rongalite; panel 3. 5 min after addition of K_2CO_3; panel 4. after 10 min; panel 5. after 15 min; panel 6. after 20 min; panel 7. purified compound **3a**.

completed and finally no trace amounts of isatin detected after 20 min. Also, we have conducted similar ^{1}H NMR experiment on isatin Schiff base to check whether isatin Schiff bases follow the same pathway like isatins or not. Isatin Schiff base **4j** (50 mg, 0.15 mmol) was treated with rongalite **2** (2 equiv) and K_2CO_3 (2 equiv) in 1 mL of DMSO-d_6 at 70 °C. A 10 µL aliquot of the reaction mixture was transferred to a NMR tube, diluted with DMSO-d_6 (0.5 mL), and recorded ^{1}H NMR spectra at noted times. The ^{1}H NMR spectra are shown in Figure 3.3.

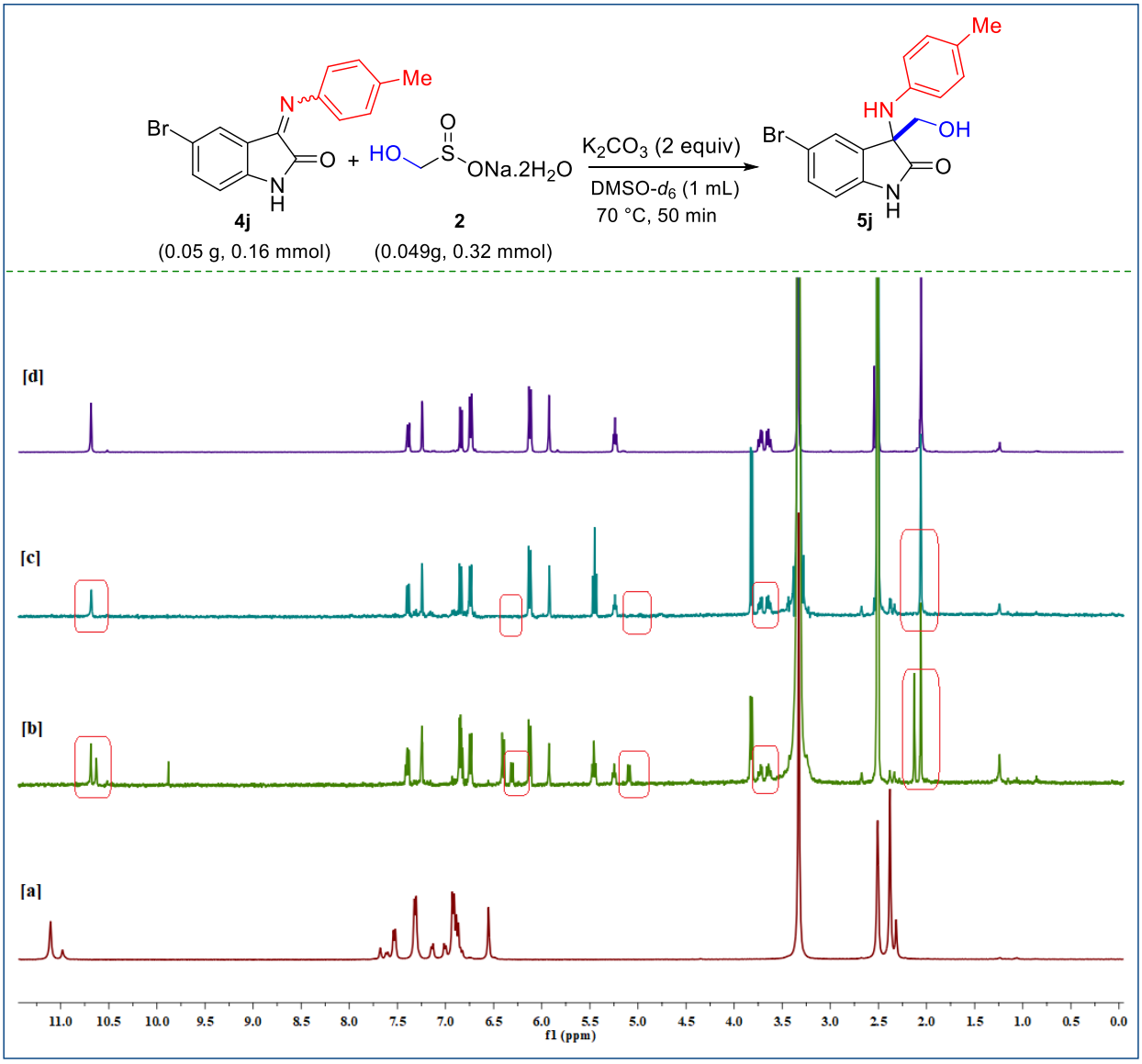
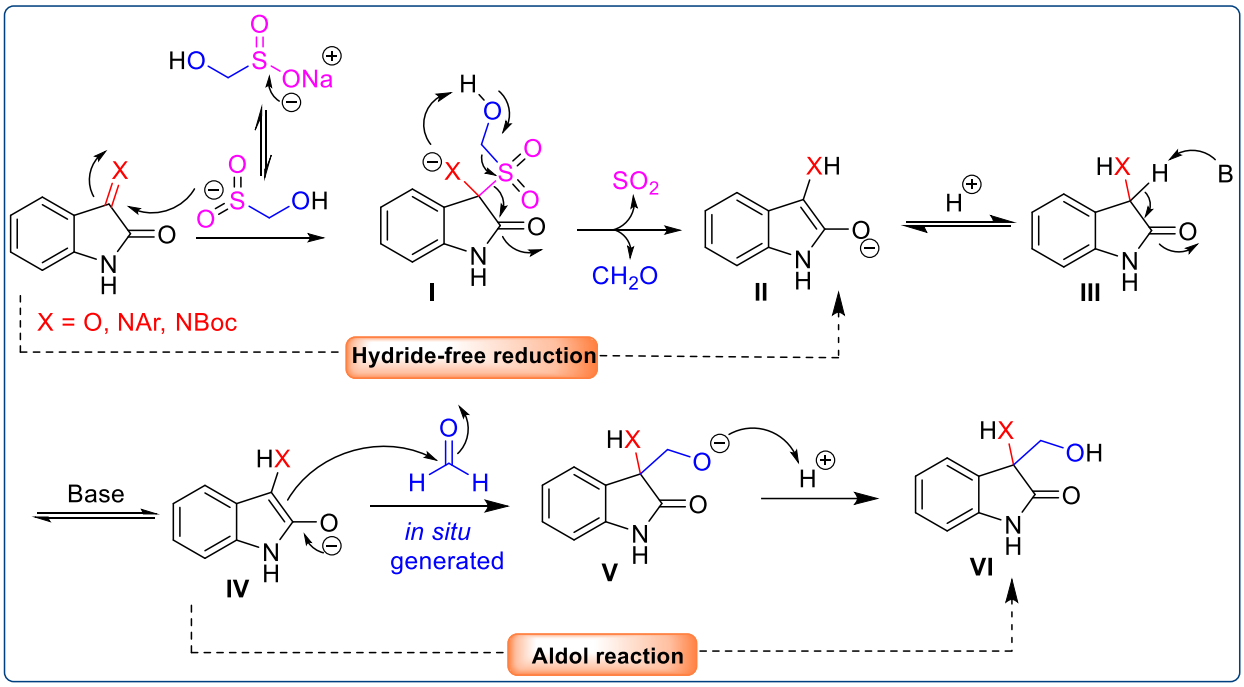


Figure 3.3. 400 MHz ^{1}H NMR spectra of aliquots taken at noted times. All spectra were recorded by diluting an aliquot of the reaction mixture in DMSO-d_6. Panel a: isatin Schiff base **4j**; panel b: isatin Schiff base, rongalite and K_2CO_3, after 25 min; panel c: after 50 min; panel d: purified compound **5j**.

Characterization data of the identified compounds are as follows. When the reaction mixture was recorded at 25 min, peaks at δ 10.63, 6.31, 5.10 and 2.13 ppm were observed, which are correspond to the intermediate i.e., 5-bromo-3-(*p*-tolylamino)indolin-2-one. The peaks at δ 10.63 ppm represents the NH proton of oxindole moiety, δ 6.31 ppm represents the NH proton of aniline, δ 5.10 ppm represents the CH proton and δ 2.13 ppm represents the CH_3 protons of aniline. Notably, at 25 min observed the formation of final product also i.e., 5-bromo-3-(hydroxymethyl)-3-(*p*-tolylamino)indolin-2-one and the corresponding peaks are observed at δ 10.68 ppm (NH proton of oxindoles), δ 5.92 ppm (NH proton of aniline), δ 5.24 ppm (OH proton) and δ 2.06 ppm (CH_3 protons). From ^{1}H NMR spectrum at 25 min, it is clear that no Schiff base is remained and mixture of intermediate and product was observed. When reaction mixture was recorded at 50 min, the peaks correspond to intermediate are completely diminished and observed only the peaks respective to final product which was compared with ^{1}H NMR spectrum of purified product **5j**.



Scheme 3.10. Plausible reaction mechanism

Based on the existing literature,[25] control experiments and collective mechanistic insights from the ^{1}H NMR studies, a full mechanistic proposal is presented in Scheme 3.10. Initially, rongalite chemoselectively reacts on the carbonyl group of isatin in a nucleophilic addition manner to form intermediate sulfone (**I**), which then liberates formaldehyde and sulfur dioxide to form the

intermediate (**II**). Later, proton abstraction from water gives the intermediate (**III**), which was identified during the reaction progress on TLC, isolated and characterized by ^{1}H and ^{13}C NMR. Furthermore, the base abstracts the proton from the intermediate (**III**) to form an enolate which further undergoes the aldol reaction with the *in situ* generated formaldehyde to form the intermediate (**V**) with subsequent abstraction of the proton from water to form the final product (**VI**).

3.2.2. Deuterium labelling studies

To gain more insights into the reduction step, deuterium labelling experiment was conducted with deuterated rongalite and it was observed that 35% of deuterium was incorporated into the product i.e., 3-hydroxy-2-oxidole **8** (Scheme 3.11, Figure 3.4).

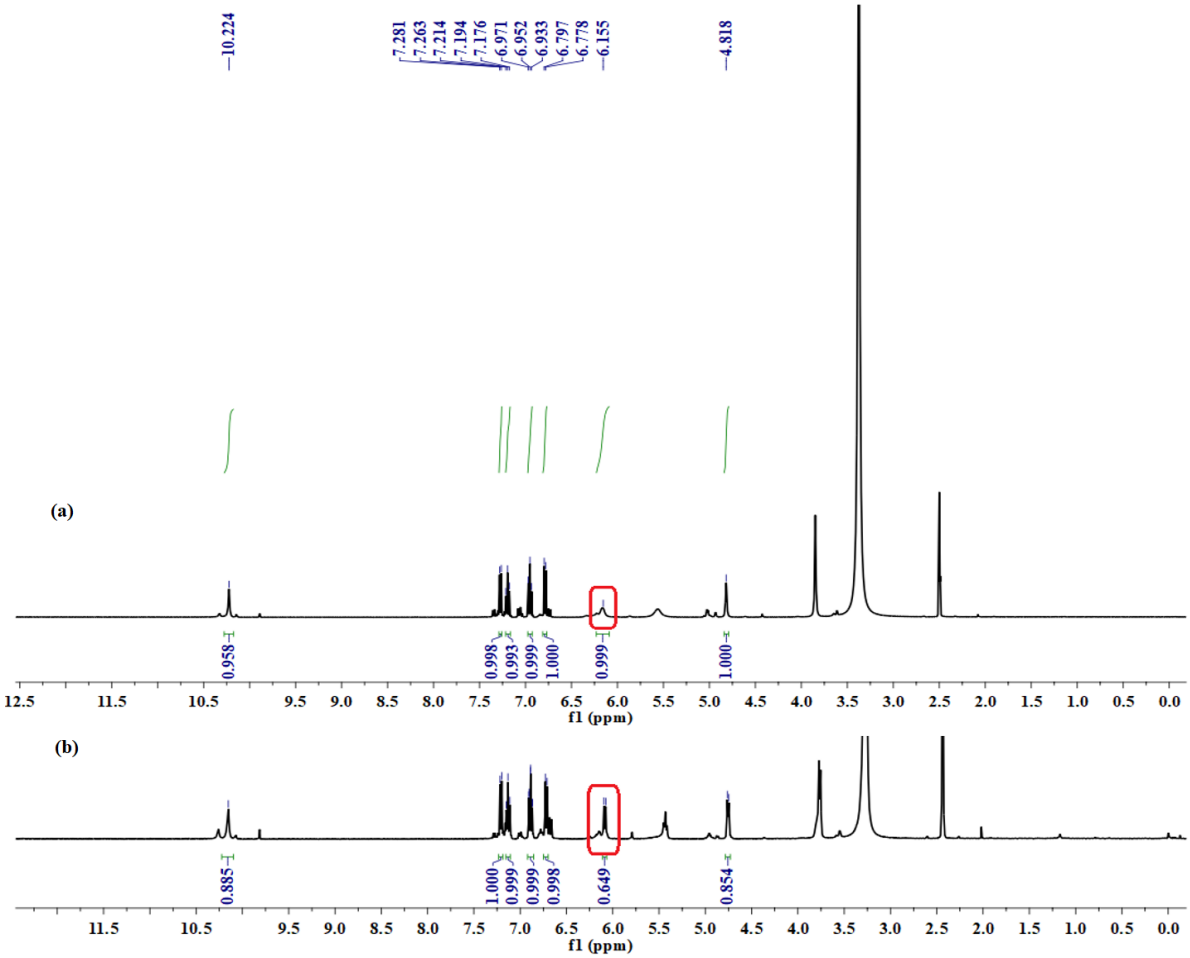
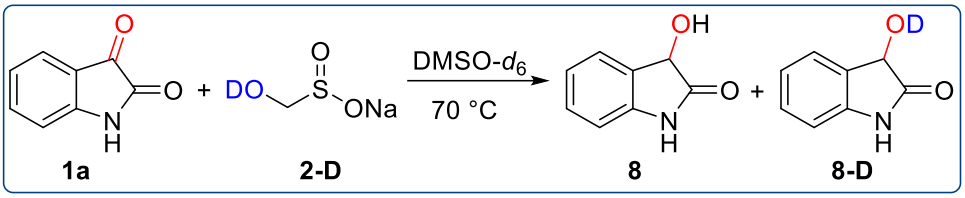


Figure 3.4. ^{1}H NMR (400 MHz, DMSO-d_6) spectrum of reaction mixture of (a) Isatin **1a** (0.05 mmol) and anhydrous rongalite **2** (0.05 mmol) in DMSO-d_6 at 70 °C; (b) Isatin **1a** (0.05 mmol) and anhydrous deuterated rongalite **2-D** (0.05 mmol) in DMSO-d_6 at 70 °C.



Scheme 3.11

An oven dried 10 mL reaction flask was charged with isatin **1a** (0.05 mmol), anhydrous deuterated rongalite **2-D** (0.05 mmol) and DMSO-d_6 (1 mL), stirred at 70 °C for 5 min under N_2 atmosphere. The reaction mixture was recorded for ^{1}H NMR and the results were shown in Figure 3.4. Based on ^{1}H NMR, we have found that 35% of deuterium was incorporated into the –OH group of the product **8.** This result suggested that the proton from the rongalite got itself incorporated into the –OH group of the final product.

3.3. Conclusion

We have developed a transition metal and hydride-free reductive aldol reaction for the synthesis of biologically active 3-hydroxy-3-(hydroxymethyl)indolin-2-ones and 3-amino-3-(hydroxymethyl)indolin-2-ones from isatin derivatives. In this protocol, rongalite, plays a vital role as a reducing agent and a source of the C1 unit. This transition metal-free reductive aldol reaction provides rapid access to various 3,3´-disubstituted oxindoles with 79-96% yields. Also, this method enables the gram scale synthesis of the potential anti-cancer agent 1-benzyl-3-((2,4-difluorophenyl)amino)-3-(hydroxymethyl)-5-ethylindolin-2-one (**5d**) in 84% yield.

3.4. Experimental section

3.4.1. General information

Isatins, anilines, sodium hydroxymethanesulfinate dihydrate, all other reagents and organic solvents were purchased from a commercial source and used as received. The reactions were monitored by analytical TLC on 200 μm aluminum-foil backed silica gel plates. Column chromatography was performed using 100-200 mesh silica gel. Bruker Avance 300/400/500 MHz spectrometer was used to record ^{1}H NMR spectra and used methanol-d_4, $CDCl_3$ and DMSO-d_6 as solvents and TMS as an internal standard. The multiplicities were described using the following acronyms: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Coupling constants, *J* were reported in Hertz unit (Hz). Bruker Avance 75/100/125 MHz

spectrometer was used to record $^{13}C\{^{1}H\}$ NMR spectra, and they were fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to the center line of a triplet at 77.16 ppm of chloroform-*d* (a multiplet at 39.52 ppm of DMSO-d_6). A Stuart SMP30 apparatus was used to determine the melting points and are uncorrected. FT-IR spectra were recorded on a Perkin Elmer spectrometer. HRMS were analyzed with Agilent Q-TOF 6230.

3.4.2. General procedure for synthesis of *N*-alkyl isatins (1k-1s, 1w)[26]

An oven dried 50 mL reaction flask was charged with appropriate isatin (10 mmol) and *N*, *N*-Dimethyl formamide (DMF) solvent (15 mL), cooled to 0-5 °C. After 5 minutes NaH (12 mmol) was added in portion wise to the above mixture in the duration of 15 minutes, then the corresponding alkyl bromide (10 mmol) (for methylation, methyl iodide is used) was added in dropwise. The reaction mixture was continued to stir under cooling condition until the completion of starting material. After that, ice cold water was added and the resulted solid was filtered under vacuum, washed with water and dried.

3.4.3. General procedure for synthesis of *N*-benzyl isatins (1t-1u)[27]

An oven dried 50 mL reaction flask was charged with appropriate isatin (10 mmol), K_2CO_3 (12 mmol) and *N*, *N*-Dimethyl formamide (DMF) solvent (15 mL), then benzyl bromide (10 mmol) was added dropwise at ambient temperature. The reaction mixture was allowed to stir at ambient temperature and after completion of reaction, cold water was added and stirring was continued to precipitate out the product. Finally, the precipitate was filtered, washed with water and air dried.

3.4.4. General procedure for synthesis of *N*-aryl isatins (1v)[28]

An oven dried 50 mL reaction flask was charged with appropriate isatin (10 mmol), appropriate phenylboronic acid (20 mmol), cupric acetate (10 mmol), pyridine (20 mmol) and dichloromethane (CH_2Cl_2) solvent (15 mL), stirred at room temperature and monitored the reaction through TLC using hexanes and ethyl acetate as an eluent. After completion of reaction, organic compound was extracted with CH_2Cl_2 and the organic layers were separated, dried on Na_2SO_4 and evaporated to give a residue that was purified on silica gel column chromatography using hexanes and ethyl acetate as an eluent.

3.4.5. General procedure for synthesis of bis-isatins (1x-1y)[29]

An oven dried 50 mL reaction flask was charged with appropriate isatin (10 mmol), K_2CO_3 (12 mmol) and dimethyl sulfoxide (DMSO) solvent (15 mL), then the corresponding dibromo alkane (5 mmol) was added in dropwise. After the completion of reaction, ice cold water was added and continued to stir for precipitation of product. The solid product was then filtered under vacuum, washed with water and cold methanol.

3.4.6. General procedure for synthesis of isatin Schiff bases (4a-4r)[23]

An oven dried 50 mL reaction flask was charged with appropriate isatin (10 mmol), aniline (10 mmol) and EtOH (15 mL), stirred at 60 °C, then the catalytic amount of glacial CH_3COOH was added. After the reaction has completed (checked by TLC), ice cold water was added and the resulted solid was filtered off under vacuum, washed with cold methanol and dried.

3.4.7. General procedure for synthesis of isatin-derived ketimines (6a-6e)[30,31]

An oven dried 25 mL reaction flask was charged with appropriate isatin (1 mmol), *N*-Boc-triphenyliminophosphorane (2 mmol) and anhydrous 1,4-dioxane (2 mL), and the mixture was kept for reflux for 4-5 h under nitrogen atmosphere. Progress of the reaction was observed by TLC. After that, crude was purified by silica gel column chromatography using hexanes/ethyl acetate as mobile phase.

3.4.8. General procedure (A) for synthesis of 3-hydroxy-3-(hydroxymethyl)indolin-2-one derivatives (3a-3y)

An oven dried 10 mL reaction flask was charged with appropriate isatin-derivative (1 mmol), rongalite (2 mmol), K_2CO_3 (2 mmol) and EtOH+H_2O (2 mL, 8:2 v/v), stirred at 70 °C for the appropriate time (10-20 min). Reaction was monitored by TLC using hexanes and ethyl acetate as an eluent. After reaction has finished, EtOH was evaporated under vacuum and the product was extracted with ethyl acetate (3 x 10 mL). The organic layers were separated, dried on Na_2SO_4 and evaporated to give a residue that was purified using silica gel column chromatography with hexanes and ethyl acetate as an eluent.

3.4.9. General experimental procedure (B) for synthesis of 3-(hydroxymethyl)-3-(phenylamino)indolin-2-one derivatives (5a-5r)

An oven dried 10 mL reaction flask was charged with appropriate isatin Schiff base/*N*-protected isatin Schiff base (1 mmol), rongalite (2 mmol), K_2CO_3 (2 mmol) and EtOH+H_2O (2 mL, 8:2 v/v), stirred at 70 °C for the appropriate time (20-50 min). The progress of the reaction was monitored by TLC using hexanes and ethyl acetate as an eluent. After completion of reaction, EtOH was evaporated under vacuum and the product was extracted with ethyl acetate (3 x 10 mL). The organic layers were separated, dried on Na_2SO_4 and evaporated to give a residue that was purified using silica gel column chromatography with hexanes and ethyl acetate as an eluent.

3.4.10. General experimental procedure (C) for synthesis of *tert*-butyl (3-(hydroxymethyl)-2-oxoindolin-3-yl)carbamate derivatives (7a-7e)

An oven dried 10 mL reaction flask was charged with appropriate isatin-derived ketimine (0.5 mmol), rongalite (1 mmol), K_2CO_3 (1 mmol) and EtOH+H_2O (2 mL, 8:2 v/v), stirred at 70 °C for the appropriate time (20-60 min). The progress of the reaction was monitored by TLC using hexanes and ethyl acetate as an eluent. After reaction has completed, solvent was evaporated under vacuum and the crude product was extracted with ethyl acetate (3 x 10 mL). The organic layers were separated, dried on Na_2SO_4 and evaporated to give a residue that was purified using silica gel column chromatography with hexanes and ethyl acetate as an eluent.

3.4.11. Experimental procedure (D) for synthesis of 3-hydroxyindolin-2-one (8)

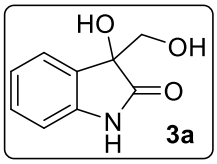
An oven dried 10 mL reaction flask was charged with isatin **1a** (1 mmol), rongalite **2** (1 mmol) and EtOH+H_2O (2 mL, 8:2 v/v), stirred at 70 °C for 10 min and the reaction was monitored by TLC using hexanes and ethyl acetate as an eluent. After completion, EtOH was evaporated under vacuum and the product was extracted with ethyl acetate (3 x 10 mL). The organic layers were separated, dried on Na_2SO_4 and evaporated to give a residue that was purified on silica gel column chromatography using hexanes and ethyl acetate as an eluent.

3.4.12. Preparation of deuterated rongalite

An oven dried 10 mL reaction flask was charged with anhydrous rongalite (0.3 g) and methanol-d_4 (3 mL), and the resulting mixture was stirred for 2 h at ambient temperature. After that, methanol-d_4 was evaporated and the deuterated rongalite was dried under vacuum.

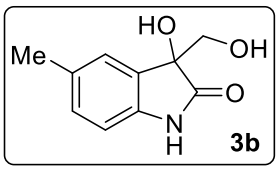
3.5. Characterization data of products 3a-3y, 5a-5r & 7a-7e

3-hydroxy-3-(hydroxymethyl)indolin-2-one (3a). White solid; Yield (165 mg, 92%); mp 146-



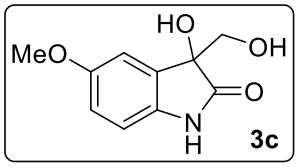
147 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3425, 3370, 3062, 1723, 1681, 1265; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.14 (s, 1H), 7.28 (d, J = 7.2 Hz, 1H), 7.20 (t, J = 7.6 Hz, 1H), 6.96 (t, J = 7.6 Hz, 1H), 6.78 (d, J = 7.6 Hz, 1H), 5.87 (s, 1H), 4.80 (t, J = 5.6 Hz, 1H), 3.66 – 3.60 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 179.2, 143.2, 131.8, 129.2, 124.9, 121.7, 109.7, 76.6, 65.8; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_9H_9NNaO_3$ 202.0480; found 202.0475.

3-hydroxy-3-(hydroxymethyl)-5-methylindolin-2-one (3b). White solid; Yield (155 mg, 80%);



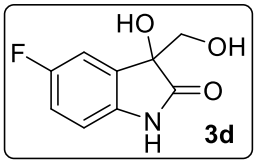
mp 187-188 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3425, 3306, 3191, 3059, 1710, 1623; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.04 (s, 1H), 7.09 (s, 1H), 6.99 (d, J = 7.6 Hz, 1H), 6.66 (d, J = 7.6 Hz, 1H), 5.81 (s, 1H), 4.78 (t, J = 5.6 Hz, 1H), 3.60 (d, J = 5.6 Hz, 2H), 2.26 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d_6) δ (ppm): 179.2, 140.7, 131.8, 130.5, 129.4, 125.6, 109.4, 76.7, 65.8, 21.2; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{10}H_{11}NNaO_3$ 216.0637; found 216.0360.

3-hydroxy-3-(hydroxymethyl)-5-methoxyindolin-2-one (3c). Off white solid; Yield (165 mg,



79%); mp 182-183 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3476, 3322, 3061, 1702, 1613; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.98 (s, 1H), 6.91 (d, J = 2.4 Hz, 1H), 6.76 (dd, J = 8.4, 2.4 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 5.87 (s, 1H), 4.79 (t, J = 5.6 Hz, 1H), 3.71 (s, 3H), 3.64 – 3.57 (m, 2H); $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6) δ (ppm): 178.5, 154.8, 135.8, 132.4, 113.5, 111.6, 109.5, 76.5, 65.4, 55.5; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{10}H_{11}NNaO_4$ 232.0586; found 232.0590.

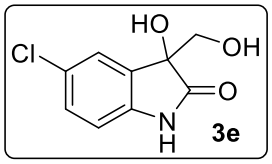
5-fluoro-3-hydroxy-3-(hydroxymethyl)indolin-2-one (3d). White solid; Yield (162 mg, 82%);



mp 174-175 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3425, 3366, 3176, 3082, 1727, 1682; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.18 (s, 1H),

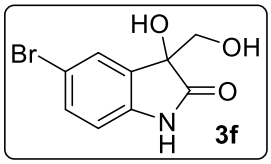
7.14 – 7.12 (m, 1H), 7.05 – 6.99 (m, 1H), 6.76 (dd, J = 8.4, 4.4 Hz, 1H), 6.01 (s, 1H), 4.87 (t, J = 5.6 Hz, 1H), 3.62 (m, 2H); $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6) δ (ppm): 178.5, 157.9 (d, $^{1}J_{C\text{-}F}$ = 234.8 Hz), 138.7, 133.0 (d, $^{3}J_{C\text{-}F}$ = 7.5 Hz), 114.8 (d, $^{2}J_{C\text{-}F}$ = 23.3 Hz), 112.1 (d, $^{2}J_{C\text{-}F}$ = 24 Hz), 109.9 (d, $^{3}J_{C\text{-}F}$ = 7.5 Hz), 76.5, 65.3; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_9H_8FNNaO_3$ 220.0386; found 220.0387.

5-chloro-3-hydroxy-3-(hydroxymethyl)indolin-2-one (3e). White solid; Yield (181 mg, 85%);



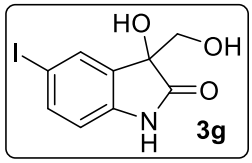
mp 192-193 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3424, 3277, 3072, 1711, 1616; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.30 (s, 1H), 7.30 (d, J = 2.0 Hz, 1H), 7.25 (dd, J = 8.0, 2.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.04 (s, 1H), 4.90 (t, J = 5.6 Hz, 1H), 3.62 (m, 2H); $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6) δ (ppm): 178.2, 141.5, 133.3, 128.5, 125.4, 124.6, 110.6, 76.3, 65.2; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_9H_8ClNNaO_3$ 236.0090; found 236.0089.

5-bromo-3-hydroxy-3-(hydroxymethyl)indolin-2-one (3f). White solid; Yield (230 mg, 89%);



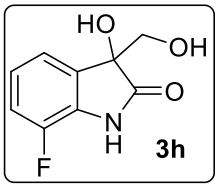
mp 194-195 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3400, 3251, 3082, 1710, 1632; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.31 (s, 1H), 7.42 (d, J = 2.0 Hz, 1H), 7.39 – 7.36 (m, 1H), 6.75 (d, J = 8.4 Hz, 1H), 6.04 (s, 1H), 4.92 (t, J = 5.6 Hz, 1H), 3.63 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 178.7, 142.5, 134.3, 131.9, 127.8, 113.6, 111.7, 76.8, 65.7; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_9H_8BrNNaO_3$ 279.9585; found 279.9571.

3-hydroxy-3-(hydroxymethyl)-5-iodoindolin-2-one (3g). White crystalline solid; Yield (262



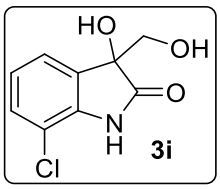
mg, 86%); mp 188-189 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3421, 3368, 3167, 3080, 1725, 1679; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.28 (s, 1H), 7.56 – 7.53 (m, 2H), 6.64 (d, J = 8.0 Hz, 1H), 6.01 (s, 1H), 4.90 (t, J = 5.6 Hz, 1H), 3.66 – 3.57 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 178.5, 143.0, 137.7, 134.6, 133.3, 112.2, 84.7, 76.7, 65.6; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_9H_8INNaO_3$ 327.9447; found 327.9444.

7-fluoro-3-hydroxy-3-(hydroxymethyl)indolin-2-one (3h). White solid; Yield (170 mg, 86%);



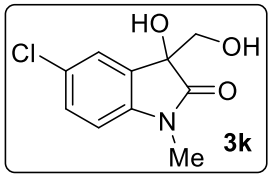
mp 177-178 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3420, 3366, 3176, 3082, 1727, 1682; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.66 (s, 1H), 7.16 – 7.09 (m, 2H), 7.00 – 6.99 (m, 1H), 6.04 (s, 1H), 4.88 (t, J = 5.6 Hz, 1H), 3.65 (d, J = 5.6 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 179.1, 146.7 (d, $^{1}J_{C\text{-}F}$ = 240.2 Hz), 134.9 (d, $^{3}J_{C\text{-}F}$ = 3.5 Hz), 130.0 (d, $^{2}J_{C\text{-}F}$ = 11.8 Hz), 122.7 (d, $^{3}J_{C\text{-}F}$ = 5.6 Hz), 120.9 (d, $^{4}J_{C\text{-}F}$ = 2.9 Hz), 116.3 (d, $^{2}J_{C\text{-}F}$ = 17.2 Hz), 76.8 (d, $^{4}J_{C\text{-}F}$ = 2.7 Hz), 65.8; HRMS (ESI) *m/z*: $[M+Na]^{+}$ calcd for $C_9H_8FNNaO_3$ 220.0386; found 220.0389.

7-chloro-3-hydroxy-3-(hydroxymethyl)indolin-2-one (3i). White crystalline solid; Yield (183



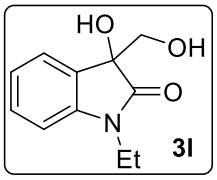
mg, 86%); mp 168-169 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3424, 3277, 3081, 1711, 1616; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.59 (s, 1H), 7.297 – 7.230 (m, 2H), 6.99 (t, J = 7.6 Hz, 1H), 6.06 (s, 1H), 4.90 (t, J = 5.6 Hz, 1H), 3.65 (d, J = 5.6 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 179.2, 140.8, 133.9, 129.2, 123.4, 123.2, 114.0, 77.3, 65.8; HRMS (ESI) *m/z*: $[M+Na]^{+}$ calcd for $C_9H_8ClNNaO_3$ 236.0090; found 236.0088.

5-chloro-3-hydroxy-3-(hydroxymethyl)-1-methylindolin-2-one (3k). White solid; Yield (204



mg, 90%); mp 174-175; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3422, 3223, 3061, 1689, 1612, 1492; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.39 – 7.34 (m, 2H), 6.99 (d, J = 8.8 Hz, 1H), 6.12 (s, 1H), 4.93 (t, J = 5.6 Hz, 1H), 3.71 – 3.61 (m, 2H), 3.09 (s, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6) δ (ppm): 176.4, 142.9, 132.6, 128.6, 126.1, 124.2, 109.4, 76.1, 65.1, 25.8; HRMS (ESI) *m/z*: $[M+Na]^{+}$ calcd for $C_{10}H_{10}ClNNaO_3$ 250.0247; found 250.0241.

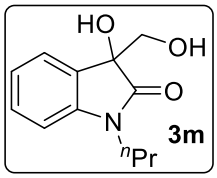
1-ethyl-3-hydroxy-3-(hydroxymethyl)indolin-2-one (3l). White solid; Yield (197 mg, 95%);



mp 118-119 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3354, 3305, 3092, 3059, 2925, 1698, 1614, 1493; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.39 (d, J = 7.2 Hz, 1H), 7.37 – 7.33 (m, 1H), 7.11 – 7.04 (m, 2H), 6.01 (s, 1H), 4.88 (t, J = 5.6 Hz, 1H), 3.75

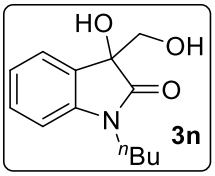
– 3.67 (m, 4H), 1.19 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d_6) δ (ppm): 177.0, 143.7, 131.3, 129.4, 124.6, 122.3, 108.6, 76.4, 65.8, 34.3, 13.0; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{11}H_{13}NNaO_3$ 230.0793; found 230.0789.

3-hydroxy-3-(hydroxymethyl)-1-propylindolin-2-one (3m). White crystalline solid; Yield



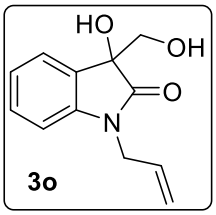
(208 mg, 94%); mp 104-105 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3394, 3063, 2966, 2934, 1702, 1614, 1489; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.33 (d, *J* = 7.2 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 5.95 (s, 1H), 4.82 (t, *J* = 5.6 Hz, 1H), 3.67 – 3.65 (m, 2H), 3.64 – 3.52 (m, 2H), 1.64 – 1.54 (m, 2H), 0.88 (t, *J* = 7.6 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 177.5, 144.1, 131.2, 129.4, 124.6, 122.2, 108.7, 76.4, 65.8, 41.0, 20.8, 11.6; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{12}H_{15}NNaO_3$ 244.0950; found 244.0947.

1-butyl-3-hydroxy-3-(hydroxymethyl)indolin-2-one (3n). Colorless liquid; Yield (221 mg,



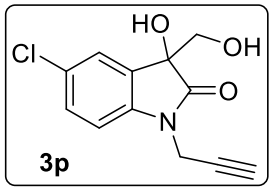
94%); The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3402, 3058, 2959, 2934, 1703, 1614; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.33 (d, *J* = 7.2 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 7.6 Hz, 1H), 5.95 (s, 1H), 4.82 (t, *J* = 5.6 Hz, 1H), 3.69 – 3.54 (m, 4H), 1.59 – 1.50 (m, 2H), 1.36 – 1.27 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 177.4, 144.1, 131.3, 129.4, 124.6, 122.2, 108.7, 76.4, 65.8, 39.2, 29.6, 19.8, 14.2; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{13}H_{17}NNaO_3$ 258.1106; found 258.1108.

1-allyl-3-hydroxy-3-(hydroxymethyl)indolin-2-one (3o). White crystalline solid; Yield (208

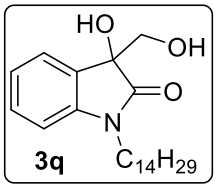


mg, 95%); mp 100-101 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3322, 3061, 2920, 1694, 1614, 1468; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.35 (d, *J* = 7.2 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.04 (t, *J* = 7.2 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.03 (s, 1H), 5.87 – 5.76 (m, 1H), 5.21 (d, *J* = 17.2 Hz, 1H), 5.12 (d, *J* = 10.4 Hz, 1H), 4.88 (s, 1H), 4.26 (dd, *J* = 45.2, 16.8 Hz, 2H), 3.69 (m, 2H); $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d_6) δ (ppm): 177.3, 143.8, 132.2, 131.2, 129.3, 124.5, 122.4, 116.9, 109.1, 76.5, 65.8, 41.7; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{12}H_{13}NNaO_3$ 242.0793; found 242.0784.

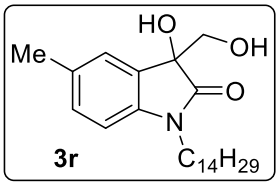
5-chloro-3-hydroxy-3-(hydroxymethyl)-1-(prop-2-yn-1-yl)indolin-2-one (3p). White solid; Yield (228 mg, 91%); mp 120-121 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3287, 3229, 3063, 2921, 2120, 1716, 1612, 1487; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.43 – 7.39 (m, 2H), 7.07 (d, J = 8.4 Hz, 1H), 6.26 (s, 1H), 4.97 (t, J = 5.6 Hz, 1H), 4.55 – 4.43 (m, 2H), 3.72 – 3.62 (m, 2H), 3.27 (s, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6) δ (ppm): 175.7, 141.0, 132.5, 128.6, 126.6, 124.4, 110.2, 77.7, 76.1, 74.3, 65.2, 28.7; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{12}H_{10}ClNNaO_3$ 274.0247; found 274.0254.



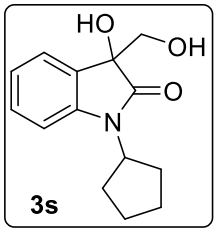
3-hydroxy-3-(hydroxymethyl)-1-tetradecylindolin-2-one (3q). White solid; Yield (353 mg, 94%); mp 85-86 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3294, 2955, 2915, 2848, 1713, 1615, 1470; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.33 (d, J = 7.2 Hz, 1H), 7.30 – 7.25 (m, 1H), 7.02 (t, J = 7.4 Hz, 1H), 6.96 (d, J = 7.6 Hz, 1H), 5.94 (s, 1H), 4.80 (t, J = 5.6 Hz, 1H), 3.69 – 3.53 (m, 4H), 1.60 – 1.50 (m, 2H), 1.31 – 1.21 (m, 22H), 0.86 (t, J = 6.8 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 177.3, 144.0, 131.3, 129.3, 124.6, 122.2, 108.6, 76.3, 65.8, 39.4, 31.8, 29.5, 29.5, 29.5, 29.2, 29.2, 27.4, 26.6, 22.6, 14.4; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{12}H_{10}ClNNaO_3$ 274.0247; found 274.0254.



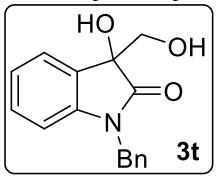
3-hydroxy-3-(hydroxymethyl)-5-methyl-1-tetradecylindolin-2-one (3r). White solid; Yield (346 mg, 89%); mp 99-100 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3437, 3388, 3023, 2954, 2840, 1710, 1614, 1465; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.15 (s, 1H), 7.07 (d, J = 8.0 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 3.78 – 3.68 (m, 2H), 3.64 – 3.51 (m, 2H), 2.27 (s, 3H), 1.62 – 1.56 (m, 2H), 1.23 – 1.17 (m, 22H), 0.82 (d, J = 6.8 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6) δ (ppm): 176.6, 141.1, 130.7, 130.5, 128.8, 124.9, 107.8, 75.9, 65.4, 31.1, 28.9, 28.6, 28.5, 26.8, 26.0, 21.9, 20.5, 13.7; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{24}H_{39}NNaO_3$ 412.2828; found 412.2832.



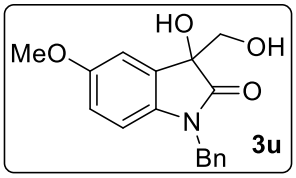
1-cyclopentyl-3-hydroxy-3-(hydroxymethyl)indolin-2-one (3s). Colorless liquid; Yield (235 mg, 95%); The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3302, 3058, 2921, 2873, 1703, 1614; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.34 (d, J = 7.6 Hz, 1H), 7.30 – 7.25 (m, 1H), 7.04 – 6.99 (m, 2H), 5.91 (s, 1H), 4.80 (t, J = 5.6 Hz, 1H), 4.63 (quint, J = 8.4 Hz, 1H), 3.63 (d, J = 5.6 Hz, 2H), 2.03 – 1.78 (m, 6H), 1.69 – 1.60 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 177.4, 143.3, 131.5, 129.3, 124.8, 122.0, 109.6, 76.1, 66.0, 52.1, 28.0, 27.7, 25.2, 25.2; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{17}NNaO_3$ 270.1106; found 270.1107.



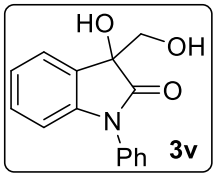
1-benzyl-3-hydroxy-3-(hydroxymethyl)indolin-2-one (3t). White solid; Yield (256 mg, 95%); mp 123-124 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3305, 3256, 3061, 2965, 1690, 1618; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.39 – 7.29 (m, 5H), 7.25 (t, J = 7.2 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.02 (t, J = 7.6 Hz, 1H), 6.76 (d, J = 7.6 Hz, 1H), 6.11 (s, 1H), 4.98 – 4.94 (m, 2H), 4.80 (d, J = 16.0 Hz, 1H), 3.80 – 3.72 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 177.7, 143.7, 136.7, 131.3, 129.3, 128.9, 127.7, 127.6, 124.6, 122.6, 109.2, 76.6, 65.9, 42.9; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{16}H_{15}NNaO_3$ 292.0950; found 292.0958.



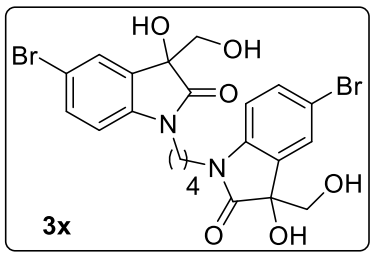
1-benzyl-3-hydroxy-3-(hydroxymethyl)-5-methoxyindolin-2-one (3u). White solid; Yield (257 mg, 86%); mp 158-159 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3406, 3051, 2928, 1703, 1602, 1490; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.35 – 7.22 (m, 5H), 7.00 (d, J = 2.4 Hz, 1H), 6.75 (dd, J = 8.4, 2.4 Hz, 1H), 6.64 (d, J = 8.4 Hz, 1H), 6.11 (s, 1H), 4.96 – 4.89 (m, 2H), 4.76 (d, J = 16.0 Hz, 1H), 3.73 (d, J = 5.6 Hz, 2H), 3.70 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6) δ (ppm): 176.8, 155.4, 136.4, 136.2, 132.0, 128.3, 127.1, 127.0, 113.2, 111.6, 109.0, 76.4, 65.5, 55.5, 42.5; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{17}H_{17}NNaO_4$ 322.1055; found 322.1052.



3-hydroxy-3-(hydroxymethyl)-1-phenylindolin-2-one (3v). Colorless semisolid; Yield (243 mg, 95%); The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3390, 3260, 3065, 1712, 1265; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.58 (t, J = 7.6 Hz, 2H), 7.46 (t, J = 7.2 Hz, 2H), 7.40 (d, J = 7.2 Hz, 2H), 7.26 (t, J = 7.6 Hz, 1H), 7.11 (t, J = 7.6 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 6.20 (s, 1H), 5.00 (t, J = 5.6 Hz, 1H), 3.82 – 3.74 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 177.2, 143.4, 133.8, 129.7, 129.7, 128.3, 128.3, 126.6, 124.9, 123.8, 109.8, 76.4, 66.8; HRMS (ESI) *m/z:* $[M+Na]^+$ calcd for $C_{15}H_{13}NNaO_3$ 278.0793; found 278.0789.

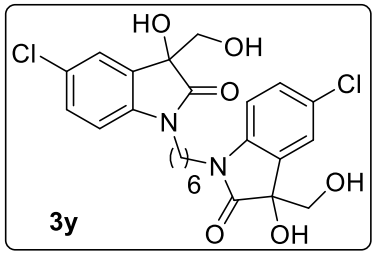


ethyl 2-(3-hydroxy-3-(hydroxymethyl)-2-oxoindolin-1-yl)acetate (3w). Colorless liquid; Yield (244 mg, 92%); The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3432, 3059, 2951, 2257, 1735, 1645, 1492; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.37 (d, J = 6.8 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 7.05 (t, J = 7.6 Hz, 1H), 6.93 (d, J = 7.6 Hz, 1H), 6.09 (s, 1H), 4.90 (t, J = 5.6 Hz, 1H), 4.49 (s, 2H), 4.14 (q, J = 7.2 Hz, 2H), 3.70 – 3.57 (m, 2H), 1.21 (t, J = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 177.5, 168.3, 143.4, 130.7, 129.3, 124.9, 122.7, 108.9, 76.5, 66.0, 61.5, 41.3, 14.5; HRMS (ESI) *m/z:* $[M+Na]^+$ calcd for $C_{13}H_{15}NNaO_5$ 288.0848; found 288.0837.

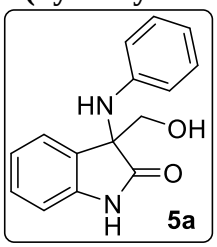


1,1'-(butane-1,4-diyl)bis(5-bromo-3-hydroxy-3-(hydroxymethyl)indolin-2-one) (3x). White solid; Yield (485 mg, 85%); mp 203-204 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3401, 3249, 3081, 2954, 1712, 1623; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.50 – 7.44 (m, 4H), 6.98 (dd, J = 8.0, 2.4 Hz, 2H), 6.13 (s, 2H), 4.92 (t, J = 5.6 Hz, 2H), 3.72 – 3.59 (m, 8H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 177.0, 143.2, 133.7, 132.0, 127.5, 114.3, 110.9, 76.5, 65.6, 39.1, 24.3; HRMS (ESI) *m/z:* $[M+H]^+$ calcd for $C_{22}H_{23}Br_2N_2O_6$ 568.9923; found 568.9913.

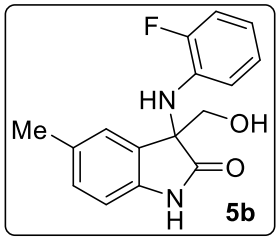
1,1'-(hexane-1,6-diyl)bis(5-chloro-3-hydroxy-3-(hydroxymethyl)indolin-2-one) (3y). White solid; Yield (438 mg, 86%); mp 168-169 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3421, 3228, 3056, 2962, 1690, 1610, 1493; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.35 (d, J = 2.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.4 Hz, 2H), 6.10 (s, 2H), 4.90 (t, J = 5.6 Hz, 2H), 3.69 – 3.51 (m, 8H), 1.50 (s, 4H), 1.29 (s, 4H); ^{13}C{^{1}H} NMR (100 MHz, methanol-d_4) δ (ppm): 177.6, 142.1, 131.9, 129.1, 127.8, 124.5, 109.9, 76.3, 65.4, 39.4, 26.7, 25.8; HRMS (ESI) *m/z:* $[M+Na]^+$ calcd for $C_{24}H_{26}Cl_2N_2NaO_6$ 531.1066; found 531.1045.



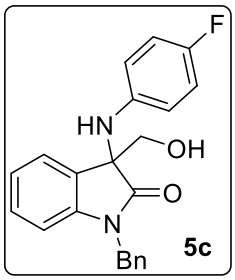
3-(hydroxymethyl)-3-(phenylamino)indolin-2-one (5a). White crystalline solid; Yield (241 mg, 95%); mp 171-172 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3421, 3321, 3280, 3068, 2911, 1710, 1680; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.56 (s, 1H), 7.21 (td, J = 7.6, 1.2 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 6.95 – 6.86 (m, 4H), 6.46 (t, J = 7.6 Hz, 1H), 6.20 (d, J = 8.8 Hz, 2H), 6.06 (s, 1H), 5.17 (t, J = 6.0 Hz, 1H), 3.73 – 3.62 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ (ppm): 178.4, 146.8, 142.4, 130.1, 129.1, 129.0, 124.4, 122.0, 117.1, 113.6, 110.1, 67.8, 66.1; HRMS (ESI) *m/z:* $[M+Na]^+$ calcd for $C_{15}H_{14}N_2NaO_2$ 277.0953; found 277.0952.



3-((2-fluorophenyl)amino)-3-(hydroxymethyl)-5-methylindolin-2-one (5b). Off white solid; Yield (249 mg, 87%); mp 181-182 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3392, 3354, 3250, 3080, 1706, 1673; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.58 (s, 1H), 7.06 – 7.01 (m, 3H), 6.81 (d, J = 7.6 Hz, 1H), 6.68 (t, J = 7.6 Hz, 1H), 6.53 (dd, J = 12.4, 6.8 Hz, 1H), 5.82 (t, J = 8.0 Hz, 1H), 5.66 (s, 1H), 5.46 (t, J = 6.0 Hz, 1H), 3.75 – 3.58 (m, 2H), 2.21 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ (ppm): 177.6, 151.6 (d, $^1J_{C\text{-}F}$ = 238 Hz), 150.6, 139.5, 134.6 (d, $^3J_{C\text{-}F}$ = 11.2 Hz), 131.0, 129.5 (d, $^2J_{C\text{-}F}$ = 28.2 Hz), 125.1, 124.9 (d, $^4J_{C\text{-}F}$ = 1.25 Hz), 117.4 (d, $^3J_{C\text{-}F}$ = 7.5 Hz), 114.9 (d, $^2J_{C\text{-}F}$ = 18.8 Hz), 113.3, 110.2, 67.7, 65.7, 21.1; HRMS (ESI) *m/z:* $[M+Na]^+$ calcd for $C_{16}H_{15}FN_2NaO_2$ 309.1015; found 309.1006.

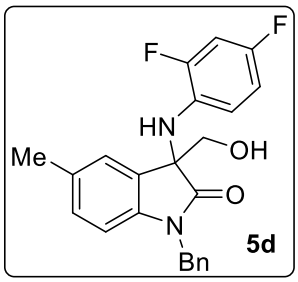


1-benzyl-3-((4-fluorophenyl)amino)-3-(hydroxymethyl)indolin-2-one (5c). Colorless



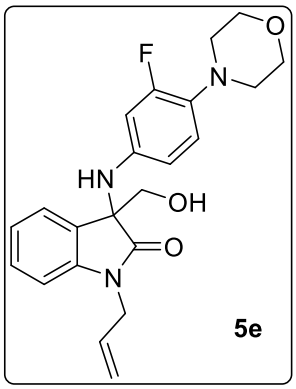
semisolid; Yield (340 mg, 94%); The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3371, 3356, 3091, 1701, 1612; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.40 – 7.27 (m, 5H), 7.25 – 7.21 (m, 2H), 7.00 (t, J = 7.6 Hz, 1H), 6.95 (d, J = 7.6 Hz, 1H), 6.67 (t, J = 8.8 Hz, 2H), 6.17 (s, 1H), 6.15 – 6.12 (m, 2H), 5.30 (t, J = 5.6 Hz, 1H), 5.00 – 4.91 (m, 2H), 3.85 – 3.75 (m, 2H); $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d_6) δ (ppm): 177.0, 155.4 (d, $^{1}J_{C\text{-}F}$ = 231.2 Hz), 143.1, 143.0, 136.7, 129.3, 129.2, 129.1, 128.0, 127.9, 124.1, 123.0, 115.4 (d, $^{2}J_{C\text{-}F}$ = 22.4 Hz), 115.3 (d, $^{3}J_{C\text{-}F}$ = 7.8 Hz), 109.7, 67.7, 66.4, 43.5; HRMS (ESI) *m/z:* $[M+H]^+$ calcd for $C_{22}H_{20}FN_2O_2$ 363.1509; found 363.1507.

1-benzyl-3-((2,4-difluorophenyl)amino)-3-(hydroxymethyl)-5-methylindolin-2-one (5d). Off



white solid; Yield (355 mg, 90%); mp 120-121 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3421, 3381, 3341, 3068, 2910, 1686, 1619; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.22 – 7.18 (m, 3H), 7.17 – 7.11 (m, 2H), 7.09 – 7.06 (m, 1H), 7.01 – 6.97 (m, 1H), 6.72 – 6.63 (m, 2H), 6.23 – 6.16 (m, 1H), 5.67 – 5.61 (m, 1H), 5.01 (d, J = 15.6 Hz, 1H), 4.64 (d, J = 15.6 Hz, 1H), 3.86 (d, J = 11.6 Hz, 1H), 3.65 (d, J = 11.6 Hz, 1H), 2.20 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 177.4, 155.5 (dd, $^{1}J_{C\text{-}F}$ = 238 Hz, $^{3}J_{C\text{-}F}$ = 11.1 Hz), 152.1 (dd, $^{1}J_{C\text{-}F}$ = 242 Hz, $^{3}J_{C\text{-}F}$ = 11.1 Hz), 139.5, 135.4, 133.5, 130.5 (dd, $^{2}J_{C\text{-}F}$ = 11.4 Hz, $^{4}J_{C\text{-}F}$ = 3.1 Hz), 130.2, 128.8, 128.0, 127.7, 127.2, 124.8, 115.1 (dd, $^{3}J_{C\text{-}F}$ = 8.8 Hz, $^{3}J_{C\text{-}F}$ = 3.5 Hz), 110.4 (dd, $^{2}J_{C\text{-}F}$ = 21.5 Hz, $^{4}J_{C\text{-}F}$ = 3.8 Hz), 110.0, 103.7 (dd, $^{2}J_{C\text{-}F}$ = 23.2 Hz, $^{2}J_{C\text{-}F}$ = 26.4 Hz), 67.9, 64.9, 44.2, 21.1; HRMS (ESI) *m/z:* $[M+Na]^+$ calcd for $C_{23}H_{20}F_2N_2NaO_2$ 417.1391; found 417.1387.

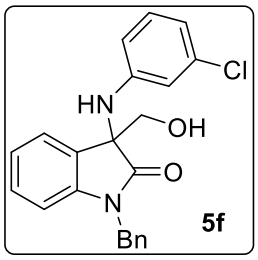
1-allyl-3-((3-fluoro-4-morpholinophenyl)amino)-3-(hydroxymethyl)indolin-2-one (5e). Off



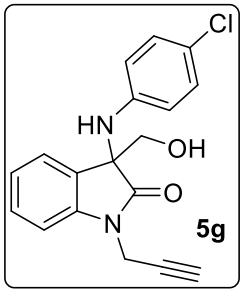
white solid; Yield (373 mg, 94%); mp 105-106 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3336, 3312, 3091, 2833, 1707, 1703, 1507; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.30 (td, J = 7.6, 1.2 Hz, 1H), 7.23 (d, J = 7.6 Hz, 1H), 7.05 – 6.99 (m, 2H), 6.66 – 6.58 (m, 1H), 6.19 (s, 1H), 5.98 (dd, J = 15.2, 2.4 Hz, 1H), 5.89 (dd, J = 8.4, 2.4 Hz, 1H), 5.87 –

5.77 (m, 1H), 5.30 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.21 (t, *J* = 5.6 Hz, 1H), 5.18 (dd, *J* = 10.4, 1.6 Hz, 1H), 4.42 – 4.29 (m, 2H), 3.76 – 3.68 (m, 2H), 3.63 (t, *J* = 4.4 Hz, 4H), 2.73 (t, *J* = 4.4 Hz, 4H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 176.4, 156.2 (d, $^{1}J_{C\text{-}F}$ = 240.0 Hz), 143.2, 143.1 (d, $^{3}J_{C\text{-}F}$ = 4.2 Hz), 132.2, 130.6 (d, $^{2}J_{C\text{-}F}$ = 9.5 Hz), 129.3 (d, $^{2}J_{C\text{-}F}$ = 11.6 Hz), 124.1, 122.8, 120.6 (d, $^{3}J_{C\text{-}F}$ = 4.2 Hz), 117.7, 109.7, 109.6 (d, $^{4}J_{C\text{-}F}$ = 1.8 Hz), 102.5, 102.2, 67.6, 66.8, 66.2, 51.8, 42.2; HRMS (ESI) *m/z:* $[M+H]^+$ calcd for $C_{22}H_{25}FN_3O_3$ 398.1880; found 398.1880.

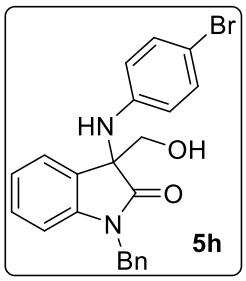
1-benzyl-3-((3-chlorophenyl)amino)-3-(hydroxymethyl)indolin-2-one (5f). Pale yellow liquid; Yield (355 mg, 94%); The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3376, 3345, 3068, 2910, 1708, 1613, 1596; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.41 (d, *J* = 7.2 Hz, 2H), 7.35 –7.23 (m, 5H), 7.01 (t, *J* = 7.2 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.82 (t, *J* = 8.0 Hz, 1H), 6.60 (s, 1H), 6.50 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.23 (s, 1H), 6.06 (dd, *J* = 8.0, 1.6 Hz, 1H), 5.34 (t, *J* = 5.6 Hz, 1H), 5.02 – 4.93 (m, 2H), 3.85 – 3.76 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 176.5, 148.1, 143.1, 136.7, 133.8, 130.6, 129.3, 129.1, 128.9, 127.9, 124.1, 123.1, 116.9, 113.3, 112.4, 109.8, 67.7, 66.0, 43.6; HRMS (ESI) *m/z:* $[M+H]^+$ calcd for $C_{22}H_{20}ClN_2O_2$ 379.1213; found 379.1200.



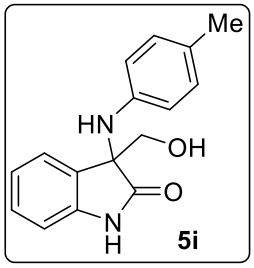
3-((4-chlorophenyl)amino)-3-(hydroxymethyl)-1-(prop-2-yn-1-yl)indolin-2-one (5g). Pale yellow liquid; Yield (310 mg, 95%); The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3394, 3341, 3065, 2965, 2934, 2135, 1706, 1610; ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ (ppm): 7.34 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 7.2 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.21 (s, 1H), 6.14 (d, *J* = 8.8 Hz, 2H), 5.23 (t, *J* = 6.0 Hz, 1H), 4.69 (dd, *J* = 17.6, 2.4 Hz, 1H), 4.47 (dd, *J* = 17.6, 2.4 Hz, 1H), 3.79 – 3.67 (m, 2H), 2.99 (s, 1H); $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d_6) δ (ppm): 175.9, 145.0, 141.7, 129.1, 128.8, 128.6, 124.2, 123.2, 121.3, 115.3, 109.8, 77.6, 73.9, 67.4, 65.9, 29.4; HRMS (ESI) *m/z:* $[M+Na]^+$ calcd for $C_{18}H_{15}ClN_2NaO_2$ 349.0720; found 349.0728.



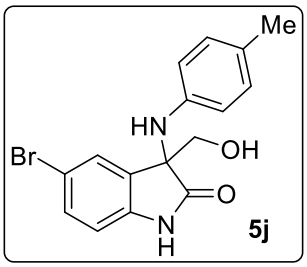
1-benzyl-3-((4-bromophenyl)amino)-3-(hydroxymethyl)indolin-2-one (5h). Brown crystalline solid; Yield (394 mg, 93%); mp 140-141 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3374, 3560, 3392, 2916, 1702, 1614; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.41 (d, J = 8.4 Hz, 2H), 7.37 – 7.32 (m, 2H), 7.32 – 7.27 (m, 1H), 7.26 – 7.21 (m, 2H), 7.03 – 6.94 (m, 4H), 6.46 (s, 1H), 6.08 (d, J = 9.2 Hz, 2H), 5.31 (t, J = 5.6 Hz, 1H), 5.01 – 4.91 (m, 2H), 3.84 – 3.75 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ (ppm): 176.6, 145.9, 143.1, 136.8, 131.6, 129.2, 129.0, 128.1, 127.9, 124.1, 122.9, 115.9, 109.8, 108.3, 67.7, 66.0, 43.6; HRMS (ESI) *m/z:* $[M+H]^+$ calcd for $C_{22}H_{20}BrN_2O_2$ 423.0708; found 423.0706.



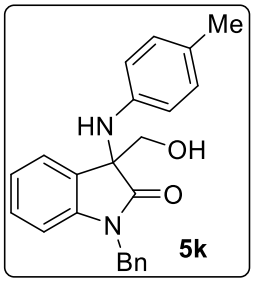
3-(hydroxymethyl)-3-(*p*-tolylamino)indolin-2-one (5i). colorless semi solid; Yield (242 mg, 90%); The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3415, 3335, 3291, 2930, 1720, 1699, 1616; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.52 (s, 1H), 7.20 (t, J = 7.6 Hz, 1H), 7.13 (d, J = 7.2 Hz, 1H), 6.92 (t, J = 7.2 Hz, 1H), 6.87 (d, J = 7.6 Hz, 1H), 6.70 (d, J = 8.0 Hz, 2H), 6.12 (d, J = 8.0 Hz, 2H), 5.83 (s, 1H), 5.15 (t, J = 6.0 Hz, 1H), 3.71 – 3.61 (m, 2H), 2.04 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ (ppm): 178.6, 144.4, 142.4, 130.3, 129.5, 128.9, 125.6, 124.4, 122.0, 114.0, 110.0, 67.8, 66.3, 20.4; HRMS (ESI) *m/z:* $[M+H]^+$ calcd for $C_{16}H_{17}N_2O_2$ 269.1290; found 269.1292.



5-bromo-3-(hydroxymethyl)-3-(*p*-tolylamino)indolin-2-one (5j). Off white solid; Yield (305 mg, 88%); mp 172-173 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3391, 3315, 3286, 3081, 2925, 1720, 1698, 1612; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.68 (s, 1H), 7.39 (dd, J = 8.0, 2.4 Hz, 1H), 7.24 (d, J = 1.6 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.74 (d, J = 8.0 Hz, 2H), 6.12 (d, J = 8.4 Hz, 2H), 5.92 (s, 1H), 5.24 (t, J = 6.0 Hz, 1H), 3.75 – 3.62 (m, 2H), 2.06 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ (ppm): 178.1, 144.1, 141.9, 133.0, 131.7, 129.7, 127.0, 125.9, 113.9, 113.9, 112.0, 67.6, 66.5, 20.4; HRMS (ESI) *m/z:* $[M+H]^+$ calcd for $C_{16}H_{16}BrN_2O_2$ 347.0395; found 347.0382.

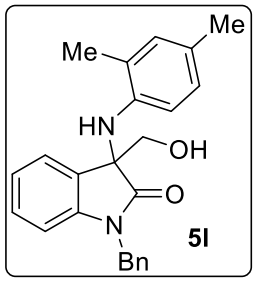


1-benzyl-3-(hydroxymethyl)-3-(*p*-tolylamino)indolin-2-one (5k). White crystalline solid;



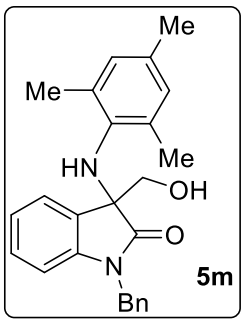
Yield (341 mg, 95%); mp 141-142 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3391, 3311, 3092, 2920, 1703, 1614; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.39 (d, J = 7.2 Hz, 2H), 7.36 – 7.27 (m, 3H), 7.22 – 7.19 (m, 2H), 6.98 (t, J = 7.6 Hz, 1H), 6.92 (d, J = 7.6 Hz, 1H), 6.64 (d, J = 8.0 Hz, 2H), 6.06 (d, J = 8.0 Hz, 2H), 5.97 (s, 1H), 5.26 (t, J = 5.6 Hz, 1H), 5.00 – 4.89 (m, 2H), 3.81 – 3.73 (m, 2H), 2.05 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ (ppm): 177.1, 144.2, 143.2, 136.9, 129.8, 129.5, 128.9, 128.0, 127.9, 126.0, 124.1, 122.8, 114.4, 109.6, 67.8, 66.3, 43.5, 20.4; HRMS (ESI) *m/z:* $[M+H]^+$ calcd for $C_{23}H_{23}N_2O_2$ 359.1760; found 359.1760.

1-benzyl-3-((2,4-dimethylphenyl)amino)-3-(hydroxymethyl)indolin-2-one (5l). White solid;



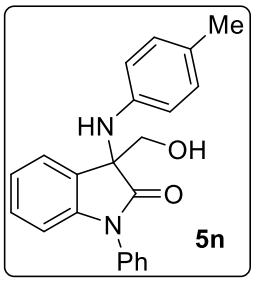
Yield (357 mg, 96%); mp 160-161 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3375, 3325, 3067, 2916, 1691, 1614; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.40 – 7.29 (m, 5H), 7.24 – 7.17 (m, 2H), 6.99 – 6.94 (m, 2H), 6.79 (s, 1H), 6.31 (d, J = 8.0 Hz, 1H), 5.55 (t, J = 6.0 Hz, 1H), 5.44 (d, J = 8.4 Hz, 1H), 5.03 – 4.89 (m, 3H), 3.82 – 3.68 (m, 2H), 2.19 (s, 3H), 2.04 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ (ppm): 176.8, 142.7, 141.7, 136.8, 131.3, 129.5, 129.0, 129.0, 128.1, 127.9, 126.9, 126.4, 124.2, 123.7, 122.8, 112.3, 109.7, 68.0, 66.1, 43.5, 20.4, 18.1; HRMS (ESI) *m/z:* $[M+H]^+$ calcd for $C_{24}H_{25}N_2O_2$ 373.1916; found 373.1907.

1-benzyl-3-(hydroxymethyl)-3-(mesitylamino)indolin-2-one (5m). Pale yellow solid; Yield



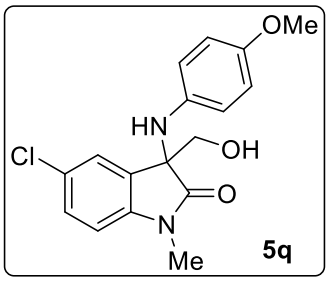
(371 mg, 96%); mp 122-123 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3362, 3311, 3061, 2912, 1701, 1614, 1484; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.30 – 7.22 (m, 5H), 7.09 (td, J = 7.6, 1.2 Hz, 1H), 6.83 – 6.73 (m, 3H), 6.61 (s, 2H), 5.41 (t, J = 5.6 Hz, 1H), 4.89 (d, J = 15.6 Hz, 1H), 4.79 (d, J = 15.6 Hz, 1H), 4.20 (s, 1H), 3.87 – 3.78 (m, 2H), 2.09 (s, 3H), 1.94 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ (ppm): 176.4, 155.9, 141.7, 136.8, 135.9, 131.3, 131.0, 129.0, 128.1, 127.9, 126.9, 126.5, 123.7, 112.3, 110.2, 68.0, 66.3, 43.5, 20.4, 18.0; HRMS (ESI) *m/z:* $[M+H]^+$ calcd for $C_{25}H_{27}N_2O_2$ 387.2073; found 387.2066.

3-(hydroxymethyl)-1-phenyl-3-(*p*-tolylamino)indolin-2-one (5n). colorless semisolid, Yield



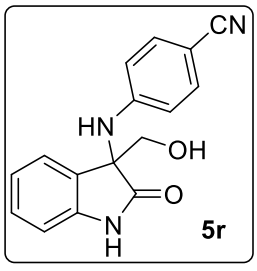
(327 mg); The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3392, 3316, 3069, 2918, 1713, 1604; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.43 (t, J = 7.6 Hz, 2H), 7.36 – 7.31 (m, 2H), 7.28 – 7.20 (m, 3H), 7.06 (t, J = 7.6 Hz, 1H), 6.82 (d, J = 7.6 Hz, 1H), 6.75 (d, J = 8.4 Hz, 2H), 6.24 (d, J = 8.8 Hz, 2H), 3.90 (d, J = 11.6 Hz, 1H), 3.74 (d, J = 11.6 Hz, 1H), 3.09 (s, 1H), 2.08 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 177.8, 143.3, 142.9, 134.1, 129.8, 129.7, 129.5, 128.8, 128.5, 127.9, 126.5, 124.5, 123.9, 115.6, 110.1, 67.9, 65.5, 20.5; HRMS (ESI) *m/z:* $[M+Na]^+$ calcd for $C_{22}H_{20}N_2NaO_2$ 367.1422; found 367.1419.

5-chloro-3-(hydroxymethyl)-3-((4-methoxyphenyl)amino)-1-methylindolin-2-one (5q).



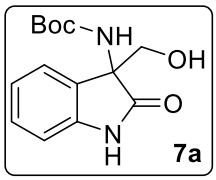
White solid; Yield (305 mg, 92%); mp 119-120 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3350, 3319, 3012, 1725, 1689, 1609; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.37 (dd, J = 8.0, 2.4 Hz, 1H), 7.21 (d, J = 2.4 Hz, 1H), 7.09 (d, J = 8.4 Hz, 1H), 6.54 (d, J = 8.8 Hz, 2H), 6.11 (d, J = 9.2 Hz, 2H), 5.79 (s, 1H), 5.22 (t, J = 5.6 Hz, 1H), 3.77 – 3.66 (m, 2H), 3.55 (s, 3H), 3.18 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 176.7, 152.0, 143.2, 140.2, 132.1, 128.9, 126.9, 124.1, 115.3, 114.8, 110.4, 67.5, 66.7, 55.5, 26.8; HRMS (ESI) *m/z:* $[M+H]^+$ calcd for $C_{17}H_{18}ClN_2O_3$ 333.1006; found 333.1009.

4-((3-(hydroxymethyl)-2-oxoindolin-3-yl)amino)benzonitrile (5r). White solid; Yield (251

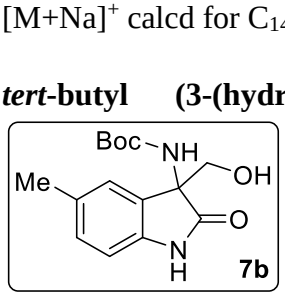


mg, 90%); mp 121-122 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3382, 3319, 3053, 2923, 2242, 1710, 1689, 1602; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.76 (s, 1H), 7.38 (d, J = 8.8 Hz, 2H), 7.29 (t, J = 7.6 Hz, 1H), 7.20 (d, J = 7.2 Hz, 1H), 7.17 (s, 1H), 7.02 – 6.95 (m, 2H), 6.31 (d, J = 8.8 Hz, 2H), 5.32 (t, J = 6.0 Hz, 1H), 3.83 – 3.70 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 178.5, 144.4, 142.4, 130.3, 129.5, 128.9, 125.6, 124.4, 121.9, 113.9, 110.0, 67.8, 66.3, 20.4; HRMS (ESI) *m/z:* $[M+Na]^+$ calcd for $C_{16}H_{13}N_3NaO_2$ 302.0905; found 302.0903.

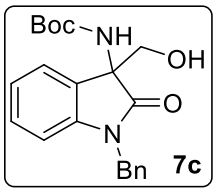
***tert*-butyl (3-(hydroxymethyl)-2-oxoindolin-3-yl)carbamate (7a).** Colorless solid; Yield (120 mg, 86%); mp 185-186 °C; The title compound is prepared according to the general procedure (C) described as above; FT-IR (KBr, cm^{-1}) 3645, 3418, 2979, 1712, 1623, 1255, 1166, 1077; ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 10.06 (s, 1H), 7.17 – 7.11 (m, 2H), 6.93 (t, J = 7.6 Hz, 1H), 6.79 (d, J = 7.6 Hz, 1H), 5.42 (s, 1H), 3.67 – 3.53 (m, 2H), 1.13 (s, 9H).; ^{13}C{^{1}H} NMR (100 MHz, methanol-d_4) δ (ppm): 178.8, 155.0, 141.8, 130.3, 128.5, 122.9, 122.1, 109.7, 80.3, 65.3, 63.9, 27.0. HRMS (ESI) *m/z:* $[M+Na]^+$ calcd for $C_{14}H_{18}N_2NaO_4$ 301.1164; found 301.1169.



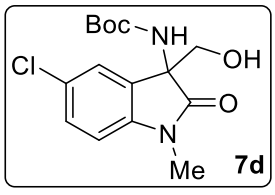
***tert*-butyl (3-(hydroxymethyl)-5-methyl-2-oxoindolin-3-yl)carbamate (7b).** Colorless semisolid; Yield (127 mg, 87%); The title compound is prepared according to the general procedure (C) described as above; FT-IR (KBr, cm^{-1}) 3644, 3402, 2981, 1711, 1613, 1251, 1156, 1076; ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 10.08 (s, 1H), 7.11 (s, 1H), 7.07 (d, J = 7.6 Hz, 1H), 6.80 (d, J = 7.6 Hz, 1H), 5.51 (s, 1H), 3.82 – 3.64 (m, 2H), 2.32 (s, 3H), 1.27 (s, 9H).; ^{13}C{^{1}H} NMR (100 MHz, methanol-d_4) δ (ppm): 178.7, 155.0, 139.3, 131.7, 130.4, 128.8, 123.7, 109.5, 80.1, 65.4, 63.9, 27.1, 19.9. HRMS (ESI) *m/z:* $[M+Na]^+$ calcd for $C_{15}H_{20}N_2NaO_4$ 315.1321; found 315.1323.



***tert*-butyl (1-benzyl-3-(hydroxymethyl)-2-oxoindolin-3-yl)carbamate (7c).**[17] Colorless semisolid; Yield (175 mg, 95%); The title compound is prepared according to the general procedure (C) described as above; FT-IR (KBr, cm^{-1}) 3433, 2256, 1654, 1648, 1166, 1048, 1025; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.51 (s, 1H), 7.43 (d, J = 7.2 Hz, 2H), 7.31 – 7.20 (m, 4H), 7.15 (s, 1H), 6.99 (s, 1H), 6.69 (s, 1H), 5.29 – 4.45 (m, 3H), 3.76 – 3.61 (m, 2H), 1.31 (s, 6H), 0.95 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ (ppm): 176.0, 154.2, 143.7, 136.9, 130.7, 128.8, 128.5, 127.6, 127.5, 123.0, 122.3, 108.8, 79.1, 65.8, 63.5, 43.3, 28.5.

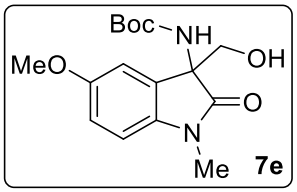


***tert*-butyl (5-chloro-3-(hydroxymethyl)-1-methyl-2-oxoindolin-3-yl)carbamate (7d).**[17] Colorless semisolid; Yield (152 mg, 93%); The title compound is prepared according to the general procedure (C) described as above; FT-IR (KBr, cm^{-1}) 3432, 2256, 1654, 1647, 1165, 1047, 1025; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.54 (s, 1H), 7.37 (d, J = 7.6 Hz, 1H), 7.25 (s, 1H), 7.02 (d, J = 8.4 Hz, 1H), 5.12 (s, 1H), 3.75 – 3.54 (m, 2H), 3.15 (s, 3H), 1.32 (s, 6H), 1.04



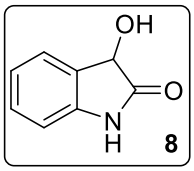
(s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 175.5, 154.1, 143.6, 132.8, 128.4, 126.3, 123.1, 109.7, 79.2, 65.4, 63.6, 28.4, 26.7.

***tert*-butyl (3-(hydroxymethyl)-5-methoxy-1-methyl-2-oxoindolin-3-yl)carbamate (7e).**[17]



White solid; mp 174 – 175 °C; Yield (146 mg, 91%); The title compound is prepared according to the general procedure (C) described as above; FT-IR (KBr, cm^{-1}) 3434, 2256, 1647, 1654, 1165, 1047, 1025; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.39 (s, 1H), 6.92 – 6.82 (m, 3H), 5.03 (s, 1H), 3.77 (s, 3H), 3.70 – 3.50 (m, 2H), 3.12 (s, 3H), 1.32 (s, 6H), 1.03 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 175.4, 155.6, 154.1, 138.1, 131.9, 112.5, 110.7, 108.5, 78.9, 65.6, 63.8, 55.9, 28.4, 26.6.

3-hydroxyindolin-2-one (**8**).[32] White solid; Yield (144 mg, 97%); mp 165-166 °C; The title compound is prepared according to the procedure (C) described as above; FT-IR (KBr, cm^{-1}) 3440, 3350, 3051, 2923, 1710, 1635, 1480; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.27 (s, 1H), 7.33 (d, J = 7.2 Hz, 1H), 7.26 (t, J = 7.6 Hz, 1H), 7.01 (t, J = 7.6 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.21 (d, J = 7.6 Hz, 1H), 4.88 (d, J = 7.6 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 178.6, 142.3, 129.6, 129.5, 125.3, 122.3, 110.2, 69.6.



3.6. References

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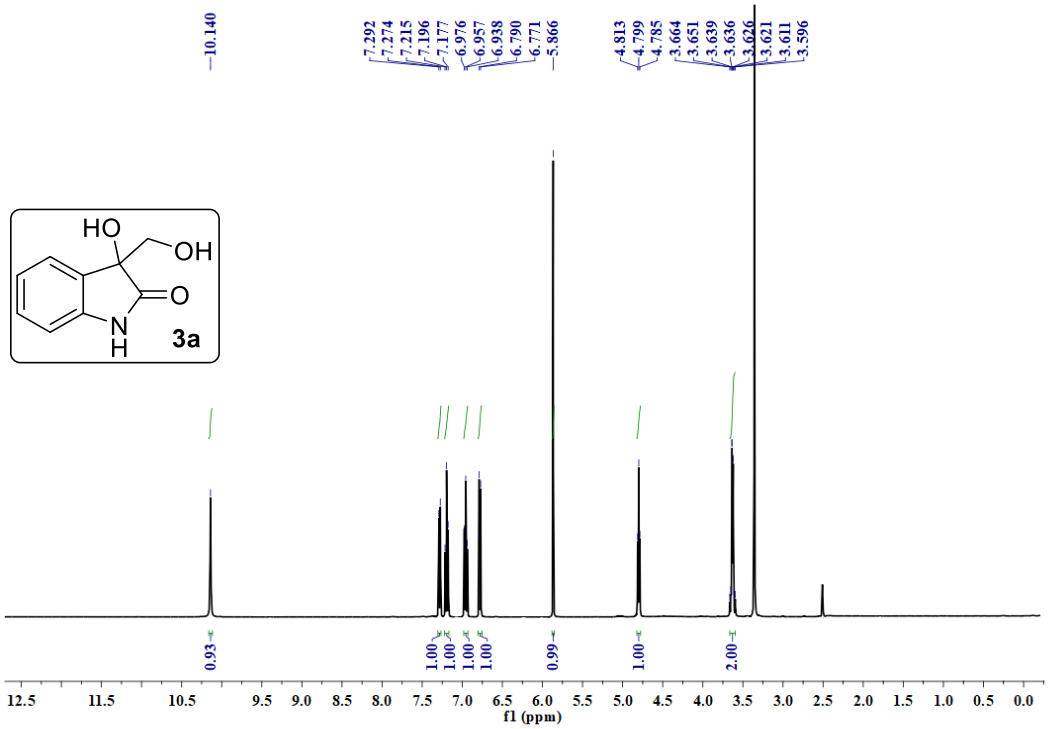
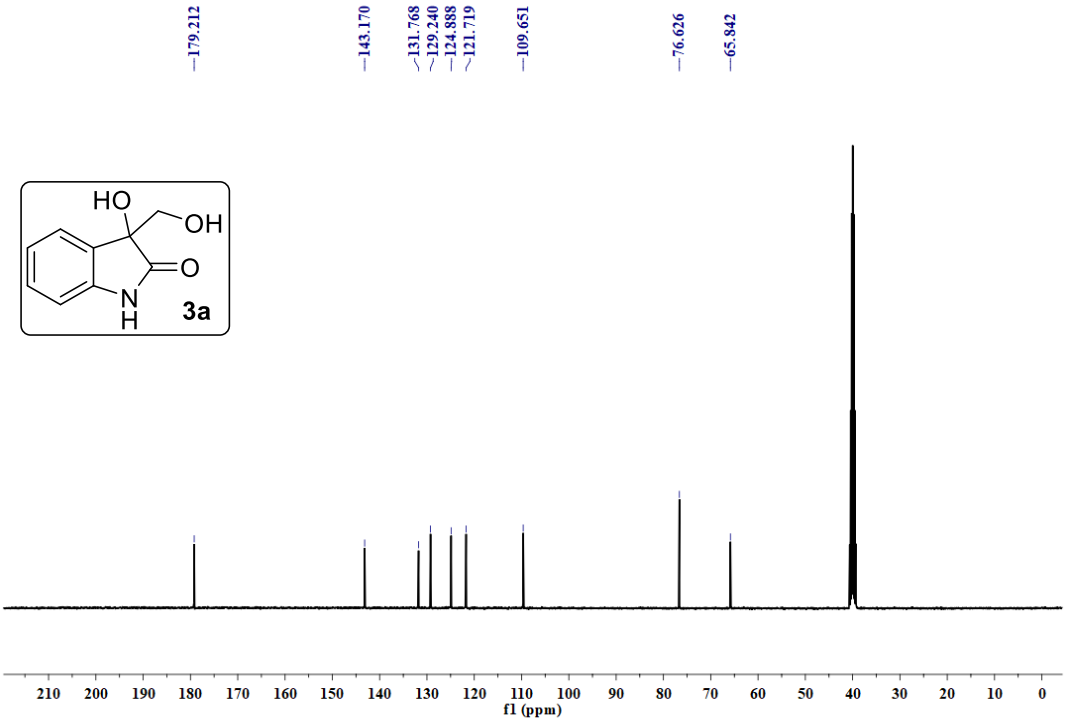
3.7. Selected NMR (^{1}H & ^{13}C) and HRMS spectra

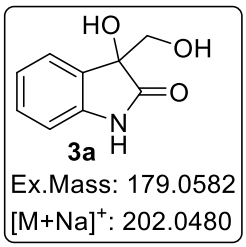
^{1}H NMR (400 MHz, DMSO-*d*$_6$) spectrum of 3-hydroxy-3-(hydroxymethyl)indolin-2-one (3a)

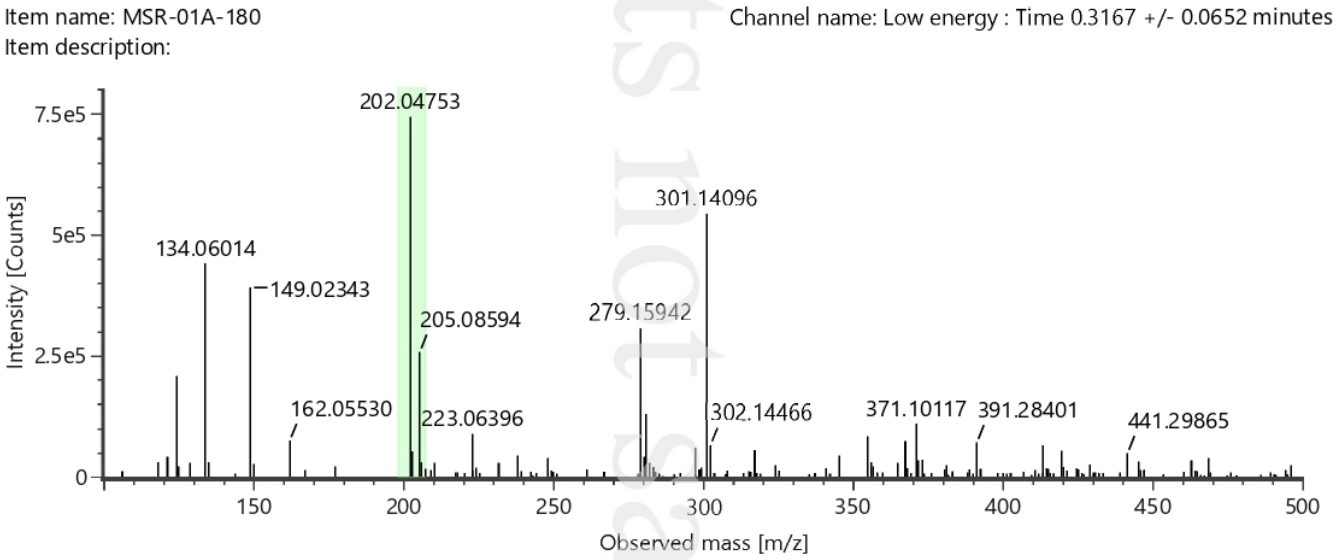


^{13}C{^{1}H} NMR (100 MHz, DMSO-*d*$_6$) spectrum of 3-hydroxy-3-(hydroxymethyl)indolin-2-one (3a)

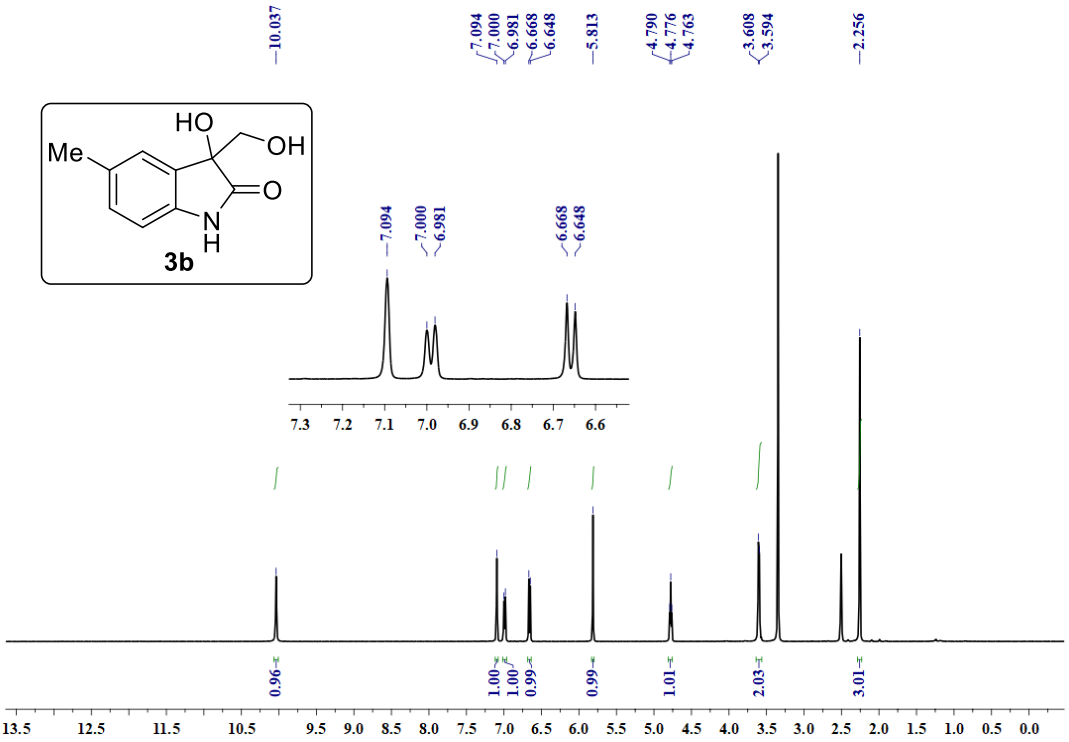


HRMS of 3-hydroxy-3-(hydroxymethyl)indolin-2-one (3a)

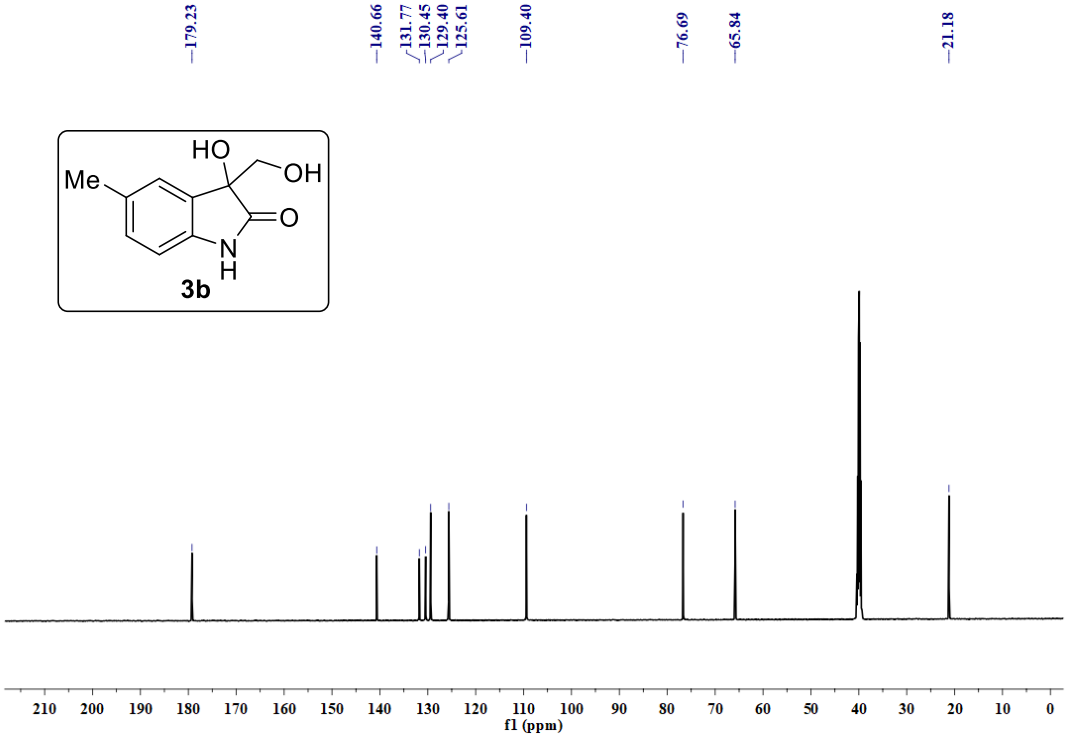




^{1}H NMR (400 MHz, DMSO-d_6) spectrum of 3-hydroxy-3-(hydroxymethyl)-5-methylindolin-2-one (3b)

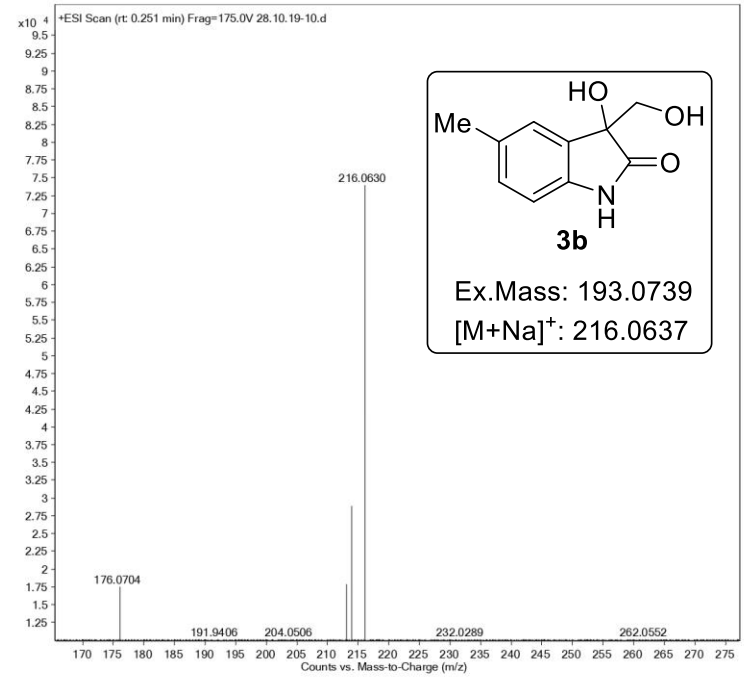


^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) spectrum of 3-hydroxy-3-(hydroxymethyl)-5-methylindolin-2-one (3b)

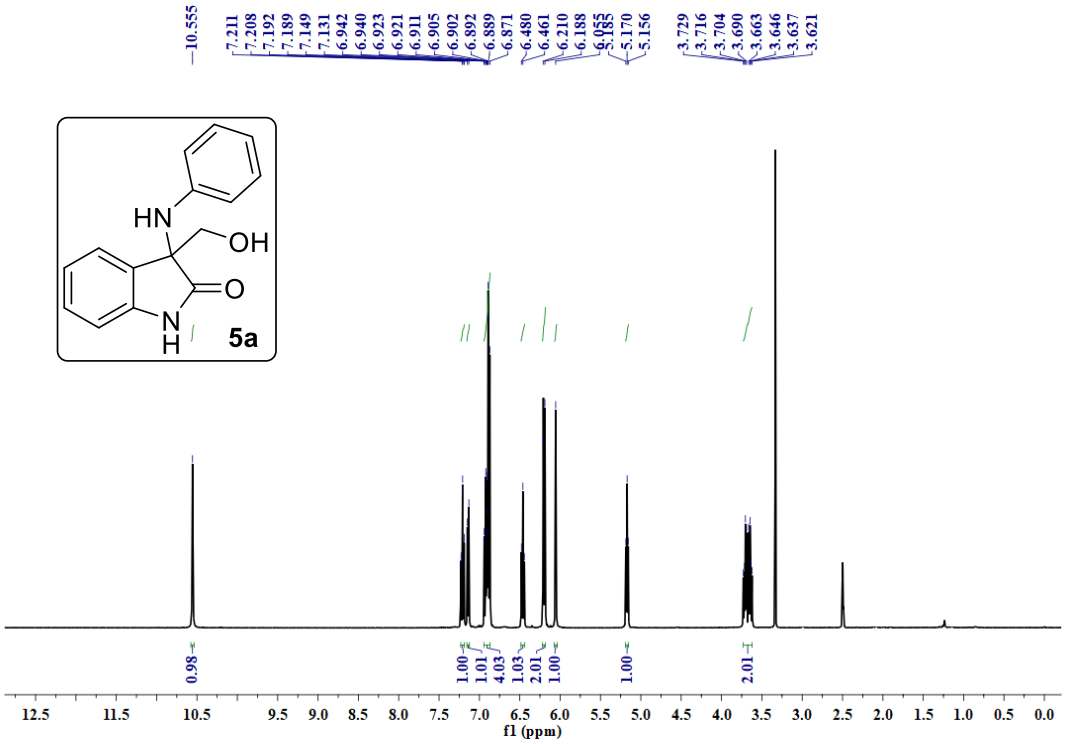


HRMS of 3-hydroxy-3-(hydroxymethyl)-5-methylindolin-2-one (3b)

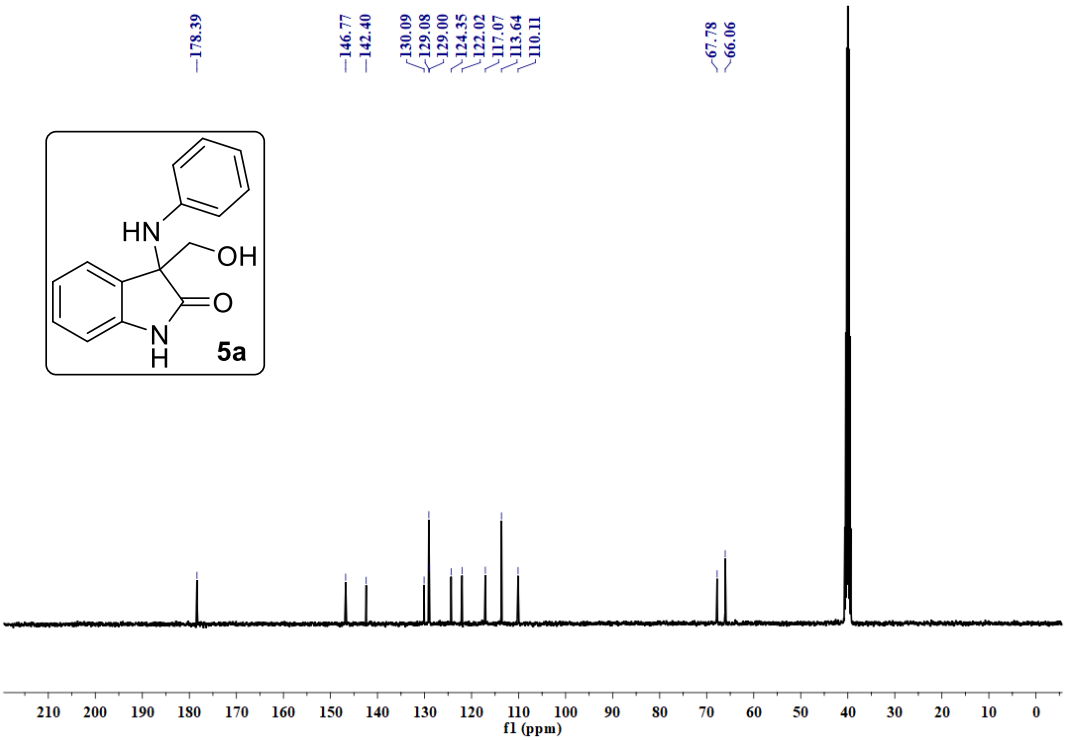
Sample Name	gsp 9	**Position**	P1-B1	**Instrument Name**	Instrument 1
User Name		**Inj Vol**	2	**InjPosition**	
Sample Type	Sample	**IRM Calibration Status**	Success	**Data Filename**	28.10.19-10.d
ACQ Method	srinu.m	**Comment**		**Acquired Time**	28-Oct-19 3:03:36 PM



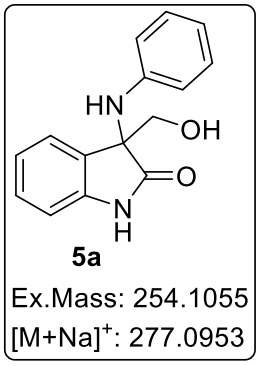
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of 3-(hydroxymethyl)-3-(phenylamino)indolin-2-one (5a)



^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) spectrum of 3-(hydroxymethyl)-3-(phenylamino)indolin-2-one (5a)



HRMS of 3-(hydroxymethyl)-3-(phenylamino)indolin-2-one (5a)



5a

Ex.Mass: 254.1055

$[M+Na]^+$: 277.0953

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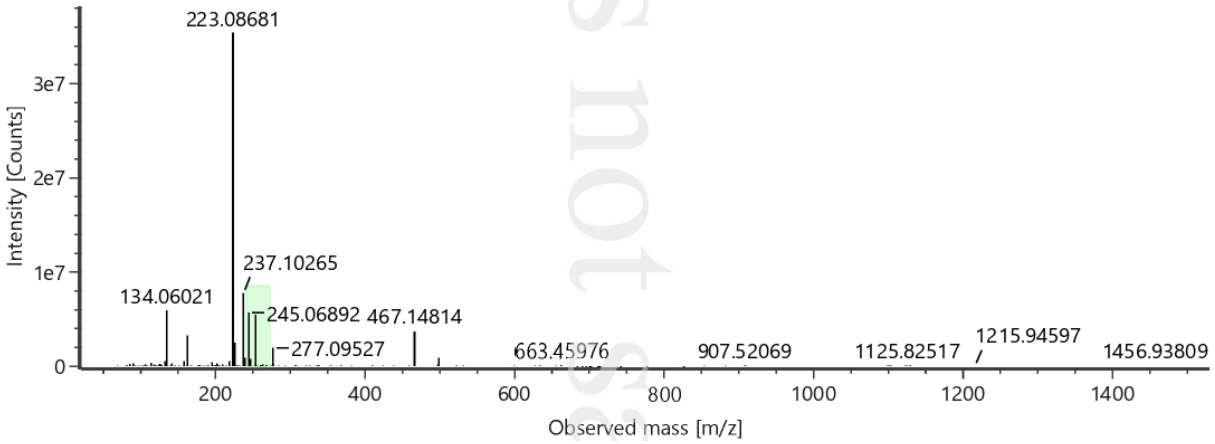
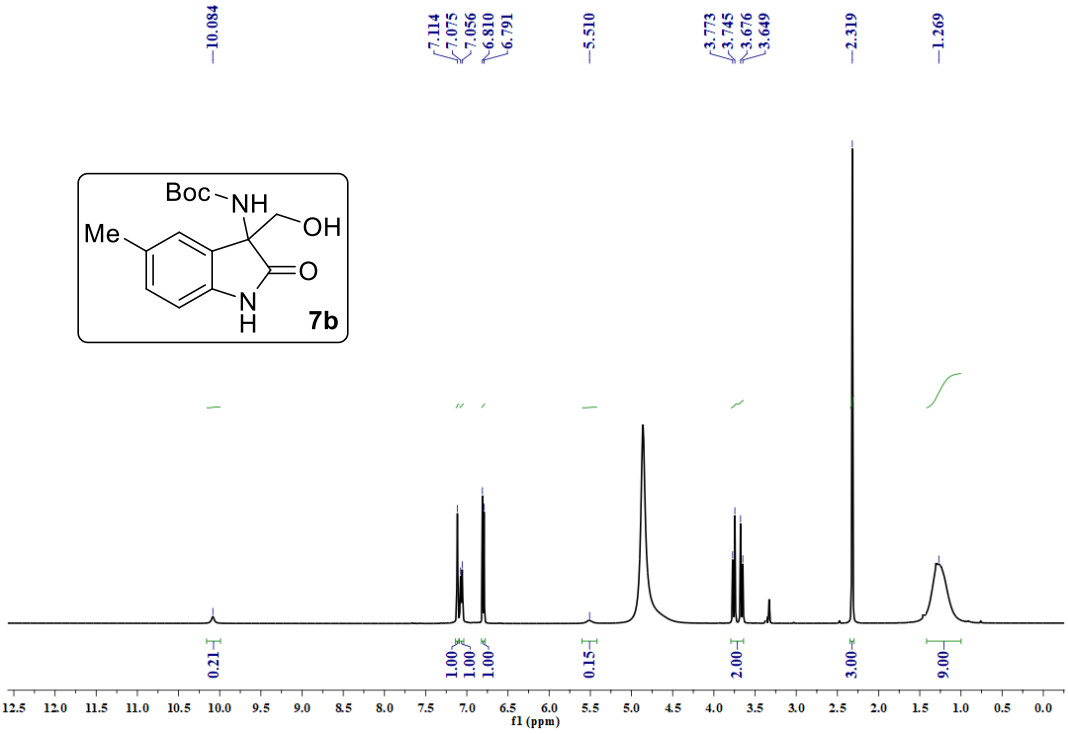
Item description:

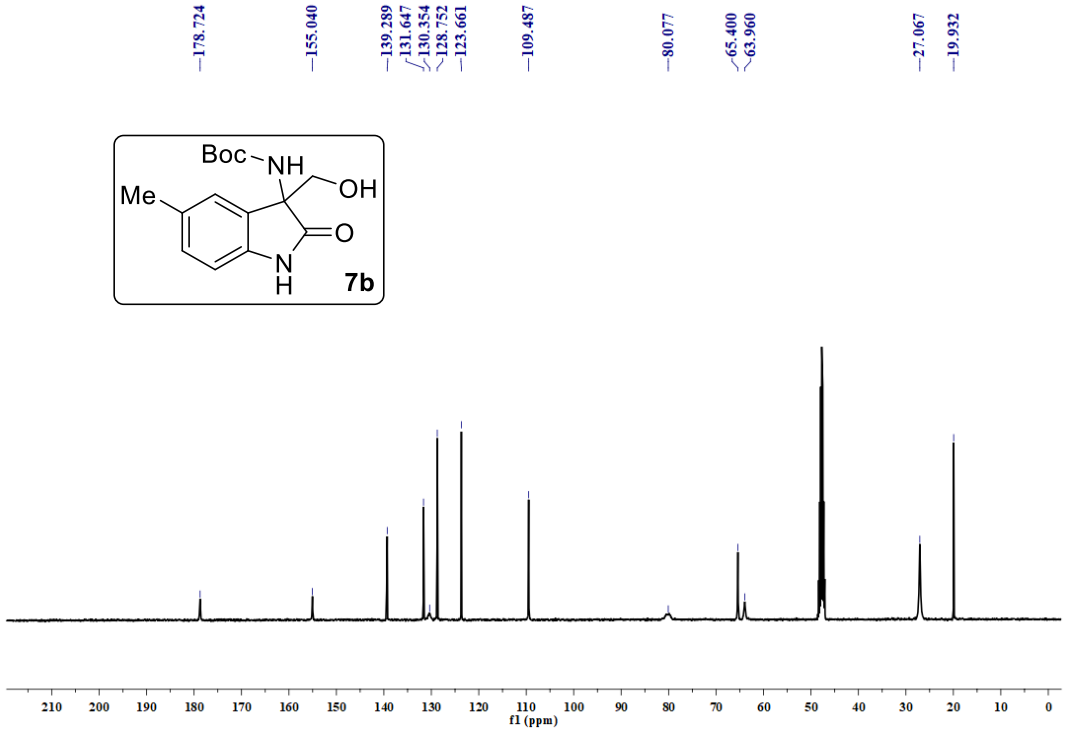
Channel name: Low energy : Time 0.3141 +/- 0.0655 minutes



^{1}H NMR (400 MHz, methanol-d_4) spectrum of *tert*-butyl (3-(hydroxymethyl)-5-methyl-2-oxoindolin-3-yl)carbamate (7b)



^{13}C{^{1}H} NMR (100 MHz, methanol-d_4) spectrum of *tert*-butyl (3-(hydroxymethyl)-5-methyl-2-oxoindolin-3-yl)carbamate (7b)



HRMS of *tert*-butyl (3-(hydroxymethyl)-5-methyl-2-oxoindolin-3-yl)carbamate (7b)

Sample Name	5-meinbocisrgn	**Position**	P1-F5	**Instrument Name**	Instrument 1
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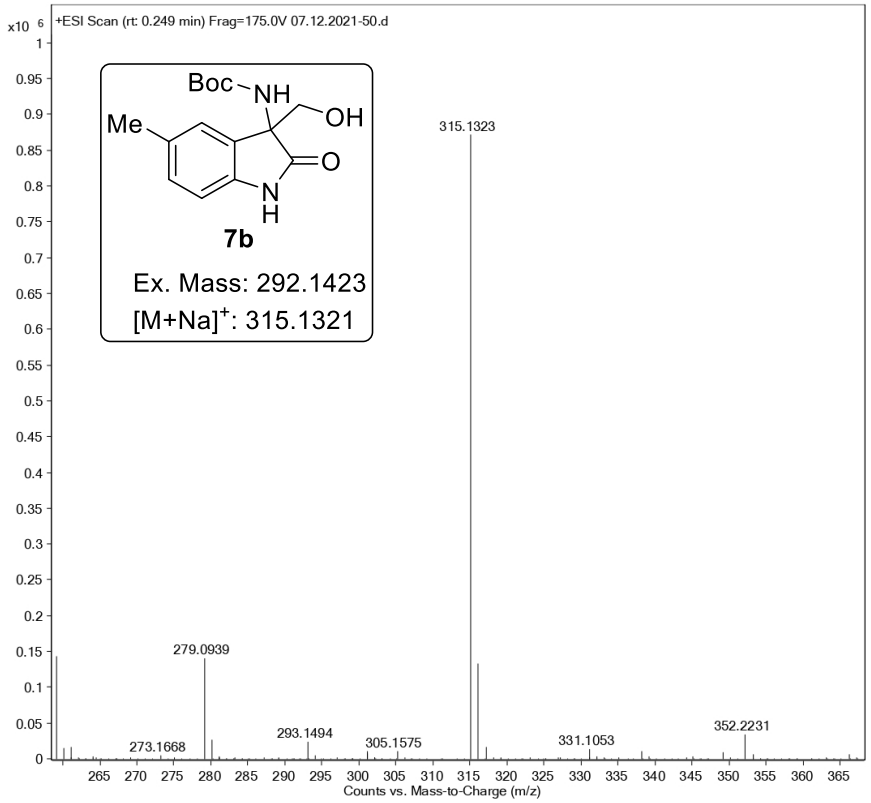
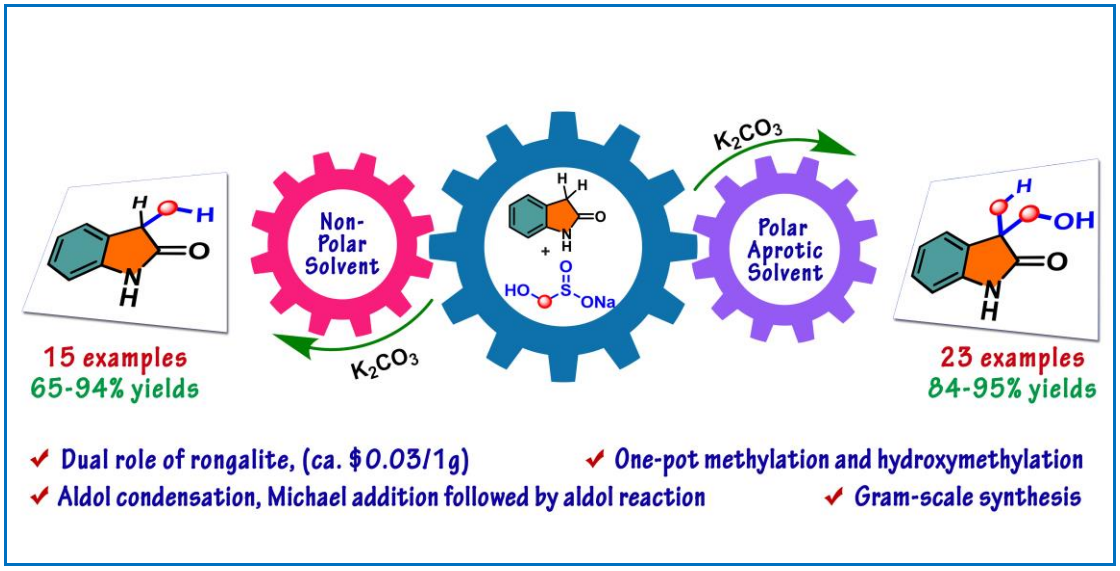
ACQ Method	NITW-W.m	**Comment**		**Acquired Time**	07-Dec-21 8:31:55 PM



CHAPTER-IV

Functionalization of 2-Oxindoles via Sequential Aldol and Reductive Aldol Reactions Using Rongalite as Double C1 Source



4.1. Introduction

Oxindole moieties are found in many plants and the first oxindole was extracted from the bark of Cat claw's plant, which is located at the central and southern parts of tropical zones of South America.[1] Oxindoles are ubiquitous motifs in bioactive natural products and pharmaceutical lead compounds,[2-6] and have drawn attention of synthetic community to develop novel 2-oxindole scaffolds with pharmacological properties.[7-13]

Among 2-oxindoles, 3-methyl-2-oxindoles and 3-(hydroxymethyl)-3-methyl-2-oxindoles are used as synthetic precursors for the total synthesis of (–)-physostigmine, which is isolated from the *Physostigma venenosum* seeds in 1864 (Figure 4.1).[14] It acts as acetylcholinesterase inhibitor,[15] and also used for glaucoma, atropine, myasthenia gravis and also works as an antidote against organophosphorous poisoning. Also, it is employed for the relief of intoxication induced by overdoses of benzodiazepines, antihistamines, antidepressants and antipsychotics.[16] Now, the analogues of this alkaloid are attracted the chemical biologists owing its improved pharmacological activities towards the Alzheimer's disease.[17] Interestingly, the (−)-physostigmine is 1000 times more potent than (+)-physostigmine. Moreover, metabolite of (−)-physostigmine is (−)-eseroline, which has a potent analgesic effect similar to that of morphine.[18]

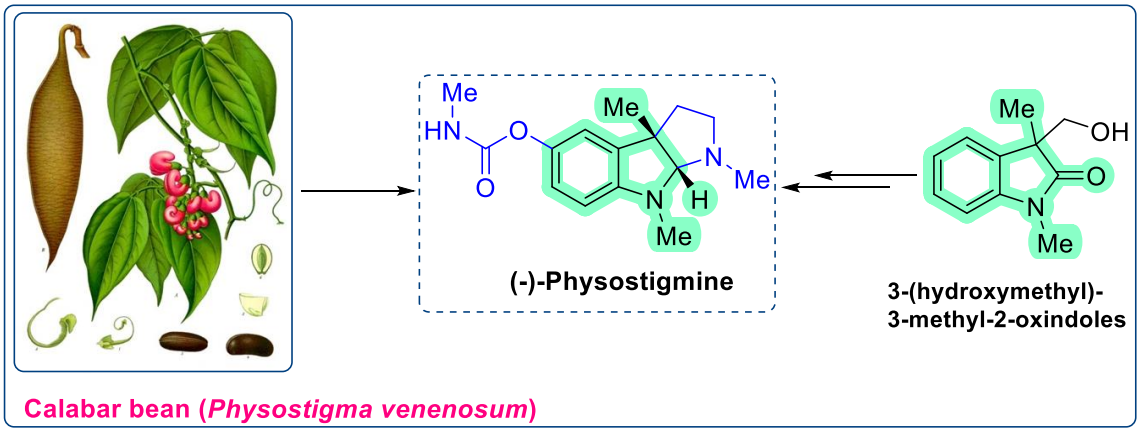
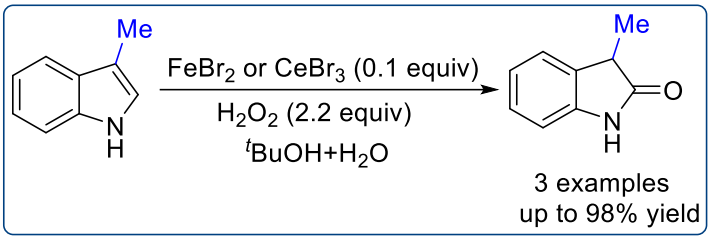


Figure 4.1

In addition to synthetic precursors to natural alkaloids, the 3-methyl-2-oxindoles are also versatile reactants for the synthesis of functionalized oxindoles such as C3-trifluoromethylated oxindoles,[19] fluorinated oxindoles,[20] 3-aryloxindoles,[21] unsymmetrical 3-thiooxindoles,[22] 3-azido indolenines,[23] benzolactams/chromones,[24] noncanonical amino acids from L-serine,[25] 3-amino-2-oxindoles[26] and 3-thiocyanated-2-oxindoles.[27]

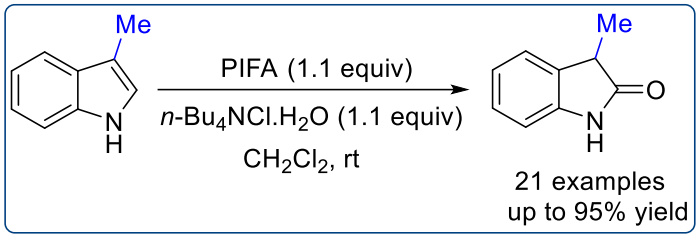
4.1.1. Previous reports for the synthesis of 3-methylindolin-2-ones and 3-(hydroxymethyl)-3-methylindolin-2-ones

Tong and co-workers developed a Fenton-bromide catalytic system for the synthesis of 3-methyl-2-oxindoles. They used a combination of $FeBr_2/CeBr_3$ and H_2O_2 to produce *in situ* reactive bromine species (RBS) i.e., hypobromous acid (HOBr) or bromine, which is used in the oxidative rearrangement of indoles to 2-oxindoles in a mixture of ^tBuOH and H_2O at room temperature (Scheme 4.1).[28]



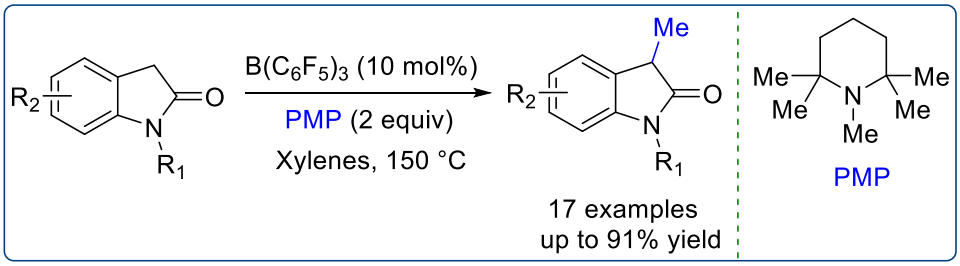
Scheme 4.1

Liang et al. reported a protocol for the synthesis of 3-methyl-2-oxindoles *via* oxidative rearrangement of indoles to 2-oxindoles using hypochlorous acid, which is generated *in situ* from the mixture of (bis(trifluoroacetoxy)iodo)benzene (PIFA) and n-$Bu_4NCl.H_2O$ in CH_2Cl_2 solvent at room temperature in open air. This methodology offers the synthesis of wide range of 3-methyl-2-oxindoles with 64-95% yields (Scheme 4.2).[29]



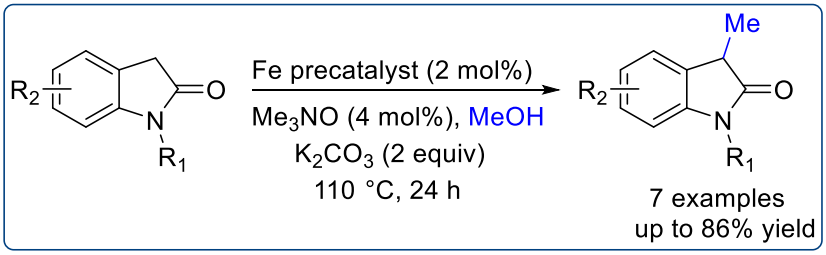
Scheme 4.2

Pulis and co-workers described a borrowing hydrogen approach for the 3-methyaltion of 2-oxindoles to synthesize 3-methyl-2-oxindoles by employing triaryl borane like, $B(C_6F_5)_3$ as a catalyst and amine like pempidine as a methylating source in xylenes solvent at 150 °C. It requires higher temperatures and affording less percentage of yields in case of *N*-unsubstituted oxindoles (scheme 4.3).[30]



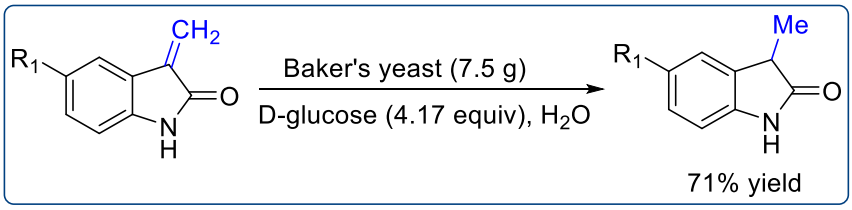
Scheme 4.3

Polidano et al. developed a borrowing hydrogen approach for the synthesis of 3-methyl-2-oxindoles from 2-oxindoles using Knölker-type (cyclopentadienone) iron carbonyl as a precatalyst in the presence of trimethylamine *N*-oxide as an activator and K_2CO_3 as a base in methanol solvent at 110 °C for 24 h. Here, methanol acts as a solvent and as well as a C1 unit source (Scheme 4.4).[31]



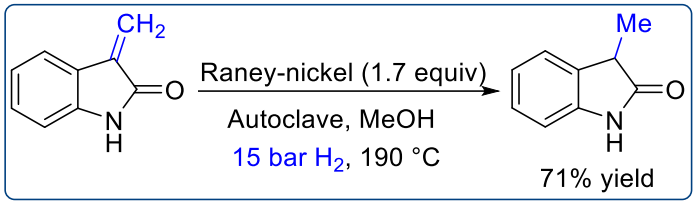
Scheme 4.4

Sacchetti and co-workers described the bio-catalyzed olefin reduction of 3-methylidene-2-oxinodole for the synthesis of 3-methyl-2-oxindole, using fresh dried baker's yeast with D-glucose and water in thermo-shaker for 2 days at 40 °C. This protocol offers the 3-methyl-2-oxindole with 71% yield (Scheme 4.5).[32]



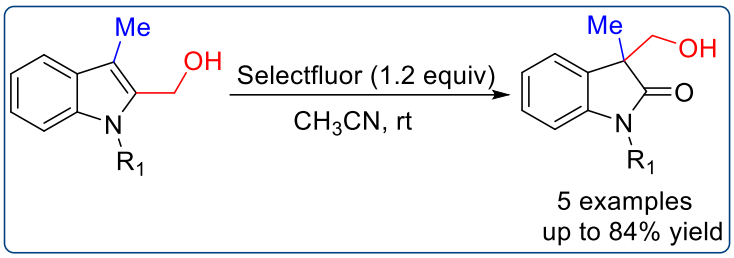
Scheme 4.5

Volk et al. developed a hydrogenation protocol for the synthesis of 3-methyl-2-oxindole using isatin and methanol by employing Raney-nickel as a catalyst with 15 bar hydrogen gas at 190 °C in an autoclave for 2 h. This protocol is a one-pot multistep synthesis and offers the 3-methyl-2-oxindole with 71% yield. (Scheme 4.6).[33]



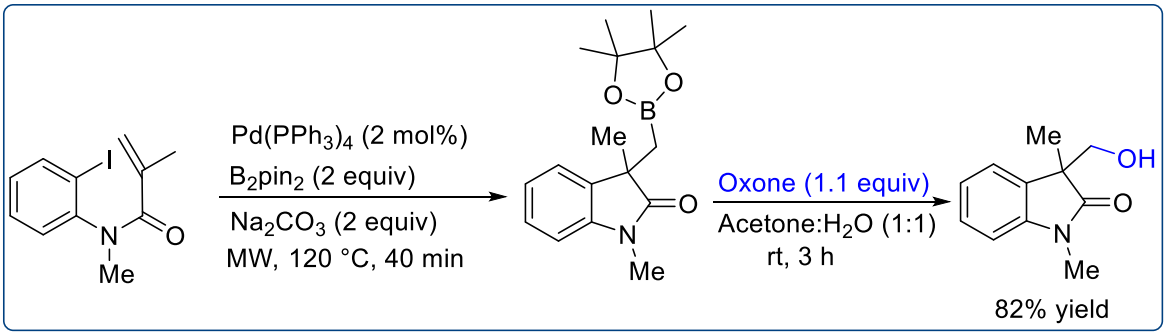
Scheme 4.6

Jiang and co-workers developed a protocol for the synthesis of 3-(hydroxymethyl)-3-methyl-2-oxindoles *via* iminium ion-intermediate triggered 1,2-rearrangement of pre-functionalized indoles using selectfluor in acetonitrile (CH_3CN) solvent at room temperature. This protocol requires small amount of water for oxidation (Scheme 4.7).[34]



Scheme 4.7

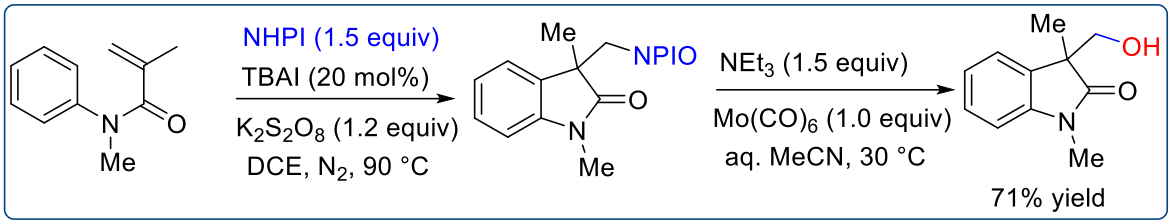
Van der Eycken and co-workers reported a palladium catalyzed domino Heck/borylation strategy to prepare indolinone-3-methyl boronic esters using B_2pin_2 from *N*-aryl acrylamides under microwave irradiation at 120 °C for 40 min. Later, they extended this protocol to prepare 3-(hydroxymethyl)-3-methyl-2-oxindoles promoted by oxone in a mixture of acetone and water at ambient temperature (Scheme 4.8).[35]



Scheme 4.8

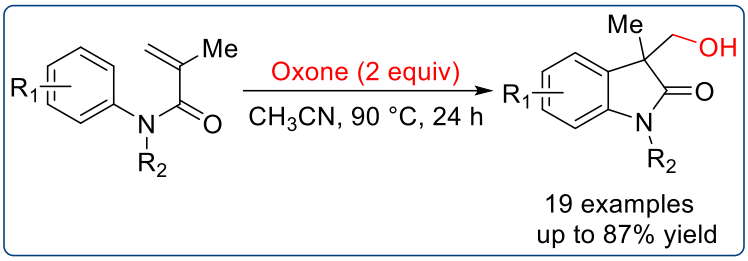
Luo et al. described the aminooxyarylation of *N*-aryl acrylamides using *N*-hydroxyphthalimide (NHPI) in the presence of catalytic amount of TBAI and potassium persulfate in DCE under N_2 at 90 °C. Later, this protocol is extended to prepare 3-(hydroxymethyl)-3-methyl-2-oxindoles

with the help of triethylamine (NEt_3) and $Mo(CO)_6$ in aq. CH_3CN at 30 °C for 12 h (Scheme 4.9).[36]



Scheme 4.9

Zhang and co-workers reported an arylhydroxylation protocol to synthesize 3-(hydroxymethyl)-3-methyl-2-oxindoles from *N*-arylacrylamides. This protocol involves the cascade epoxidation and Friedel-Crafts alkylation of activated alkenes induced by oxone in acetonitrile (CH_3CN) solvent at 90 °C for 24 h. Here, oxone acts as an oxidizing agent and also acts as a proton source (Scheme 4.10).[37]

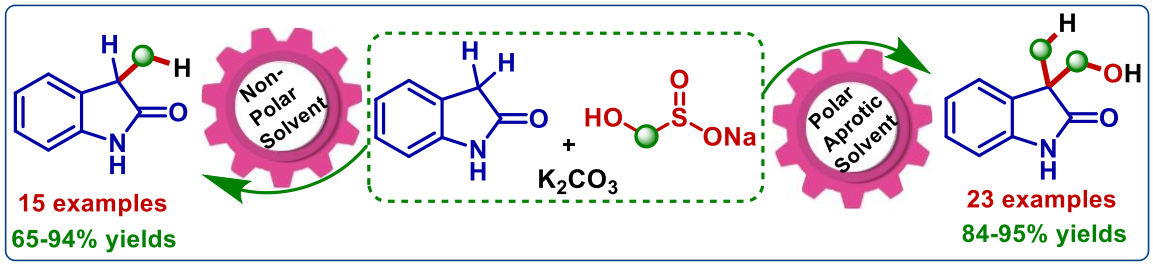


Scheme 4.10

The strategies available for the synthesis of 3-methyl-2-oxindoles include, the olefin hydrocarbamoylation, Friedel-Crafts alkylation, borrowing hydrogen approach, various reducing and oxidizing reagents, but these methods suffer with its own set of limitations such as formation of side products, poor regioselectivity, expensive chemicals, transition metal catalysts, long reaction times, high reaction temperatures and limited substrate scope. Also, the methods developed for the 3-(hydroxymethyl)-3-methyl-2-oxindoles include, domino Heck/borylation, aminooxyarylation of *N*-arylacrylamides, but these two methods require one more step to get the hydroxylated products. Along with, oxidative rearrangement of indoles and arylhydroxylation of *N*-arylacrylamides are reported, albeit these protocols require pre-functionalized indoles and suffers from regioselectivity. To overcome all the problems associated with the previous reports, we planned to develop an efficient method for the construction of 3-methyl-2-oxindoles and 3-(hydroxymethyl)-3-methyl-2-oxindoles from 2-oxindoles.

4.2. Present study

In light of the significance of the 3-methyl-2-oxindoles and 3-(hydroxymethyl)-3-methyl-2-oxindoles in organic and natural product synthesis, we have developed a one-pot methylation and hydroxymethylation protocol from 2-oxindoles using multifaceted reagent rongalite. Here, rongalite acts as a hydride-free reducing agent and a source of double C1 unit donor. This protocol is consisting of sequential classical aldol condensation, Michael addition followed by aldol reaction. This transition metal and hydride-free strategy allows the rapid synthesis of 3-methylindoline-2-ones and 3-(hydroxymethyl)-3-methylindolin-2-ones with 65-95% yields. Also, this protocol enables the gram-scale synthesis. In this protocol, we achieved the two classes of products selectively *via* changing the medium of the reaction. A graphical abstract is shown in the Scheme 4.11.



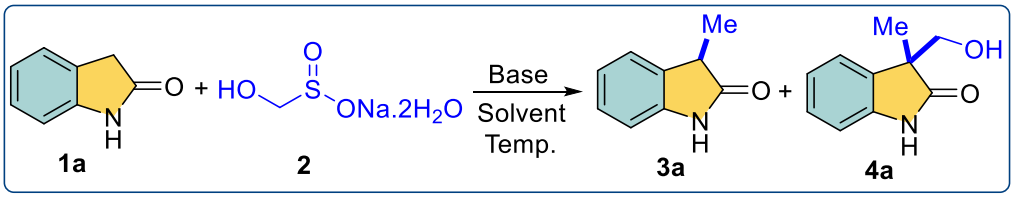
Scheme 4.11. Synthesis of 3-methyl-2-oxindoles and 3-(hydroxymethyl)-3-methyl-2-oxindoles

4.2.1. Results and discussion

To test our hypothesis, indolin-2-one **1a** (1 mmol) was attempted to react with rongalite **2** (2 mmol) and K_2CO_3 (2 mmol) in EtOH+H_2O (8:2 v/v) at room temperature and observed that there is no progress in the reaction even after 24 h (Table 4.1, entry 1). Later, same reaction was carried out at 80 °C, which interestingly resulted in a mixture of two products i.e., 3-methylindolin-2-one **3a** and 3-(hydroxymethyl)-3-methylindolin-2-one **4a** with 40% and 20% yields, respectively (Table 4.1, entry 2), which were later confirmed by ^{1}H, ^{13}C NMR and HRMS data.

Inspired by this preliminary result, further screening was carried out in polar protic solvents such as aq. MeOH and aq. *i*-PrOH resulted in mixture of products **3a** and **4a** (Table 4.1, entries 3-4). Further, tested the reaction in chlorinated solvents such as aq. $CHCl_3$ and aq. 1,2-DCE acquired **3a** predominantly albeit got less yields (Table 4.1, entries 5-6). This result provoked us to test the effect of non-polar solvents on product selectivity.

Table 4.1 Optimization of reaction conditions[a]



Entry	Solvent (8:2 v/v)	Rongalite (equiv)	Base (equiv)	Temp. (°C)	Time (h)	Yield (%)[b] **3a**	**4a**
1	EtOH+H_2O	2	K_2CO_3 (2)	rt	24	n.r.	n.r.
2	EtOH+H_2O	2	K_2CO_3 (2)	80	6	40	20
3	MeOH+H_2O	2	K_2CO_3 (2)	65	6	49	16
4	*i*-PrOH++H_2O	2	K_2CO_3 (2)	80	6	40	17
5	$CHCl_3$+H_2O	2	K_2CO_3 (2)	60	6	45	0
6	1,2-DCE+H_2O	2	K_2CO_3 (2)	80	6	60	0
7	Benzene+H_2O	2	K_2CO_3 (2)	80	6	55	10
8	*p*-Xylene+H_2O	2	K_2CO_3 (2)	80	1	70	5
9	Toluene+H_2O	2	K_2CO_3 (2)	80	1	81	0
10	Toluene+H_2O	2	K_2CO_3 (2)	90	1	85	0
11	**Toluene+H_2O**	**2**	**K_2CO_3 (2)**	**100**	**1**	**94**	**0**
12	Toluene+H_2O	2	K_2CO_3 (2)	110	1	94	0
13	Toluene+H_2O	2	K_2CO_3 (2)	100	6	94	0
14	Toluene+H_2O	3	K_2CO_3 (2)	100	1	94	0
15	Acetone+H_2O	2	K_2CO_3 (2)	55	6	30	10
16	THF+H_2O	2	K_2CO_3 (2)	60	6	5	0
17	CH_3CN+H_2O	2	K_2CO_3 (2)	80	6	40	15
18	DMF	2	K_2CO_3 (2)	80	6	35	43
19	DMSO	2	K_2CO_3 (2)	80	6	35	59
20	DMSO	2.5	K_2CO_3 (2.5)	80	6	14	81
21	**DMSO**	**3**	**K_2CO_3 (2.5)**	**80**	**5**	**0**	**91**
22	DMSO	3	K_2CO_3 (2.5)	70	6	trace	85
23	DMSO	3.5	K_2CO_3 (2.5)	80	5	0	91
24	DMSO	3	DBU (2.5)	80	6	0	79
25	DMSO	3	4-DMAP (2.5)	80	6	0	51
26	DMSO	3	Cs_2CO_3 (2.5)	80	6	0	80
27	DMSO	3	KOH (2.5)	80	6	0	85
28[c]	DMSO	--	K_2CO_3 (2)	80	6	--	n.r.

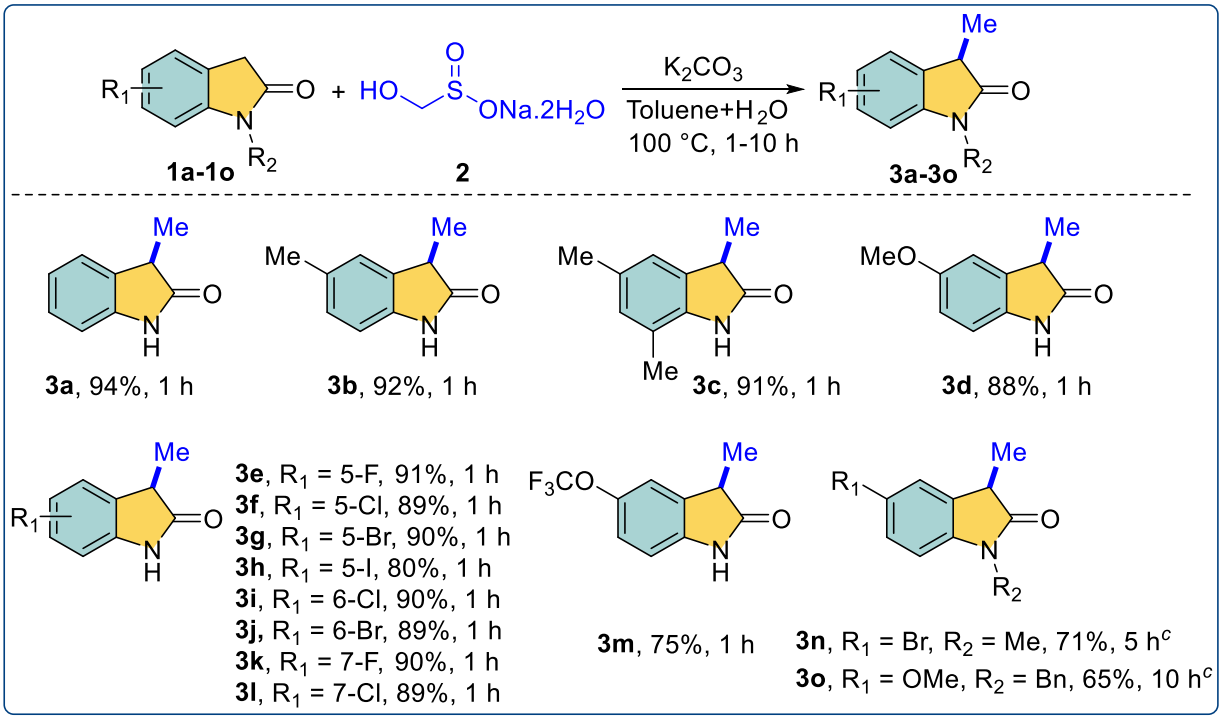
[a]Reaction conditions: indolin-2-one **1a** (1 mmol), rongalite **2** and base in different reaction media at different temperatures. [b]Yields of isolated products. [c]3-Methylindolin-2-one **3a** (1 mmol) and K_2CO_3 (2 equiv) in DMSO at 80 °C. rt = room temperature. n.r. = no reaction.

Thus, same reaction was conducted in non-polar solvents such as aq. benzene, aq. *p*-xylene and aq. toluene. To our delight, as we go from aq. benzene to aq. *p*-xylene, the yield of **3a** is increased while that of **4a** is decreased (Table 4.1, entries 7-8). When aq. toluene is used, 3-methylindolin-2-one **3a** obtained predominantly with 81% yield within 1 h without forming any trace amounts of **4a** (Table 4.1, entry 9). Further, increments in temperatures led to improved yields (Table 4.1, entries 10-12). Notably, prolonging the reaction time and increasing the equiv of rongalite did not affect the product yield **3a** (Table 4.1, entries 13-14).

Later, we shifted our attention towards the synthesis of **4a** selectively. In this regard, screening was done in polar aprotic solvents such as aq. acetone, aq. THF, aq. CH_3CN, DMF and DMSO (Table 4.1, entries 15-19). Among all, good amount of **4a** is observed in DMSO (Table 4.1, entry 19). With this promising result, next we screened the equiv of rongalite and base and acquired **4a** predominantly (Table 4.1, entries 20-21). Further, variants in temperature and loadings of rongalite were not useful (Table 4.1, entry 22-23). Moreover, we tested the reaction with organic and inorganic bases and got inferior results (Table 4.1 entries 24-27). Also, to identify the source of C1 unit in **4a**, a test reaction was conducted on 3-methylindolin-2-one **3a** with K_2CO_3 and DMSO at 80 °C in the absence of rongalite but they were found to be unreactive (Table 4.1, entry 28). This result clearly indicates that the C1 unit is coming from rongalite and not from the DMSO solvent. Therefore, the optimized reaction conditions are entry 11 and entry 21 for obtaining 3-methylindolin-2-one **3a** and 3-(hydroxymethyl)-3-methylindolin-2-one **4a** respectively.

With the optimized reaction conditions in hand for compound **3a** (Table 4.1, entry 11), we commenced to evaluate the scope of the reaction with various 2-oxindoles (Table 4.2). Electron-donating groups on benzene ring of 2-oxindole such as methyl and methoxy underwent reaction smoothly with rongalite to furnish **3b**-**3d** in 88-92% yields (Table 4.2). Halogens (–F, –Cl, –Br and –I) present on various positions of benzene ring of oxindoles readily participated in the reaction to produce **3e**-**3l** in 80-91% yields (Table 4.2). Electron-withdrawing group on benzene ring i.e., trifluoromethoxy substituted oxindole also efficiently involved in the reaction to afford **3m** in 75% yield (Table 4.2). Also, *N*-alkylated oxindoles offered the respective 3-methyl-2-oxindoles **3n** and **3o** in 5-10 h (Table 4.2).

Table 4.2. Substrate scope of rongalite mediated 3-methylation of indolin-2-ones[a,b]

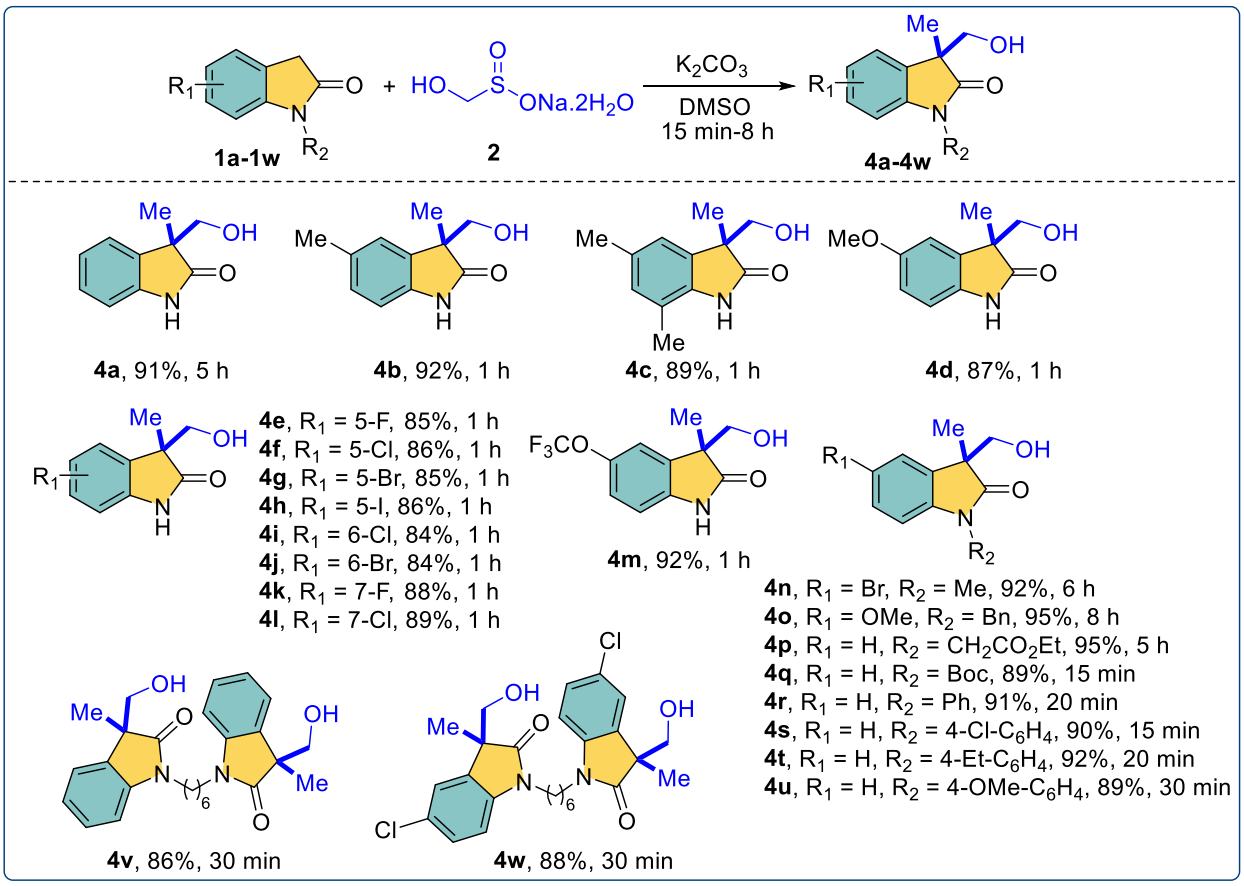


[a]Reaction Conditions: indolin-2-one **1** (1 mmol), rongalite **2** (2 mmol) and K_2CO_3 (2 mmol) in 2 mL of toluene+H_2O (8:2 v/v) at 100 °C. [b]yields of isolated products. [c]KOH (2 mmol) was used instead of K_2CO_3.

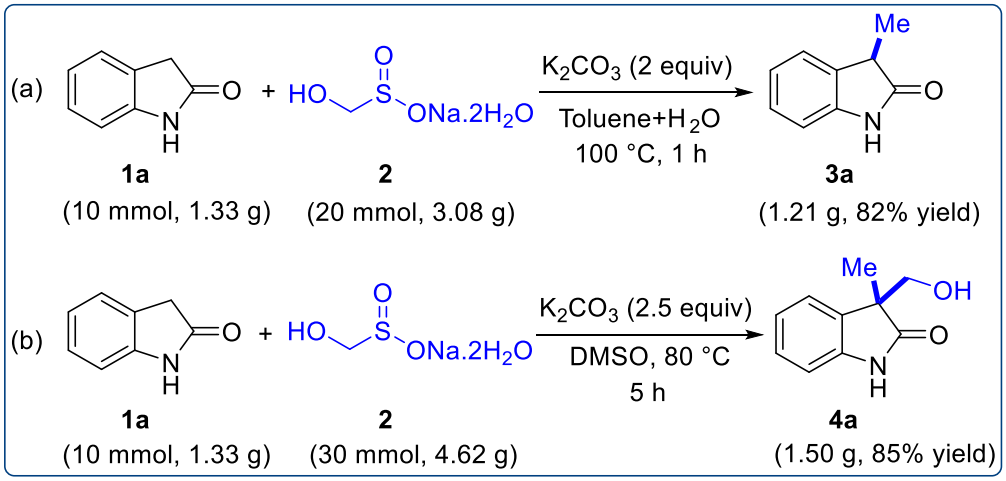
Next, we paid our attention towards the synthesis of diversely substituted 3-(hydroxymethyl)-3-methylindolin-2-ones **4** under optimized conditions (Table 4.1, entry 21). Electron-donating groups present on benzene ring such as methyl and methoxy substituted oxindoles reacted smoothly with rongalite to furnish **4b**-**4d** in 87-92% yields (Table 4.3). This method also can tolerate various halogen-derivatives (–F, –Cl, –Br, and –I) and afforded hydroxymethylated products **4e**-**4l** in 84-89% yields (Table 4.3). Electron withdrawing group i.e., trifluoromethoxy substituted oxindole was also efficiently involved in the reaction to deliver **4m** in 92% yield (Table 4.3).

Both *N*-alkylated and *N*-arylated oxindoles effortlessly reacted with rongalite and offered the respective products **4n**, **4o** and **4r**-**4u** in 89-95% yields and moreover we observed that *N*-arylated oxindoles are more reactive with rongalite compared to *N*-alkylated oxindoles. Also, ester and Boc protecting groups are stable with rongalite and delivered **4p** and **4q** in 95% and 89% yields, respectively (Table 4.3). This protocol is also applicable to bis-oxindoles and produced **4v**-**4w** in 86-88% yields (Table 4.3).

Table 4.3. Substrate scope of rongalite mediated 3,3´-methylation and hydroxymethylation of indolin-2-ones[a,b]



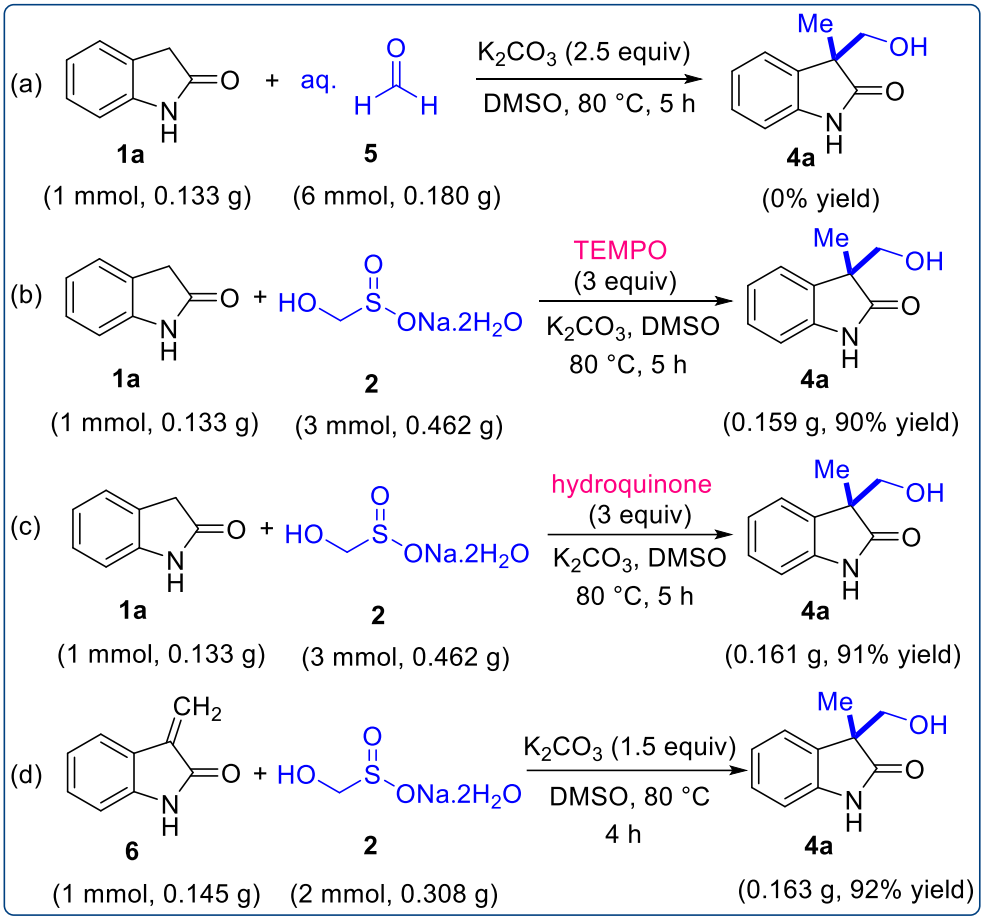
[a]Reaction conditions: indolin-2-one **1** (1 mmol), rongalite **2** (3 mmol) and K_2CO_3 (2.5 mmol) in 2 mL of DMSO at 80 °C. [b]Yields of isolated products. [c]Rongalite (6 mmol) and K_2CO_3 (5 mmol) is used**.**



Scheme 4.12. Gram-scale synthesis

Finally, we evaluated the gram scale synthesis of protocols by employing indolin-2-one **1a** (10 mmol), rongalite **2** (20 mmol) and K_2CO_3 (20 mmol) in 15 mL of toluene+H_2O (8:2 v/v) at 100

°C for 1 h, resulted the 3-methylindolin-2-one **3a** in 82% yield (Scheme 4.12a). Also, 3-(hydroxymethyl)-3-methylindolin-2-one **4a** is synthesized in gram scale using indolin-2-one **1a** (10 mmol), rongalite **2** (30 mmol) and K_2CO_3 (25 mmol) in 15 mL of DMSO at 80 °C for 5 h in 85% yield (Scheme 4.12b).

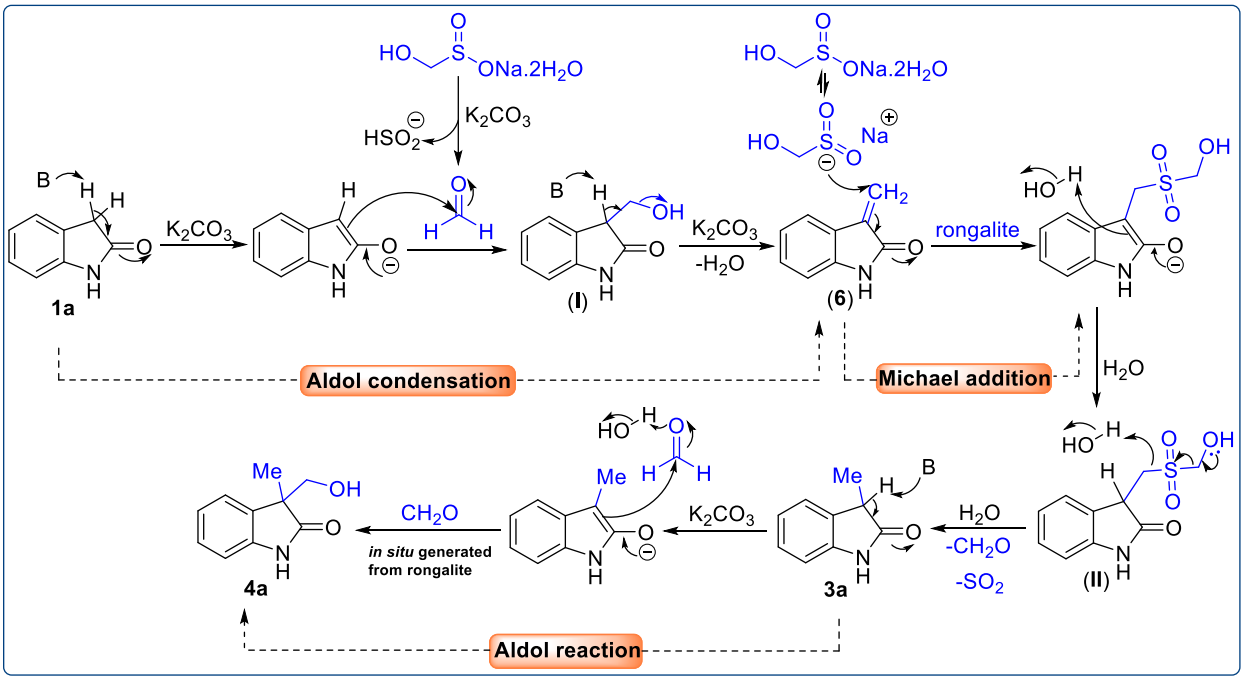


Scheme 4.13. Control experiments

In order to unveil the reaction mechanism and to know the role of rongalite, we have conducted some control experiments (Scheme 4.13). Firstly, we have conducted a reaction between indolin-2-one **1a** (1 mmol), aq. formaldehyde **5** (6 mmol) and K_2CO_3 (2.5 mmol) in DMSO at 80 °C for 5 h, formation of product **4a** i.e., 3-(hydroxymethyl)-3-methylindolin-2-one was not observed. This control experiment indicates that the rongalite is not only acting as a source of C1 unit and also working as a reducing agent (Scheme 4.13a). Further, we have done two more control experiments using radical scavengers such as TEMPO and hydroquinone to know the reaction pathway and observed no significant change in the product **4a** yield (Scheme 4.13b-c). Additionally, we have conducted another reaction between 3-methyleneindolin-2-one **6** (1 mmol)

and rongalite **2** (2 mmol) in the presence of K_2CO_3 (1.5 mmol) in DMSO at 80 °C. To our delight, the product i.e., 3-(hydroxymethyl)-3-methylindolin-2-one **4a** is formed in 92% yield within 4 h and supporting our hypothesis (Scheme 4.13d). Based on this control experiment, we are assuming that 3-methyleneindolin-2-one **6** could be a possible reaction intermediate. Also, the ^{1}H NMR spectra of reaction mixture at different intervals of time clearly indicating that the 3-methylindolin-2-one **3a** is an intermediate for the final product **4a** (Figure 4.2) and is also observed from the control experiment that 3-methyleneindolin-2-one **6** is found to be another intermediate.

Based on existing literature[38] and collective information, a full mechanistic proposal is summarized in Scheme 4.14. Firstly, 2-oxindole reacts with *in situ* generated formaldehyde from rongalite in basic condition to form intermediate (**I**) which further undergoes dehydration to yield intermediate **6**. Later, rongalite undergoes Michael addition with intermediate **6** to form the intermediate (**II**). Further, decomposition of (**II**) leads to the formation of 3-methylindolin-2-one **3a** *via* loss of formaldehyde and sulfur dioxide. Finally, **3a** undergoes second aldol reaction with *in situ* generated formaldehyde to form the desired product **4a** under basic condition.



Scheme 4.14. Plausible reaction mechanism

4.2.2. Illustration of one-pot methylation & hydroxymethylation by ^{1}H NMR spectroscopy

An oven dried 10 mL reaction flask was charged with indolin-2-one **1a** (66 mg, 0.5 mmol), rongalite **2** (3 equiv), K_2CO_3 (2.5 equiv) and DMSO-d_6 (1 mL) at 80 °C. At different intervals of time, 10 µL aliquot of the reaction mixture was transferred to an NMR tube, diluted with DMSO-d_6 (0.5 mL) and recorded ^{1}H NMR. The ^{1}H NMR spectra of all the aliquots are shown in Figure 4.2.

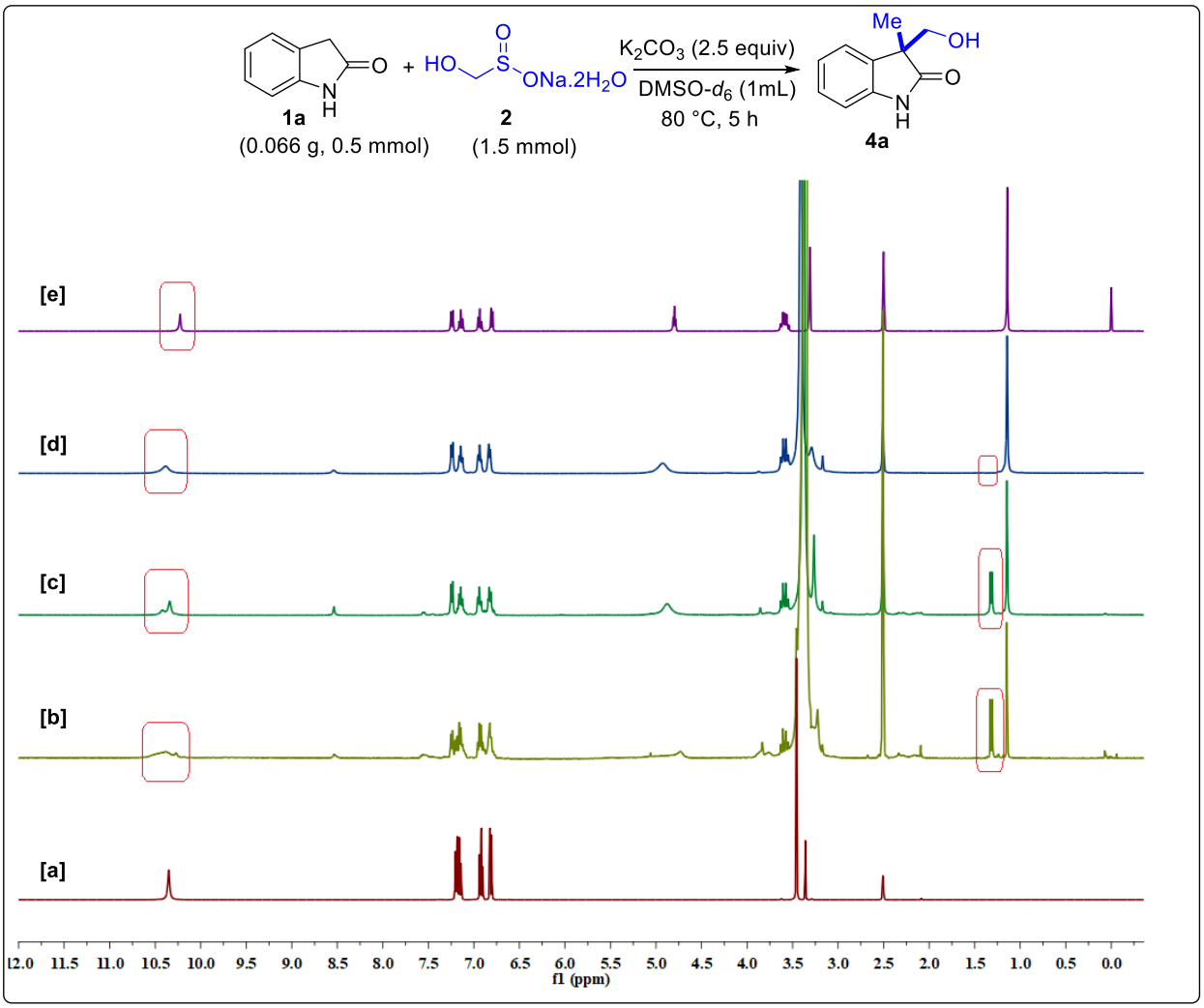


Figure 4.2. 400 MHz ^{1}H NMR spectra of aliquots taken at noted times. All spectra were recorded by diluting an aliquot of the reaction mixture in DMSO-d_6. Panel [a]. 2-oxindole; panel [b]. aliquot of 2-oxindole **1a**, rongalite **2** and K_2CO_3 after 1 h; panel [c]. after 3 h; panel [d]. After 5 h; panel [e]. Purified compound **4a**.

Characterization data of the identified compounds are as follows. ^{1}H NMR spectrum of indolin-2-one **1a** is shown in panel [a] (Figure 4.2). When the reaction mixture is recorded at 1 h, peaks at δ 10.42, 10.34, 3.45, 1.32 and 1.15 ppm were observed, which correspond to the mixture of

indolin-2-one **1a**, 3-methylindolin-2-one **3a** and 3-(hydroxymethyl)-3-methylindolin-2-one **4a** (Figure 4.2, panel [b]). The singlet peaks at δ 10.42 ppm represents the NH proton of **3a**, δ 10.34 ppm represents the NH proton of **4a**, δ 3.45 ppm represents the CH_2 protons of **1a** and δ 1.15 represents the CH_3 protons of **4a**. The doublet at δ 1.32 ppm represents the CH_3 protons of **3a**. Notably, decreasing the intensity of peak at δ 10.42 ppm and increasing the intensity of peak at δ 10.34 ppm was observed and also the intensity of the doublet peak at δ 1.32 ppm is decreased and the peak at δ 1.15 ppm is increased, when aliquot was recorded at 3 h and there is no peak correspond to the indolin-2-one **1a** (Figure 4.2, panel [c]). Finally, the singlet at δ 10.42 ppm and doublet at δ 1.32 ppm peaks were disappeared after 5 h, which indicates that the intermediate product **3a** is completely converted to final compound **4a** using rongalite (Figure 4.2, panel [d]). The ^{1}H NMR spectrum of aliquot at 5 h is comparable with the ^{1}H NMR spectrum of purified compound **4a** (Figure 4.2, panel [e]).

4.3. Conclusion

We have developed an efficient sequential one-pot methylation and hydroxymethylation strategy, which involves a classical aldol condensation followed by reductive aldol reaction using rongalite. In this method, rongalite is an industrial product with low-cost (1g, 0.03$), which plays vital role of hydride-free reducing agent and double C1 unit donor. This transition-metal and hydride-free reductive aldol protocol allows rapid access to 3-methylindoline-2-ones and 3-(hydroxymethyl)-3-methylindolin-2-ones, which are the key building blocks of many natural products such as (-)-physostigmine and its derivatives. This one-pot method is also applicable to gram-scale synthesis for industrial applications.

4.4. Experimental section

4.4.1. General information

All chemicals and solvents were purchased from Alfa Aesar, SRL, Finar and used as received. Thin layer chromatography was performed on 200 µm aluminum-foil backed silica gel plates and the column chromatography was performed using 100-200 mesh silica gel (Merk). Bruker Avance 400 MHz spectrometer was used to record ^{1}H NMR spectra and used $CDCl_3$ and DMSO-d_6 as solvents and TMS as an internal standard. The multiplicities were described using the following acronyms: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet.

Coupling constants, *J* were reported in Hertz unit (Hz). Bruker Avance 100 MHz spectrometer was used to record $^{13}C\{^{1}H\}$ NMR spectra, and they were fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to the center line of a triplet at 77.16 ppm of chloroform-*d* (a multiplet at 39.52 ppm of DMSO-d_6). A Stuart SMP30 apparatus was used to determine the melting points and are uncorrected. FT-IR spectra were recorded on a Perkin Elmer spectrometer. HRMS were analyzed with Agilent Q-TOF 6230.

4.4.2. General Procedure (A) for synthesis of 3-methylindolin-2-ones (3a-3o)

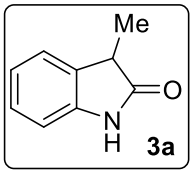
An oven dried 10 mL reaction flask was charged with appropriate indolin-2-one-derivative **1** (1 mmol), rongalite **2** (2 mmol), K_2CO_3 (2 mmol) and toluene+H_2O (2 mL, 8:2 v/v), stirred at 100 °C for the appropriate time (1-10 h). Reaction was monitored by TLC using hexanes and ethyl acetate as an eluent. After reaction has completed, toluene was evaporated under vacuum and the product was extracted with ethyl acetate (3 x 10 mL). The organic layers were separated, dried on Na_2SO_4 and evaporated to give a residue that was purified on silica gel column chromatography using hexanes and ethyl acetate as an eluent.

4.4.3. General Procedure (B) for synthesis of 3-(hydroxymethyl)-3-methylindolin-2-ones (4a-4w)

An oven dried 10 mL reaction flask equipped with a magnetic stirring bar was charged with appropriate indolin-2-one-derivative **1** (1 mmol), rongalite **2** (3 mmol), K_2CO_3 (2.5 mmol) and DMSO (2 mL), stirred at 80 °C for the appropriate time (15 min-8 h). Reaction was monitored by TLC using hexanes and ethyl acetate as an eluent. After completion, reaction mixture was extracted with ethyl acetate (3 x 10 mL). The organic layers were separated, dried on Na_2SO_4 and evaporated to give a residue that was purified on silica gel column chromatography using hexanes and ethyl acetate as an eluent.

4.5. Characterization data of products 3a-3o & 4a-4w

3-methylindolin-2-one (3a). White solid; Yield (138 mg, 94%); mp: 115-116 °C; The title

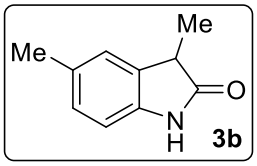


3a

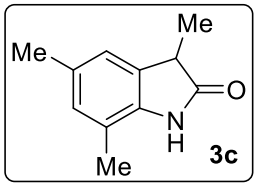
compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3398, 3016, 2980, 1708, 1641, 881; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.30 (s, 1H), 7.24 (d, *J* = 7.2 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 6.94 (t, *J* = 7.6 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 3.39 (q, *J* = 7.6 Hz, 1H), 1.32 (d, *J*

= 7.6 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 181.7, 141.3, 131.3, 127.9, 123.8, 122.4, 109.8, 41.1, 15.2; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_9H_{10}NO$ 148.0762; found 148.0764.

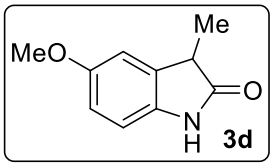
3,5-dimethylindolin-2-one (3b). Off-white crystalline solid; Yield (148 mg, 92%); mp: 148-149 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3415, 3064, 2982, 1667, 1552, 880; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.06 (s, 1H), 7.03 (s, 1H), 7.00 (d, *J* = 7.6 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 3.43 (q, *J* = 7.6 Hz, 1H), 2.32 (s, 3H), 1.49 (d, *J* = 7.6 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 181.7, 138.9, 131.8, 131.4, 128.1, 124.6, 109.5, 41.2, 21.1, 15.3; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{10}H_{12}NO$ 162.0919; found 162.0917.



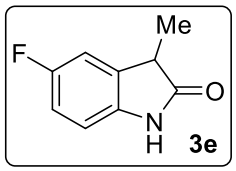
3,5,7-trimethylindolin-2-one (3c). White solid; Yield (159 mg, 91%); mp: 178-179 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3436, 3077, 2970, 1705, 1625, 741; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.26 (s, 1H), 6.87 (s, 1H), 6.78 (s, 1H), 3.32 (q, *J* = 7.6 Hz, 1H), 2.21 (s, 3H), 2.15 (s, 3H), 1.29 (d, *J* = 7.6 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 180.5, 138.9, 131.5, 130.5, 129.7, 122.2, 118.6, 40.9, 21.1, 16.8, 15.7; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{14}NO$ 176.1075; found 176.1075.



5-methoxy-3-methylindolin-2-one (3d). White solid; Yield (156 mg, 88%); mp: 140-141 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3456, 3062, 2980, 1697, 1602, 785; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.97 (s, 1H), 6.77 – 6.73 (m, 2H), 6.66 (dd, *J* = 8.4, 2.0 Hz, 1H), 3.71 (s, 3H), 3.38 (q, *J* = 7.6 Hz, 1H), 1.42 (d, *J* = 7.6 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 181.5, 155.8, 134.8, 132.7, 112.3, 111.1, 110.1, 55.8, 41.6, 15.3; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{10}H_{12}NO_2$ 178.0868; found 178.0864.

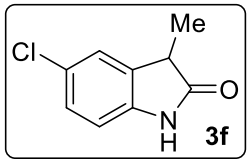


5-fluoro-3-methylindolin-2-one (3e). Off-white solid; Yield (150 mg, 91%); mp: 183-184 °C;



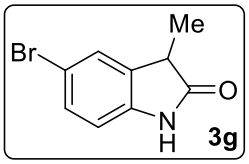
The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3437, 3095, 2929, 1713, 1691, 706; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.38 (s, 1H), 7.23 (dd, J = 8.4, 1.6 Hz, 1H), 7.07 – 7.01 (m, 1H), 6.85 (dd, J = 8.4, 4.4 Hz, 1H), 3.49 (q, J = 7.6 Hz, 1H), 1.38 (d, J = 7.6 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 180.2, 158.5 (d, $^{1}J_{C\text{-}F}$ = 236.4 Hz), 138.6 (d, $^{4}J_{C\text{-}F}$ = 1.6 Hz), 133.1 (d, $^{3}J_{C\text{-}F}$ = 8.0 Hz), 113.8 (d, $^{2}J_{C\text{-}F}$ = 24.0 Hz), 111.6 (d, $^{2}J_{C\text{-}F}$ = 24.0 Hz), 110.1 (d, $^{3}J_{C\text{-}F}$ = 8.0 Hz), 41.3 (d, $^{5}J_{C\text{-}F}$ = 1.2 Hz), 15.2; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for C_9H_9FNO 166.0668; found 166.0667.

5-chloro-3-methylindolin-2-one (3f). Off-white solid; Yield (161 mg, 89%); mp: 201-202 °C;



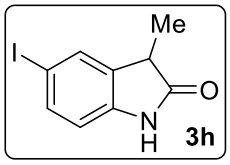
The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3444, 3061, 2980, 1725, 1670, 817; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.45 (s, 1H), 7.34 (s, 1H), 7.21 (dd, J = 8.0, 1.6 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 3.45 (q, J = 7.6 Hz, 1H), 1.33 (d, J = 7.6 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 179.7, 141.5, 133.5, 127.6, 126.2, 124.1, 110.7, 40.9, 15.2; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for C_9H_9ClNO 182.0373; found 182.0370.

5-bromo-3-methylindolin-2-one (3g). Off-white solid; Yield (203 mg, 90%); mp: 189-190 °C;



The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3307, 3065, 1716, 1674, 1117, 811; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.99 (s, 1H), 7.30 – 7.23 (m, 2H), 6.73 (d, J = 8.4 Hz, 1H), 3.40 (q, J = 7.6 Hz, 1H), 1.42 (d, J = 7.6 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 180.9, 140.3, 133.3, 130.8, 127.1, 115.1, 111.2, 41.2, 15.1; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for C_9H_9BrNO 225.9868; found 225.9862.

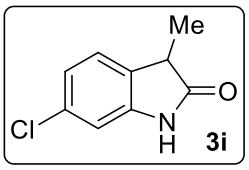
5-iodo-3-methylindolin-2-one (3h). White solid; Yield (218 mg, 80%); mp: 173-174 °C; The



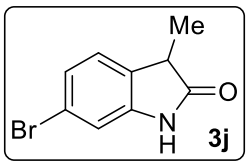
title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3302, 3093, 2979, 1703, 1562, 815; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.66 (s, 1H), 7.56 – 7.50 (m, 2H), 6.70 (d, J =

8.0 Hz, 1H), 3.46 (q, *J* = 7.6 Hz, 1H), 1.48 (d, *J* = 7.6 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 180.4, 140.8, 136.8, 133.7, 132.8, 111.7, 84.9, 40.9, 15.1; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for C_9H_9INO 273.9729; found 273.9724.

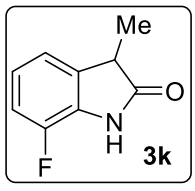
6-chloro-3-methylindolin-2-one (3i). Off-white crystalline solid; Yield (163 mg, 90%); mp: 145-146 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3444, 3061, 2980, 1725, 1670, 815; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.01 (s, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.94 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.86 (d, *J* = 1.6 Hz, 1H), 3.37 (q, *J* = 7.6 Hz, 1H), 1.42 (d, *J* = 7.6 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 181.5, 142.4, 133.6, 129.6, 124.7, 122.3, 110.5, 40.7, 15.2; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for C_9H_9ClNO 182.0373; found 182.0371.



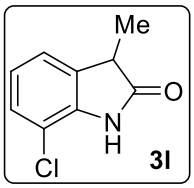
6-bromo-3-methylindolin-2-one (3j). Off-white solid; Yield (201 mg, 89%); mp: 182-183 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3307, 3065, 1716, 1674, 1117, 809; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.46 (s, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 1.6 Hz, 1H), 3.39 (q, *J* = 7.6 Hz, 1H), 1.31 (d, *J* = 7.6 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 181.3, 142.5, 130.1, 125.3, 125.1, 121.3, 113.2, 40.8, 15.1; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for C_9H_9BrNO 225.9868; found 225.9862.



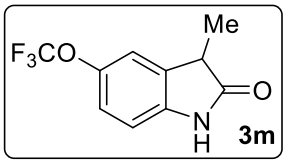
7-fluoro-3-methylindolin-2-one (3k). White crystalline solid; Yield (149 mg, 90%); mp: 147-148 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3437, 3095, 2929, 1713, 1691, 702; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.83 (s, 1H), 7.13 – 7.05 (m, 2H), 6.99 – 6.93 (m, 1H), 3.50 (q, *J* = 7.6 Hz, 1H), 1.34 (d, *J* = 7.6 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 180.3, 147.0 (d, $^{1}J_{C\text{-}F}$ = 242.4 Hz), 133.9 (d, $^{3}J_{C\text{-}F}$ = 3.2 Hz), 128.4 (d, $^{2}J_{C\text{-}F}$ = 12.0 Hz), 123.0 (d, $^{3}J_{C\text{-}F}$ = 5.8 Hz), 119.5 (d, $^{4}J_{C\text{-}F}$ = 3.2 Hz), 115.0 (d, $^{2}J_{C\text{-}F}$ = 17.2 Hz), 41.3 (d, $^{5}J_{C\text{-}F}$ = 2.0 Hz), 15.3; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for C_9H_9FNO 166.0668; found 166.0668.



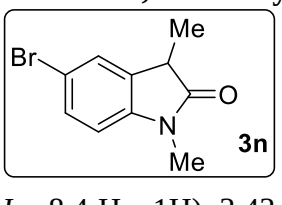
7-chloro-3-methylindolin-2-one (3l). White crystalline solid; Yield (161 mg, 89%); mp: 131-132 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3399, 3078, 2981, 1719, 1620, 774; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.76 (s, 1H), 7.28 – 7.20 (m, 2H), 6.97 (t, J = 7.6 Hz, 1H), 3.54 (q, J = 7.6 Hz, 1H), 1.34 (d, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 179.8, 138.9, 132.5, 127.9, 123.3, 122.1, 114.9, 41.9, 15.3; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for C_9H_9ClNO 182.0373; found 182.0372.



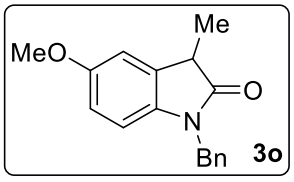
3-methyl-5-(trifluoromethoxy)indolin-2-one (3m). Colorless semi-solid; Yield (173 mg, 75%); The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3435, 3045, 2926, 1716, 1703, 761; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.04 (s, 1H), 7.12 – 7.07 (m, 2H), 6.92 – 6.88 (m, 1H), 3.50 (q, J = 7.6 Hz, 1H), 1.52 (d, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 181.3, 144.7, 139.9, 132.6, 121.2, 120.6 (q, $^1J_{C\text{-}F}$ = 255 Hz), 117.8, 110.2, 41.4, 15.0; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{10}H_9F_3NO_2$ 232.0585; found 232.0582.



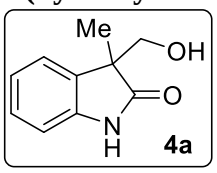
5-bromo-1,3-dimethylindolin-2-one (3n). White solid; Yield (170 mg, 71%); mp: 80-81 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3091, 2982, 1642, 1550, 1079, 818; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.42 – 7.33 (m, 2H), 6.70 (d, J = 8.4 Hz, 1H), 3.43 (q, J = 7.6 Hz, 1H), 3.19 (s, 3H), 1.47 (d, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 177.9, 143.1, 132.7, 130.7, 126.8, 115.1, 109.3, 40.6, 26.3, 15.2; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{10}H_{11}BrNO$ 240.0024; found 240.0026.



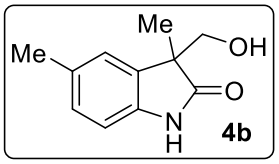
5-methoxy-1,3-dimethylindolin-2-one (3o).[39] Colorless semi-solid; Yield (173 mg, 65%); The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3444, 3036, 2926, 1707, 1600, 804; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.31 – 7.24 (m, 5H), 6.86 (dd, J = 2.4, 0.8 Hz, 1H), 6.69 – 6.65 (m, 1H), 6.59 (d, J = 8.4 Hz, 1H), 4.88 (s, 2H), 3.76 (s, 3H), 3.52 (q, J = 7.6 Hz, 1H), 1.53 (d, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 178.5, 155.9, 136.5, 136.1, 132.04, 128.8, 127.5, 127.3, 111.9, 111.2, 109.3, 55.8, 43.8, 40.9, 15.7.



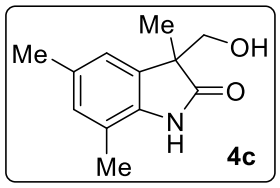
3-(hydroxymethyl)-3-methylindolin-2-one (4a). White solid; Yield (161 mg, 91%); mp: 165-166 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3351, 3040, 2922, 1707, 1012, 655; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.25 (s, 1H), 7.25 (d, J = 7.6 Hz, 1H), 7.15 (td, J = 7.6, 1.6 Hz, 1H), 6.94 (td, J = 7.6, 1.2 Hz, 1H), 6.84 – 6.80 (m, 1H), 4.82 (t, J = 5.6 Hz, 1H), 3.65 – 3.55 (m, 2H), 1.15 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 181.1, 142.6, 134.1, 127.9, 123.8, 121.6, 109.5, 66.8, 50.8, 19.6; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{10}H_{11}NNaO_2$ 200.0687; found 200.0687.



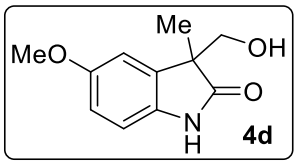
3-(hydroxymethyl)-3,5-dimethylindolin-2-one (4b). White solid; Yield (176 mg, 92%); mp: 160-161 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3323, 3201, 3024, 2968, 1704, 1490; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.14 (s, 1H), 7.07 (d, J = 1.2 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 4.80 (t, J = 5.6 Hz, 1H), 3.62 – 3.53 (m, 2H), 2.26 (s, 3H), 1.13 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 181.1, 140.1, 134.2, 130.3, 128.0, 124.6, 109.2, 66.8, 50.8, 21.3, 19.6; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{11}H_{13}NNaO_2$ 214.0844; found 214.0843.



3-(hydroxymethyl)-3,5,7-trimethylindolin-2-one (4c). White crystalline solid; Yield (182 mg, 89%); mp: 178-179 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3501, 3280, 3005, 2971, 1700, 744; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.19 (s, 1H), 6.89 (s, 1H), 6.77 (s, 1H), 4.77 (t, J = 5.6 Hz, 1H), 3.61 – 3.54 (m, 2H), 2.23 (s, 3H), 2.16 (s, 3H), 1.12 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 181.6, 138.7, 133.9, 130.2, 129.6, 121.8, 118.3, 66.9, 50.9, 21.2, 19.8, 16.9; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{16}NO_2$ 206.1181; found 206.1181.

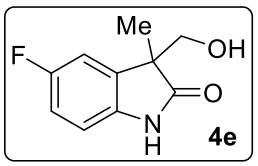


3-(hydroxymethyl)-5-methoxy-3-methylindolin-2-one (4d). White crystalline solid; Yield (180 mg, 87%); mp: 161-162 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3368, 3049, 2962, 1705, 1654, 617; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.06 (s, 1H), 6.91 (s, 1H), 6.72 (d, J = 1.6 Hz, 2H), 4.80 (t, J = 5.6 Hz, 1H), 3.71 (s, 3H),



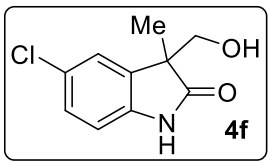
3.64 – 3.53 (m, 2H), 1.14 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 180.9, 155.1, 135.9, 135.5, 112.4, 111.2, 109.6, 66.7, 55.9, 51.3, 19.6; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{11}H_{13}NNaO_3$ 230.0793; found 230.0793.

5-fluoro-3-(hydroxymethyl)-3-methylindolin-2-one (4e). Off-white crystalline solid; Yield



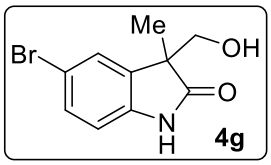
(166 mg, 85%); mp: 219-220 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3478, 3377, 3065, 2974, 1707, 752; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.31 (s, 1H), 7.21 (dd, J = 8.8, 2.8 Hz, 1H), 7.05 – 6.99 (m, 1H), 6.84 (dd, J = 8.4, 4.4 Hz, 1H), 4.93 (t, J = 5.2 Hz, 1H), 3.72 – 3.60 (m, 2H), 1.20 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 181.1, 158.4 (d, $^{1}J_{C\text{-}F}$ = 234.4 Hz), 138.8 (d, $^{4}J_{C\text{-}F}$ = 1.0 Hz), 136.1 (d, $^{3}J_{C\text{-}F}$ = 8.4 Hz), 113.9 (d, $^{2}J_{C\text{-}F}$ = 24 Hz), 111.8 (d, $^{2}J_{C\text{-}F}$ = 24.2 Hz), 109.9 (d, $^{3}J_{C\text{-}F}$ = 8.0 Hz), 66.6, 51.5 (d, $^{5}J_{C\text{-}F}$ = 1.2 Hz), 19.3; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{10}H_{10}FNNaO_2$ 218.0595; found 218.0595.

5-chloro-3-(hydroxymethyl)-3-methylindolin-2-one (4f). Off-white solid; Yield (181 mg,



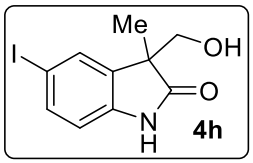
86%); mp: 207-208 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3393, 3069, 2928, 1719, 1616, 732; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.37 (s, 1H), 7.35 (d, J = 2.0 Hz, 1H), 7.20 (dd, J = 8.4, 2.4 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 4.89 (t, J = 5.6 Hz, 1H), 3.68 – 3.55 (m, 2H), 1.16 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 180.8, 141.6, 136.3, 127.7, 125.7, 124.2, 110.8, 66.6, 51.4, 19.2; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{10}H_{10}ClNNaO_2$ 234.0298; found 234.0296.

5-bromo-3-(hydroxymethyl)-3-methylindolin-2-one (4g). White crystalline solid; Yield (218

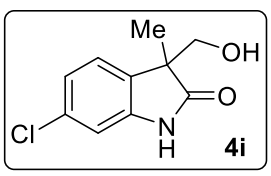


mg, 85%); mp: 189-190 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3498, 3022, 2980, 1642, 1554, 816; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.12 (s, 1H), 7.06 (s, 1H), 6.94 (d, J = 8.4 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 4.78 (t, J = 5.6 Hz, 1H), 3.63 – 3.52 (m, 2H), 1.14 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 181.1, 140.1, 134.2, 130.2, 127.9, 124.5, 109.1, 66.8, 50.8, 19.6; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{10}H_{11}BrNO_2$ 255.9973; found 255.9971.

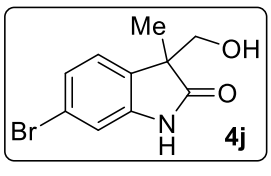
3-(hydroxymethyl)-5-iodo-3-methylindolin-2-one (4h). White solid; Yield (260 mg, 86%); mp: 188-189 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3456, 3301, 3031, 2929, 1703, 1553, 805; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.37 (s, 1H), 7.59 (d, J = 1.6 Hz, 1H), 7.49 (dd, J = 8.0, 1.6 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 4.89 (t, J = 5.2 Hz, 1H), 3.66 – 3.53 (m, 2H), 1.14 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 180.5, 142.5, 137.0, 136.4, 132.3, 111.9, 84.6, 66.6, 51.1, 19.3; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{10}H_{10}INNaO_2$ 325.9654; found 325.9649.



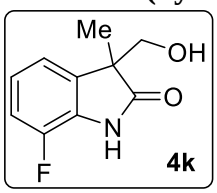
6-chloro-3-(hydroxymethyl)-3-methylindolin-2-one (4i). Off-white solid; Yield (177 mg, 84%); mp: 175-176 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3393, 3069, 2928, 1719, 1616, 729; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.39 (s, 1H), 7.26 (d, J = 8.0 Hz, 1H), 6.99 (dd, J = 8.0, 2.0 Hz, 1H), 6.82 (d, J = 2.0 Hz, 1H), 4.86 (t, J = 5.6 Hz, 1H), 3.65 – 3.55 (m, 2H), 1.15 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 181.0, 144.2, 133.0, 132.2, 125.2, 121.2, 109.5, 66.7, 50.7, 19.2; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{10}H_{10}ClNNaO_2$ 234.0298; found 234.0297.



6-bromo-3-(hydroxymethyl)-3-methylindolin-2-one (4j). White crystalline solid; Yield (215 mg, 84%); mp: 157-158 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3498, 3022, 2980, 1642, 1554, 810; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.40 (s, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.13 (dd, J = 7.6, 2.0 Hz, 1H), 6.94 (d, J = 2.0 Hz, 1H), 4.88 (t, J = 5.6 Hz, 1H), 3.64 – 3.53 (m, 2H), 1.13 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 180.9, 144.5, 133.5, 125.7, 124.1, 120.4, 112.3, 66.6, 50.8, 19.1; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{10}H_{10}BrNNaO_2$ 277.9793; found 277.9792.

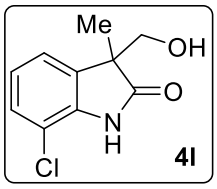


7-fluoro-3-(hydroxymethyl)-3-methylindolin-2-one (4k). White solid; Yield (172 mg, 88%); mp: 210-211 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3478, 3377, 3065, 2978, 1705, 755; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.75 (s, 1H), 7.12 (d, J = 7.2 Hz, 1H), 7.09 – 7.04 (m, 1H), 6.99 – 6.93 (m, 1H), 4.89 (t, J = 5.2 Hz, 1H), 3.67 – 3.58 (m,

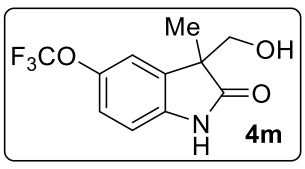


2H), 1.17 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 180.9, 146.7 (d, $^{1}J_{C\text{-}F}$ = 240 Hz), 137.3 (d, $^{3}J_{C\text{-}F}$ = 3.7 Hz), 129.5 (d, $^{2}J_{C\text{-}F}$ = 11.6 Hz), 122.5 (d, $^{3}J_{C\text{-}F}$ = 5.7 Hz), 119.9 (d, $^{4}J_{C\text{-}F}$ = 2.7 Hz), 115.0 (d, $^{2}J_{C\text{-}F}$ = 17.2 Hz), 66.8, 51.4 (d, $^{5}J_{C\text{-}F}$ = 1.7 Hz), 19.4; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{10}H_{10}FNNaO_2$ 218.0593; found 218.0595.

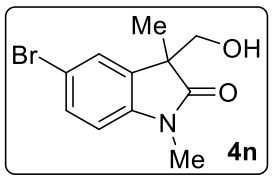
7-chloro-3-(hydroxymethyl)-3-methylindolin-2-one (4l). White crystalline solid; Yield (188 mg, 89%); mp: 196-197 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3393, 3068, 2929, 1718, 1610, 728; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.67 (s, 1H), 7.25 – 7.19 (m, 2H), 6.97 (dd, *J* = 8.4, 7.6 Hz, 1H), 4.89 (t, *J* = 5.6 Hz, 1H), 3.67 – 3.58 (m, 2H), 1.16 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 181.0, 140.4, 136.1, 127.9, 122.9, 122.5, 113.8, 66.8, 51.9, 19.4; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{10}H_{10}ClNNaO_2$ 234.0298; found 234.0293.



3-(hydroxymethyl)-3-methyl-5-(trifluoromethoxy)indolin-2-one (4m). White solid; Yield (240 mg, 92%); mp: 164-165 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3407, 3025, 2974, 1709, 1631, 617; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.36 (s, 1H), 7.24 (d, *J* = 1.6 Hz, 1H), 7.10 – 7.06 (m, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 4.83 (t, *J* = 5.2 Hz, 1H), 3.62 – 3.48 (m, 2H), 1.10 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 181.1, 143.5, 141.9, 136.0, 121.0, 120.7 (q, $^{1}J_{C\text{-}F}$ = 253.4 Hz), 117.7, 110.1, 66.6, 51.5, 19.2; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{11}F_3NO_3$ 262.0691; found 262.0686.



5-bromo-3-(hydroxymethyl)-1,3-dimethylindolin-2-one (4n). White solid; Yield (248 mg, 92%); mp: 185-186 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3467, 3083, 2979, 1643, 1554, 1075, 818; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.53 (d, *J* = 2.0 Hz, 1H), 7.45 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 4.90 (t, *J* = 5.6 Hz, 1H), 3.71 – 3.57 (m, 2H), 3.11 (s, 3H), 1.18 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 178.8, 143.6, 135.9, 130.7, 126.5, 114.3, 110.4, 66.6, 51.0, 26.5, 19.2; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{13}BrNO_2$ 270.0130; found 270.0125.



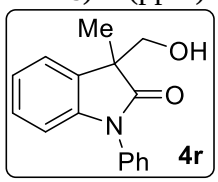
1-benzyl-3-(hydroxymethyl)-5-methoxy-3-methylindolin-2-one (4o). White solid; Yield (282 mg, 95%); mp: 175-176 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3361, 3065, 2925, 1686, 1496, 719; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.32 – 7.23 (m, 5H), 7.02 (d, J = 2.4 Hz, 1H), 6.72 – 6.65 (m, 2H), 4.97 – 4.92 (m, 2H), 4.80 (d, J = 16.0 Hz, 1H), 3.75 – 3.68 (m, 5H), 1.23 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 179.2, 155.8, 136.9, 136.5, 134.8, 128.9, 127.6, 127.4, 112.2, 111.2, 109.4, 66.8, 55.9, 51.1, 42.9, 19.7; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{20}NO_3$ 298.1443; found 298.1440.

ethyl 2-(3-(hydroxymethyl)-3-methyl-2-oxoindolin-1-yl)acetate (4p). White crystalline solid; Yield (250 mg, 95%); mp: 115-116 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3427, 3017, 2974, 1642, 1415, 810; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.23 – 7.16 (m, 2H), 7.04 (t, J = 7.6 Hz, 1H), 6.69 (d, J = 7.6 Hz, 1H), 4.40 (d, J = 2.0 Hz, 2H), 4.13 (q, J = 7.2 Hz, 2H), 3.82 (d, J = 10.8 Hz, 1H), 3.70 (d, J = 10.8 Hz, 1H), 2.07 (s, 1H), 1.36 (s, 3H), 1.17 (d, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 179.9, 167.6, 142.3, 131.6, 128.3, 123.1, 123.1, 108.2, 67.8, 61.9, 50.2, 41.3, 18.9, 14.1; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{17}NNaO_4$ 286.1055; found 286.1052.

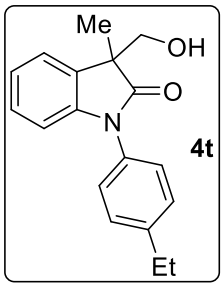
***tert*-butyl 3-(hydroxymethyl)-3-methyl-2-oxoindoline-1-carboxylate (4q).** White solid; Yield (246 mg, 89%); mp: 90-91 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3465, 3021, 2980, 1642, 1557, 816; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.80 (d, J = 8.4 Hz, 1H), 7.28 – 7.23 (m, 1H), 7.17 – 7.10 (m, 2H), 3.82 (d, J = 10.8 Hz, 1H), 3.71 (d, J = 10.8 Hz, 1H), 1.85 (s, 1H), 1.58 (s, 9H), 1.35 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 178.6, 149.2, 139.7, 130.6, 128.6, 124.7, 122.6, 115.3, 84.5, 68.2, 50.6, 28.1, 19.9; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{15}H_{19}NNaO_4$ 300.1212; found 300.1211.

3-(hydroxymethyl)-3-methyl-1-phenylindolin-2-one (4r). White solid; Yield (230 mg, 91%); mp: 121-122 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3415, 3013, 2972, 1689, 1648, 542; ^1H NMR (400 MHz,

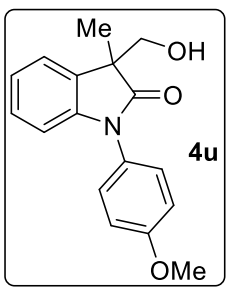
$CDCl_3$) δ (ppm): 7.54 – 7.49 (m, 2H), 7.43 – 7.38 (m, 3H), 7.28 (dd, J = 7.2, 0.8 Hz, 1H), 7.22 (td, J = 7.8, 1.2 Hz, 1H), 7.12 (td, J = 7.6, 1.2 Hz, 1H), 6.85 (d, J = 7.8 Hz, 1H), 3.95 – 3.81 (m, 2H), 2.38 (dd, J = 8.8, 3.6 Hz, 1H), 1.51 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 179.4, 143.7, 134.4, 131.7, 129.6, 128.3, 128.1, 126.6, 123.2, 123.1, 109.6, 67.9, 50.1, 19.3; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{16}NO_2$ 254.1181; found 254.1179.



1-(4-chlorophenyl)-3-(hydroxymethyl)-3-methylindolin-2-one (4s). White solid; Yield (258 mg, 90%); mp: 103-104 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3456, 3083, 2956, 1706, 1610, 757; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.63 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 8.8 Hz, 2H), 7.43 (dd, J = 7.2, 0.8 Hz, 1H), 7.22 (td, J = 7.6, 1.2 Hz, 1H), 7.11 (td, J = 7.6, 1.2 Hz, 1H), 6.78 (d, J = 7.6 Hz, 1H), 5.01 (t, J = 5.2 Hz, 1H), 3.75 (d, J = 5.2 Hz, 2H), 1.30 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 178.9, 143.5, 133.9, 133.2, 132.5, 130.0, 128.9, 128.1, 124.1, 123.2, 108.9, 67.3, 50.8, 19.6; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{15}ClNO_2$ 288.0791; found 288.0792.



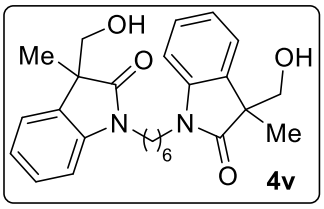
1-(4-ethylphenyl)-3-(hydroxymethyl)-3-methylindolin-2-one (4t). White solid; Yield (258 mg, 90%); mp: 107-108 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3415, 3013, 2972, 1689, 1648, 541; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.36 – 7.30 (m, 4H), 7.28 (d, J = 7.2 Hz, 1H), 7.22 (td, J = 7.6, 1.2 Hz, 1H), 7.11 (td, J = 7.6, 1.2 Hz, 1H), 6.85 (d, J = 7.6 Hz, 1H), 3.96 – 3.82 (m, 2H), 2.72 (q, J = 7.6 Hz, 2H), 2.33 (s, 1H), 1.52 (s, 3H), 1.28 (t, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 179.5, 144.4, 143.9, 131.8, 131.6, 129.1, 128.3, 126.4, 123.1, 122.9, 109.7, 67.9, 49.9, 28.6, 19.3, 15.5; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{20}NO_2$ 282.1494; found 282.1488.



3-(hydroxymethyl)-1-(4-methoxyphenyl)-3-methylindolin-2-one (4u). Colorless semi-solid; Yield (252 mg, 89%); The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3428, 3073, 2975, 1640, 1414, 508; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.30 (d, J = 9.2 Hz, 2H), 7.28 – 7.25 (m, 1H), 7.21 (td, J = 7.6, 1.2 Hz, 1H), 7.10 (td, J = 7.6, 1.2 Hz, 1H), 7.02 (d, J = 9.2 Hz, 2H), 6.79 (d, J = 7.6 Hz, 1H), 3.92 – 3.80

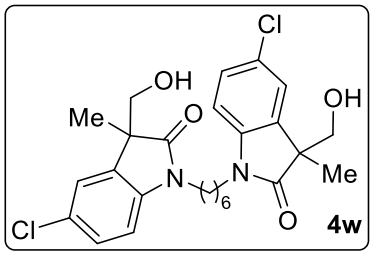
(m, 5H), 2.48 (s, 1H), 1.49 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 179.7, 159.2, 144.1, 131.6, 128.3, 127.9, 126.9, 123.1, 122.9, 114.9, 109.5, 67.9, 55.6, 50.1, 19.2; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{18}NO_3$ 284.1287; found 284.1279.

1,1'-(hexane-1,6-diyl)bis(3-(hydroxymethyl)-3-methylindolin-2-one) (4v). White solid; Yield



(375 mg, 86%); mp: 147-148 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3368, 3084, 2924, 1683, 1610, 755; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.30 (d, J = 7.2 Hz, 2H), 7.22 (t, J = 7.6 Hz, 2H), 7.01 (t, J = 7.6 Hz, 2H), 6.97 (d, J = 7.6 Hz, 2H), 4.82 (t, J = 5.2 Hz, 2H), 3.67 – 3.56 (m, 8H), 1.54 (s, 4H), 1.30 (s, 4H), 1.15 (s, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 179.2, 143.4, 133.5, 128.0, 123.6, 122.1, 108.6, 66.7, 50.4, 39.4, 27.3, 26.2, 19.6; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{26}H_{32}N_2NaO_4$ 459.2260; found 459.2252.

1,1'-(hexane-1,6-diyl)bis(5-chloro-3-(hydroxymethyl)-3-methylindolin-2-one) (4w). White



solid; Yield (444 mg, 88%); mp: 192-193 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3432, 3021, 2977, 1640, 1558, 816; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.41 (d, J = 2.0 Hz, 2H), 7.26 (dd, J = 8.4, 2.0 Hz, 2H), 6.99 (d, J = 8.4 Hz, 2H), 4.88 (t, J = 5.2 Hz, 2H), 3.70 – 3.54 (m, 8H), 1.51 (s, 4H), 1.27 (s, 4H), 1.15 (s, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 178.9, 142.4, 135.6, 127.8, 126.3, 124.0, 110.0, 66.6, 50.9, 39.6, 27.2, 26.1, 19.3; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{26}H_{30}Cl_2N_2NaO_4$ 527.1480; found 527.1474.

4.6. References

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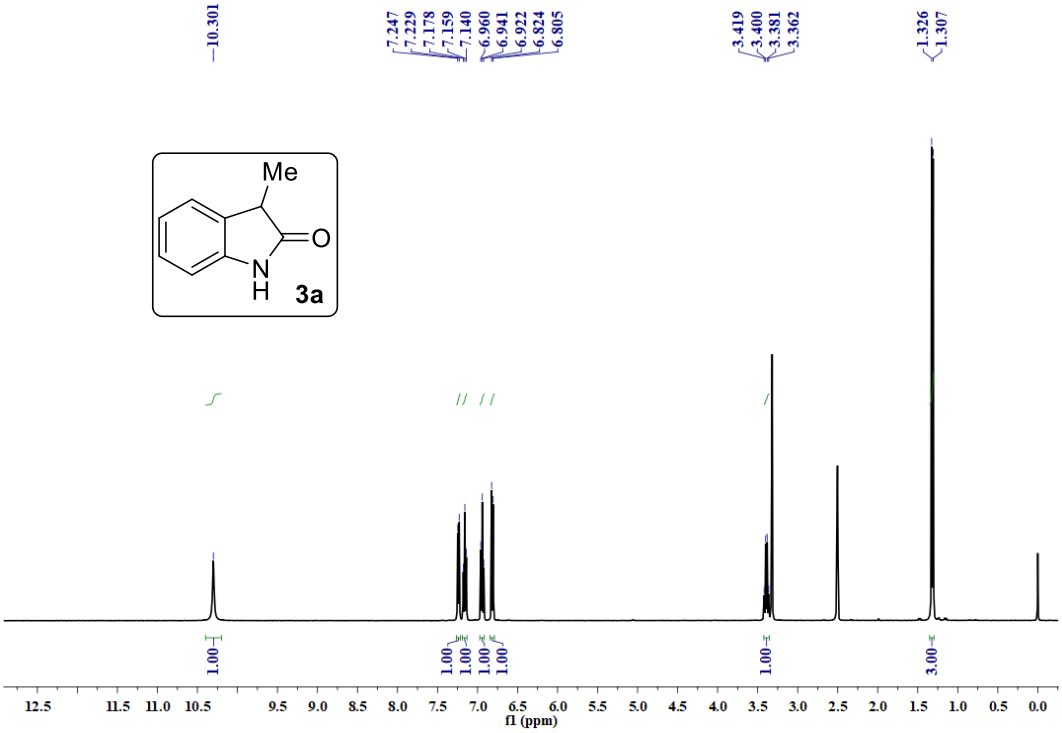
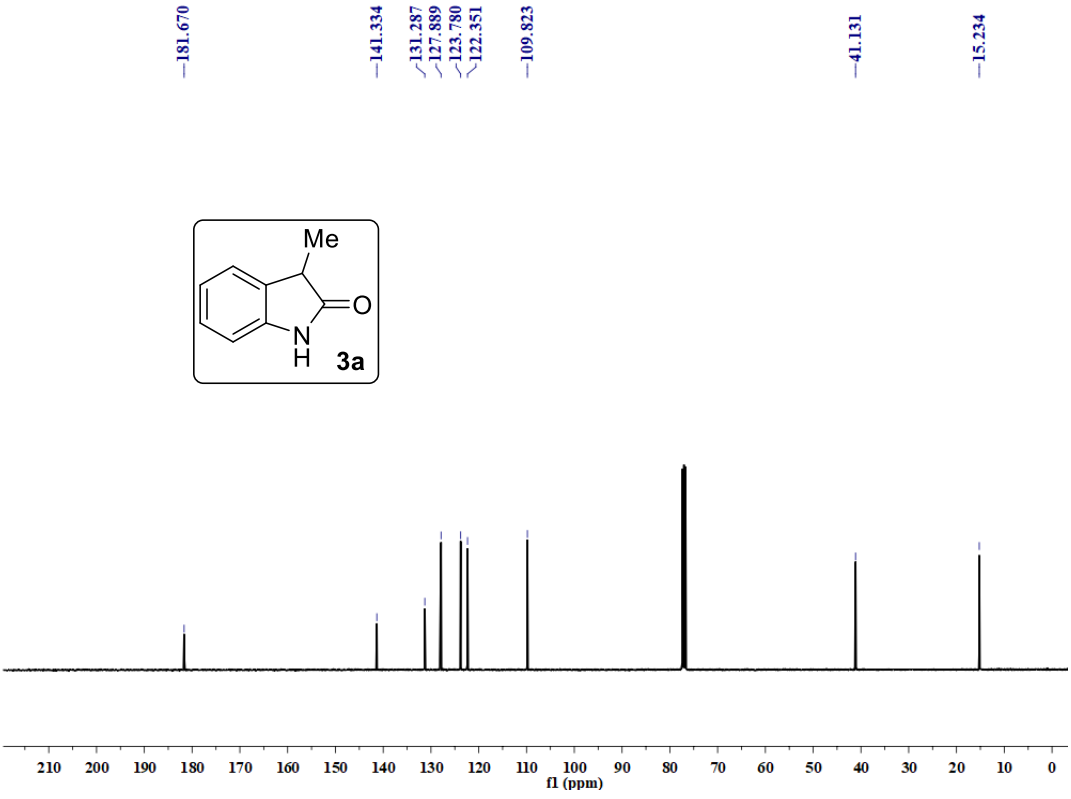
4.7. Selected NMR (^{1}H & ^{13}C) and HRMS spectra

^{1}H NMR (400 MHz, DMSO-*d*$_6$) spectrum of 3-methylindolin-2-one (3a)

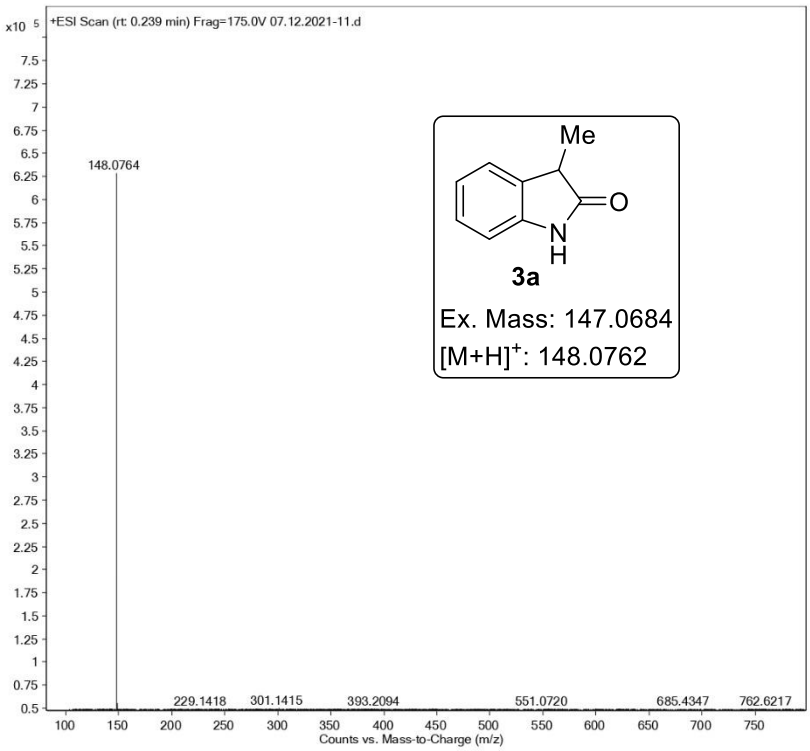


^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of 3-methylindolin-2-one (3a)

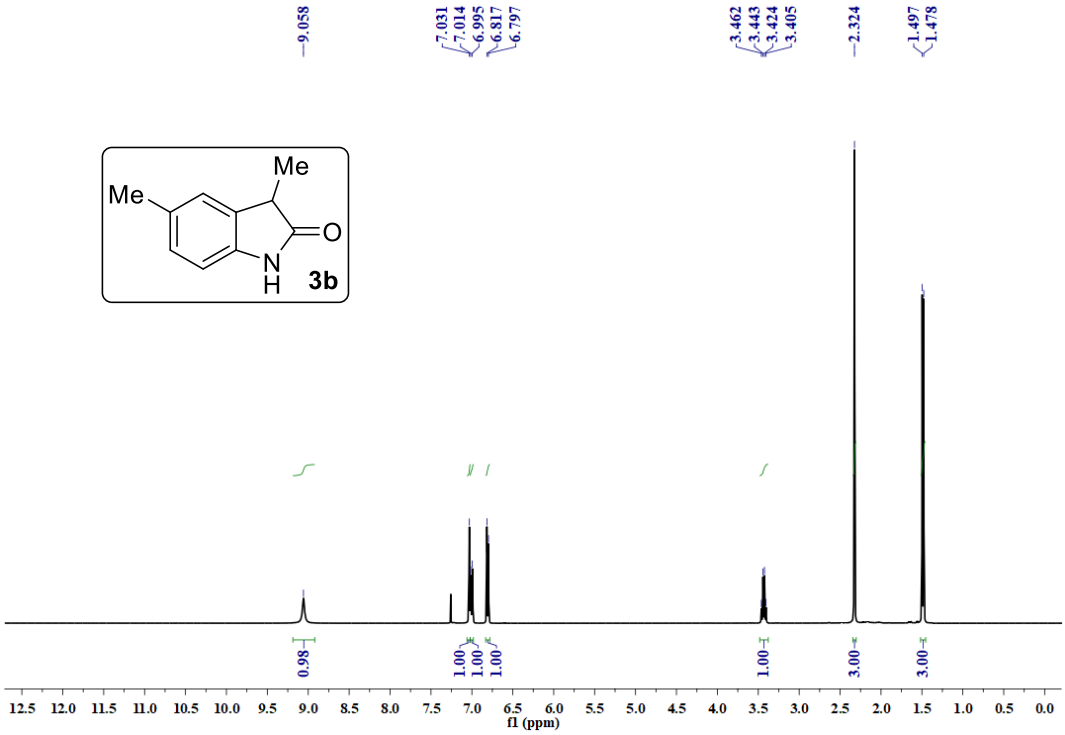


HRMS of 3-methylindolin-2-one (3a)

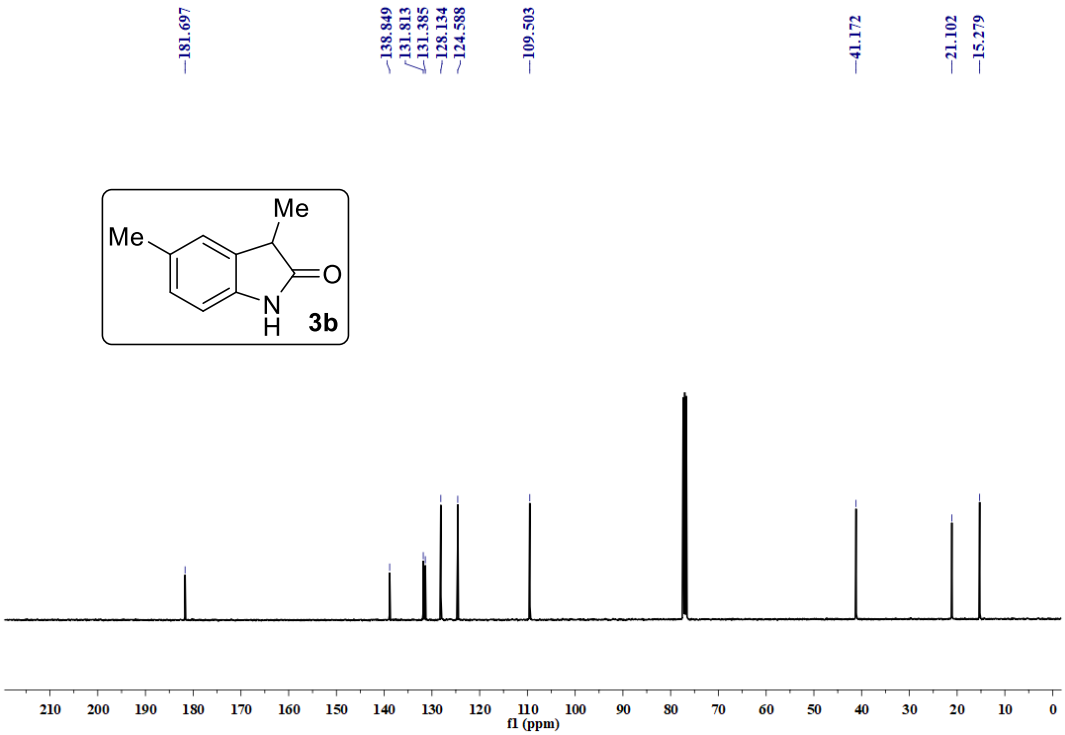
Sample Name	shivaparwathi-1	**Position**	P1-B2	**Instrument Name**	Instrument 1
User Name		**Inj Vol**	2	**InjPosition**	
Sample Type	Sample	**IRM Calibration Status**	Success	**Data Filename**	07.12.2021-11.d
ACQ Method	NITW-W.m	**Comment**		**Acquired Time**	07-Dec-21 5:33:18 PM



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3,5-dimethylindolin-2-one (3b)

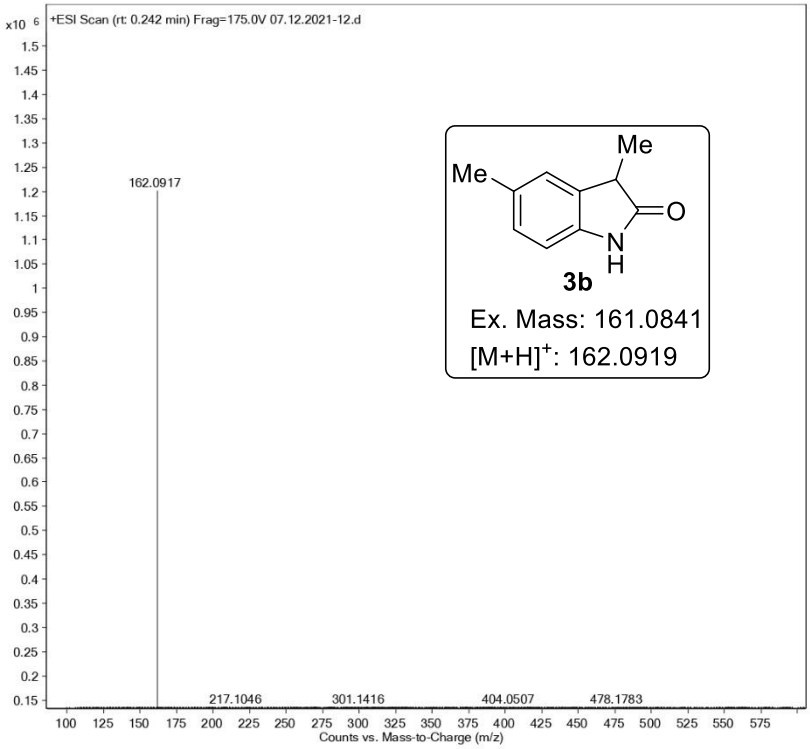


^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of 3,5-dimethylindolin-2-one (3b)

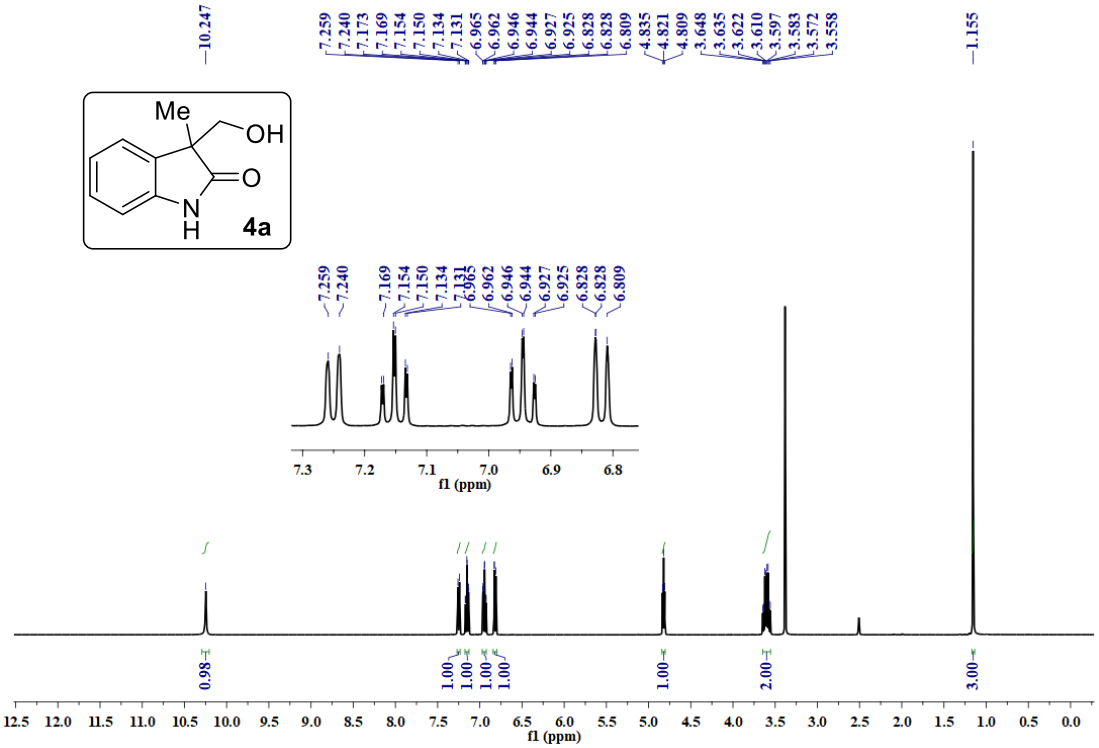


HRMS of 3,5-dimethylindolin-2-one (3b)

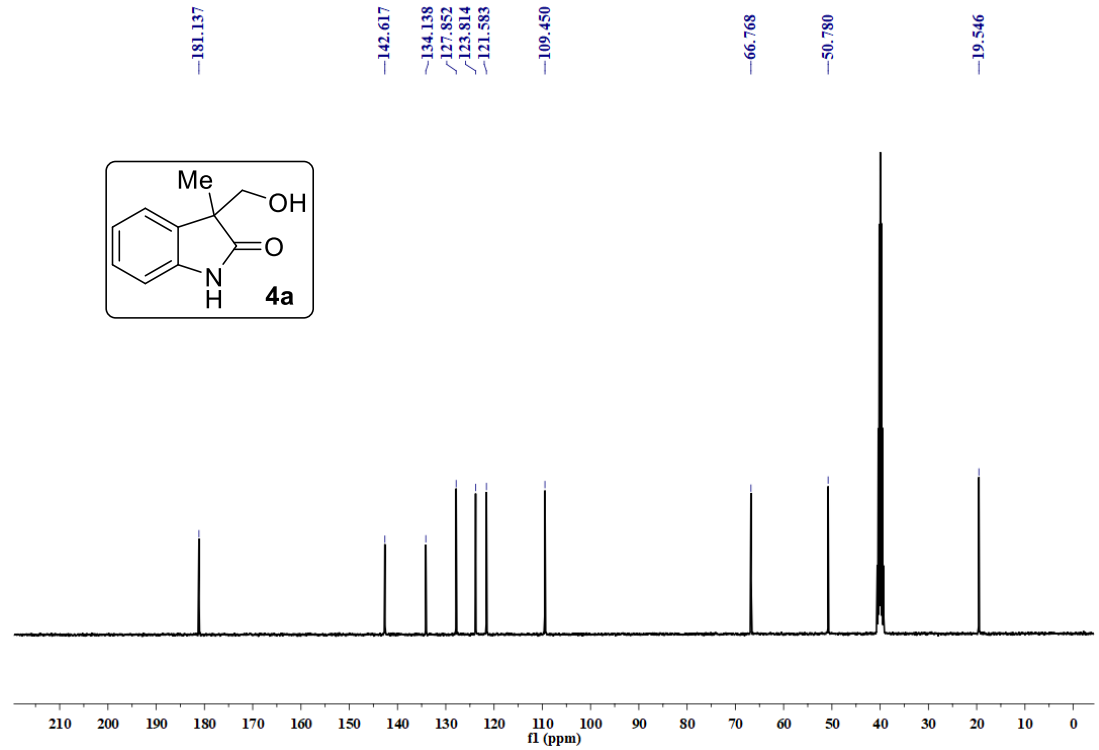
Sample Name	shivaparwathi-2	**Position**	P1-B3	**Instrument Name**	Instrument 1
User Name		**Inj Vol**	2	**InjPosition**	
Sample Type	Sample	**IRM Calibration Status**	Success	**Data Filename**	07.12.2021-12.d
ACQ Method	NITW-W.m	**Comment**		**Acquired Time**	07-Dec-21 5:37:17 PM



^{1}H NMR (400 MHz, DMSO-d_6) spectrum of 3-(hydroxymethyl)-3-methylindolin-2-one (4a)

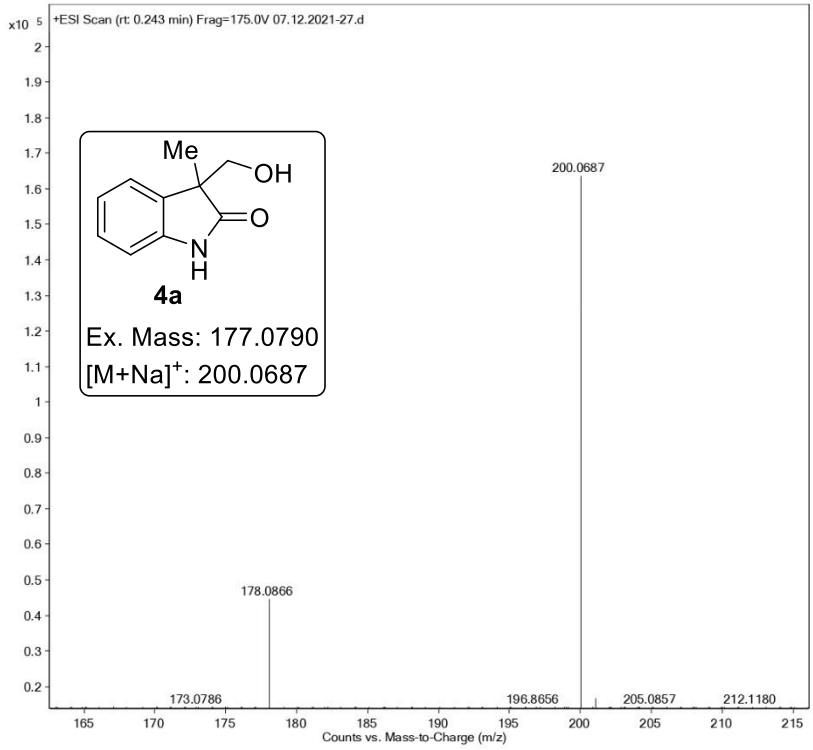


^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) spectrum of 3-(hydroxymethyl)-3-methylindolin-2-one (4a)

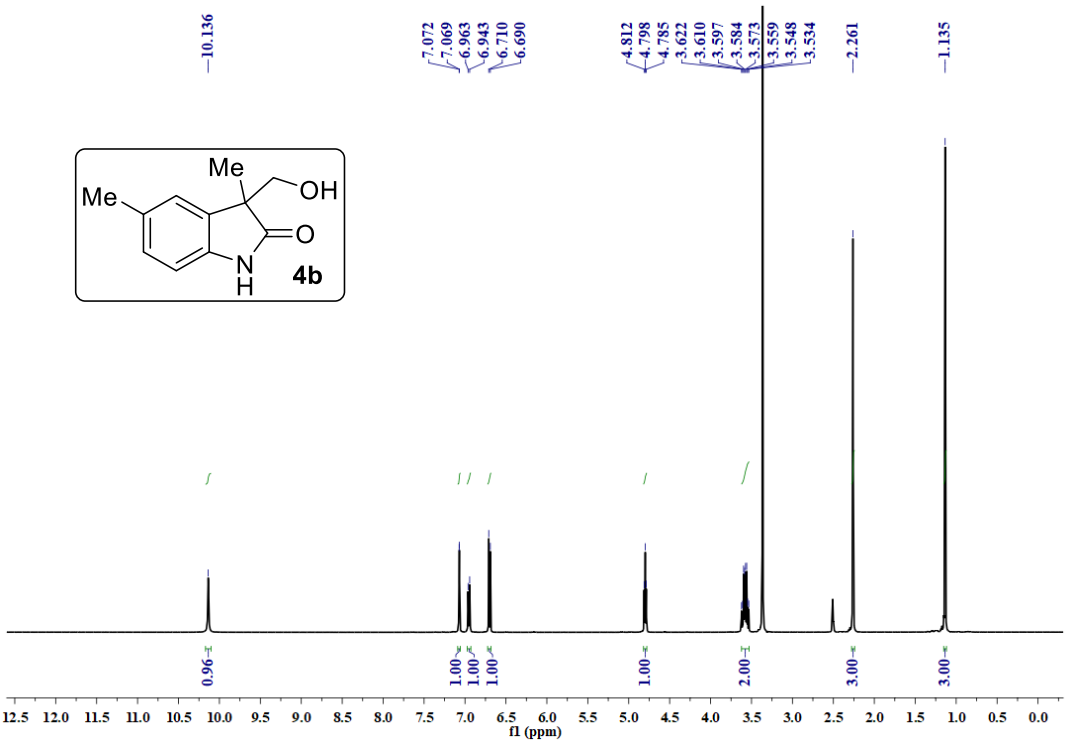


HRMS of 3-(hydroxymethyl)-3-methylindolin-2-one (4a)

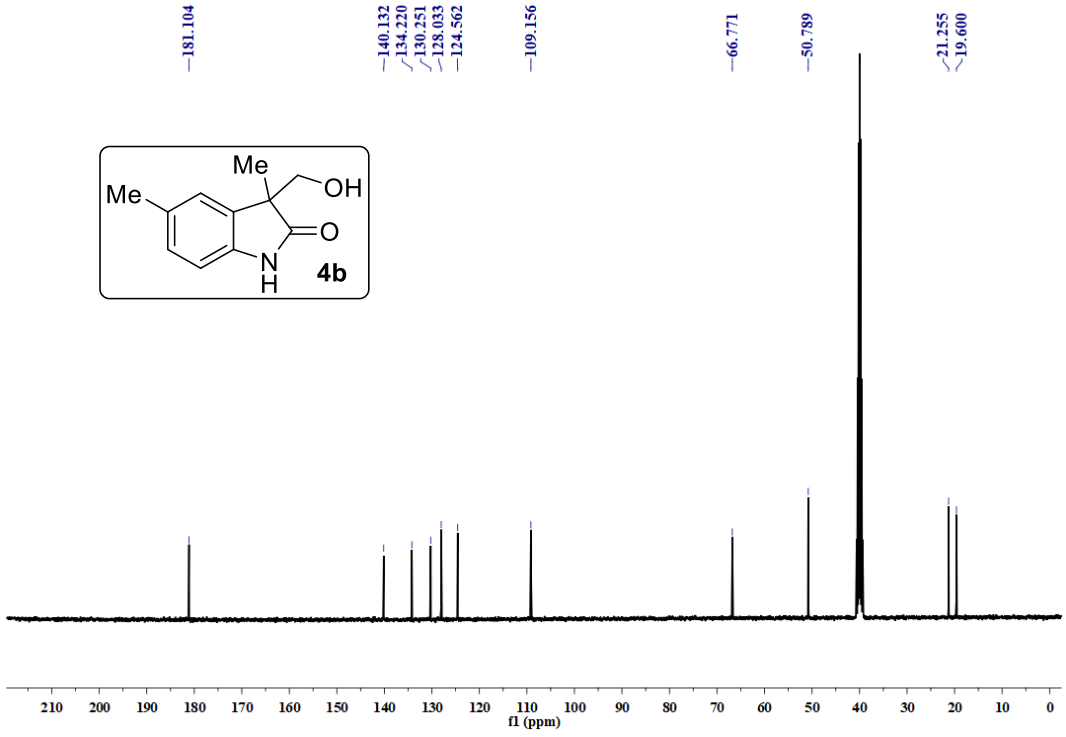
Sample Name	oxis-2	**Position**	P1-C9	**Instrument Name**	Instrument 1
User Name		**Inj Vol**	2	**InjPosition**	
Sample Type	Sample	**IRM Calibration Status**	Success	**Data Filename**	07.12.2021-27.d
ACQ Method	NITW-W.m	**Comment**		**Acquired Time**	07-Dec-21 7:00:30 PM



^{1}H NMR (400 MHz, DMSO-d_6) spectrum of 3-(hydroxymethyl)-3,5-dimethylindolin-2-one (4b)

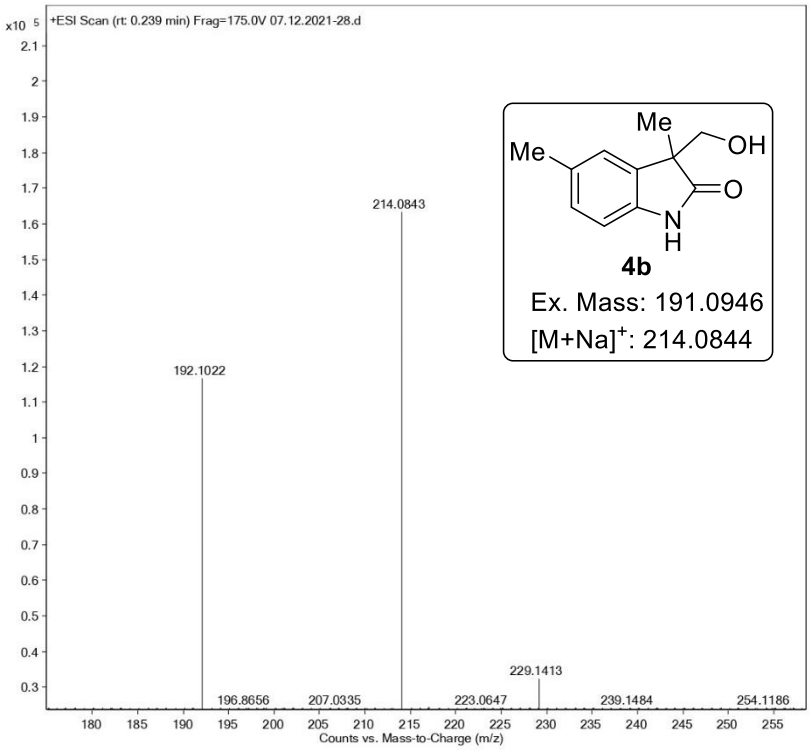


^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) spectrum of 3-(hydroxymethyl)-3,5-dimethylindolin-2-one (4b)



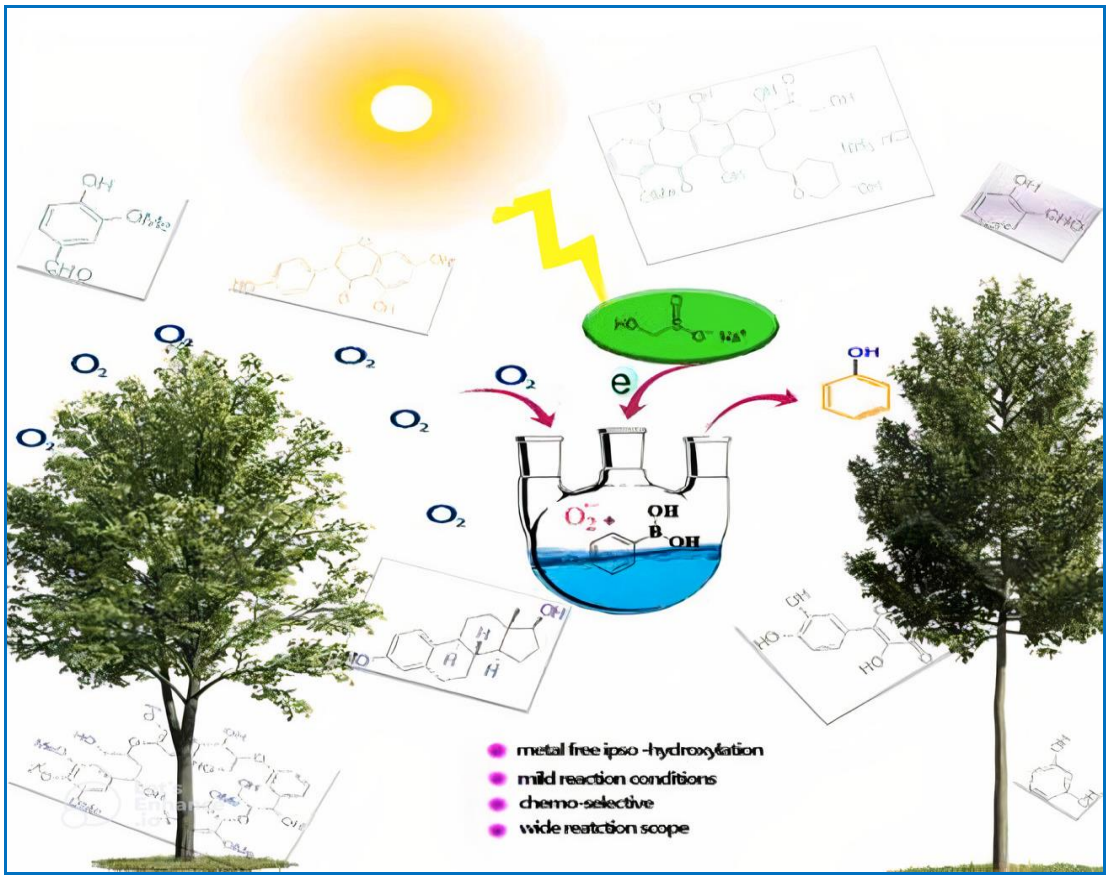
HRMS of 3-(hydroxymethyl)-3,5-dimethylindolin-2-one (4b)

Sample Name	5-meoxi-2	**Position**	P1-D1	**Instrument Name**	Instrument 1
User Name		**Inj Vol**	2	**InjPosition**	
Sample Type	Sample	**IRM Calibration Status**	Success	**Data Filename**	07.12.2021-28.d
ACQ Method	NITW-W.m	**Comment**		**Acquired Time**	07-Dec-21 7:04:26 PM



CHAPTER-VA

Sunlight-Promoted Aerobic *ipso*-Hydroxylation of Arylboronic Acids Using Rongalite



5A.1. Introduction

Phenols are ubiquitous in nature and found many applications. Phenol was first isolated by Friedlieb Ferdinand Runge from coal tar (in impure form) and named it as 'coal oil acid' or 'carbolic acid' in 1834.[1] Phenol is a white crystalline solid with melting point 40.5 °C and it has volatile nature. A British surgeon, Joseph Lister used phenol as a disinfectant for sterilizing surgical dressings, instruments and wounds and it was accepted universally as Lister spray.[2]

Dietary plants and medicinal herbs are the major sources of phenols, which categorizes into phenolic acids, tannins, lignans, quinones, stilbenes, flavonoids, curcuminoids, coumarins etc.[3] These phenolic compounds exhibit broad spectrum of biological activities such as i) desvenlafaxine[4], is used to reduce major depression disorder, ii) thyroxine,[5] used in the treatment of hypothyroidism, iii) dihydrokaempferol,[6] acts as peroxy radical scavenger, iv) lariciresinol,[7] which inhibits lipid peroxidation, v) quercetin,[8] reduces swelling, controls blood sugar and kills

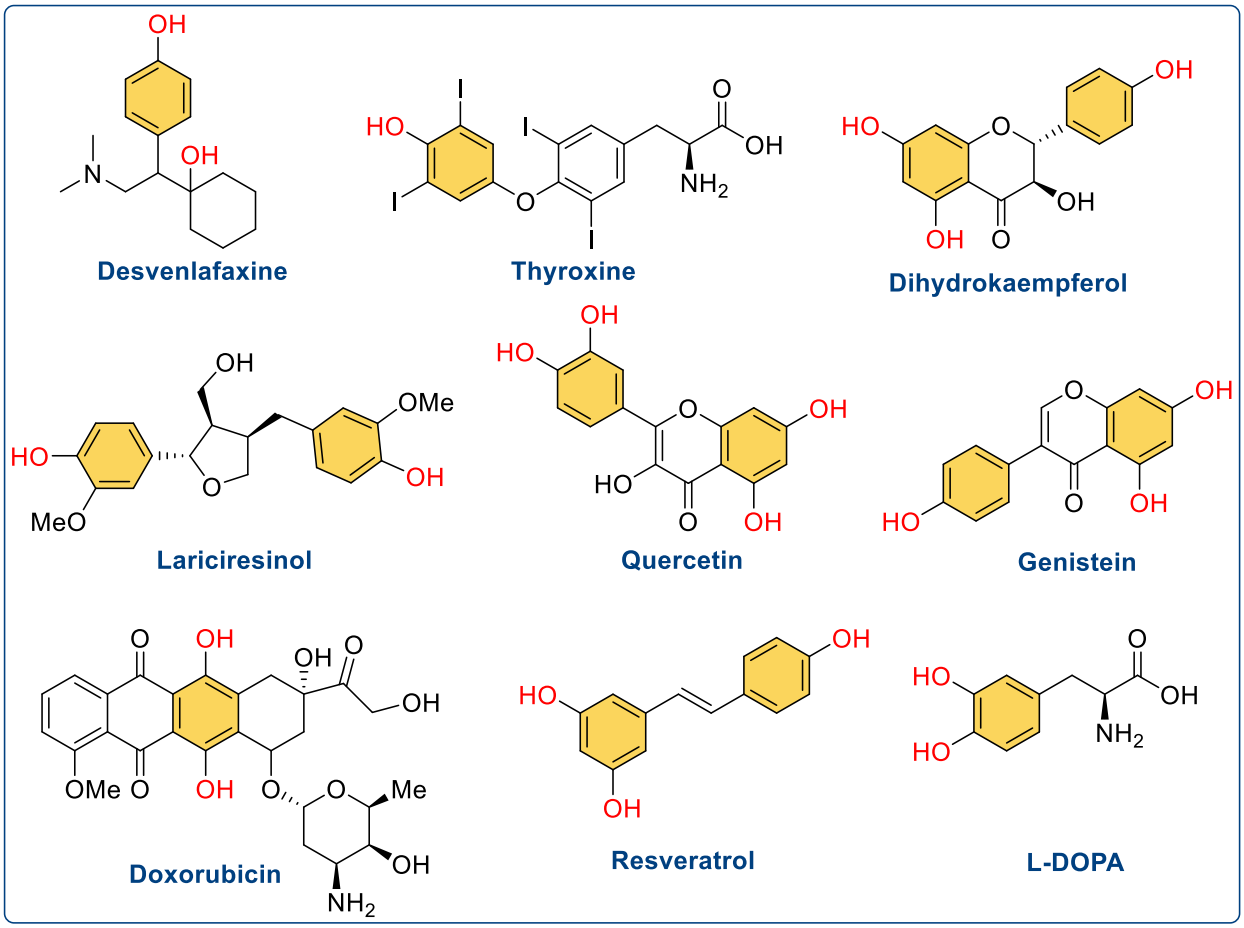


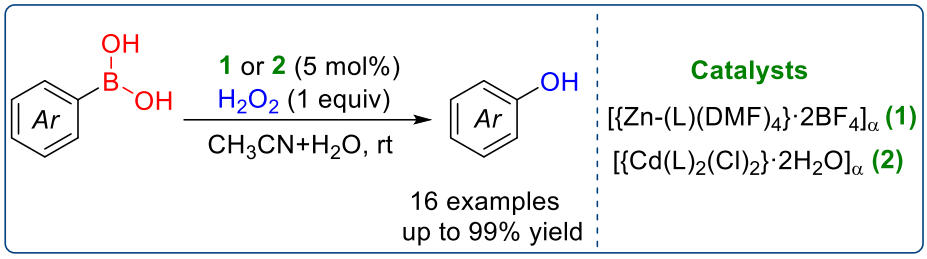
Figure 5A.1. Some of the biologically active phenols from natural products

cancer cells, vi) Genistein,[9] prevents cardiovascular diseases, breast and prostate cancers, vii) doxorubicin,[10] used to treat myriad of cancers, viii) resveratrol,[11] has cardioprotective activity, ix) L-DOPA,[12] used in the treatment of Parkinson's disease (Figure 5A.1). In addition to medicinal applications, phenols are also employed in the polymer chemistry to make electrical appliances.[13]

Phenols are the prominent starting materials in organic synthesis. The electron donating nature of –OH group on benzene ring of phenol facilitates to undergo electrophilic substitutions such as halogenation, nitration, sulfonation, Kolbe-Schmitt, Riemer-Tiemann reactions[14] etc. Phenols are the versatile substrates for the preparation of *O*-containing heterocycles such as chromenes,[15] chromones,[16] flavones,[17] benzofurans,[18] coumarins[19] and xanthones.[20] Also, phenols are useful in the preparation of aryl carbonates,[21] diaryl ethers[22] and azo compounds.[23] Hence, several methods are reported for the preparation of phenols and some of the important methods are discussed below.

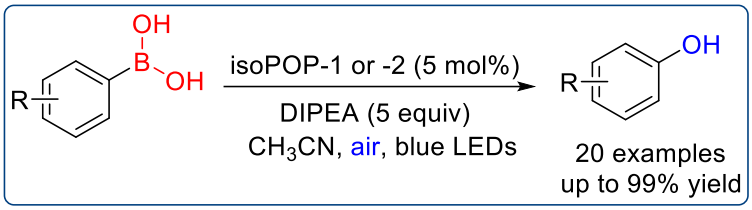
5A.1.1. Reported methods for the synthesis of phenols

Kumar and co-workers established a protocol for the *ipso*-hydroxylation of aryl/heteroaryl boronic acids to respective phenols using 1D Zn and Cd coordination polymers as heterogeneous catalysts and hydrogen peroxide as an oxidant in a mixture of CH_3CN and H_2O at ambient temperature. The main features of this methodology include, recyclability of both catalysts, no loss of efficiency even after five cycles, and high yields (Scheme 5A.1).[24]



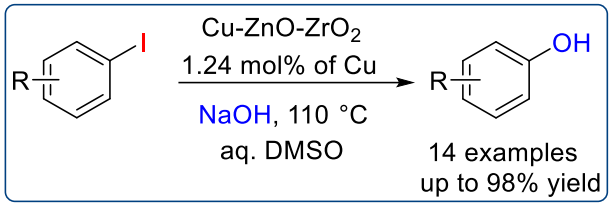
Scheme 5A.1

Zhang and co-workers have developed metal-free two isotruxene-based porous organic polymers such as isoPOP-1 and isoPOP-2 and employed them as photocatalysts in oxidative transformation of arylboronic acids to aryl alcohols using molecular oxygen as an oxidant under visible light irradiation in CH_3CN (Scheme 5A.2).[25]



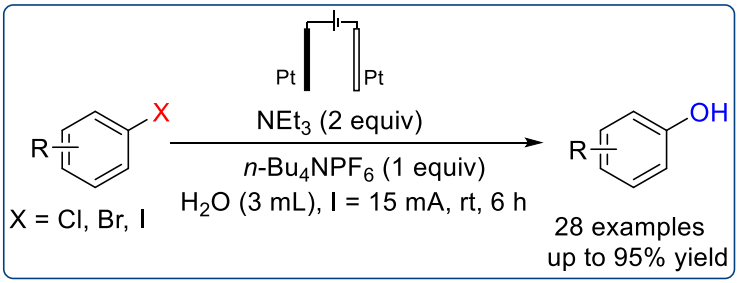
Scheme 5A.2

Hao et al. prepared a novel atomically dispersed copper catalyst and hired as a catalyst in cross-coupling of aryl iodides with sodium hydroxide (NaOH) in aq. DMSO at 110 °C to obtain phenols. The key features of this methodology are 1.24 mol% of Cu loading, ligand free, low-cost, air and moisture tolerant catalyst and high selectivity towards the iodides allows the synthesis of other halogenated phenols (Scheme 5A.3).[26]



Scheme 5A.3

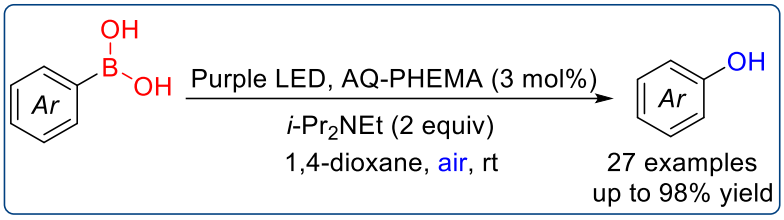
Ke and co-workers developed a strategy for synthesis of phenols through electrochemical-induced hydroxylation of aryl halides in the presence of triethyl amine (NEt_3) and *n*-Bu_4NPF_6 as an electrolyte using Pt as both anode and cathode in an undivided cell under atmospheric oxygen in water. This protocol applicable to aryl chlorides, aryl bromides and aryl iodides. This methodology applicable to gram-scale synthesis and also allows the synthesis of natural product deoxyphomalone (Scheme 5A.4).[27]



Scheme 5A.4

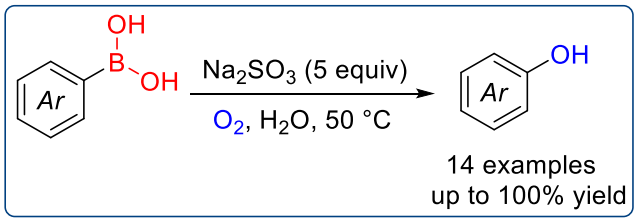
Chen et al. developed a polymeric photosensitizer, which contains anthraquinone (AQ-PHEMA). Later, they applied this photosensitizer in the oxidative hydroxylation of arylboronic acids to achieve phenols under purple LED and atmospheric oxygen in the presence of *N*,*N*-

diisopropylethylamine in 1,4-dioxane at ambient temperature. Broad substrate scope, good yields and simple catalyst recovery are some of the important aspects of this protocol (Scheme 5A.5).[28]



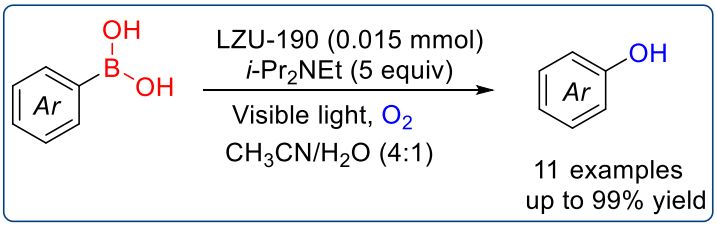
Scheme 5A.5

Argüello and co-workers reported a protocol for synthesis of phenols from arylboronic acids and arylboronic esters using sodium sulfite as a reducing agent and molecular oxygen as an oxidizing agent in water at 50 °C. Here, the electron-donating property of sodium sulfite is disclosed. Inexpensive sodium sulfite and less-toxic by-products made this protocol as environmentally friendly (Scheme 5A.6).[29]



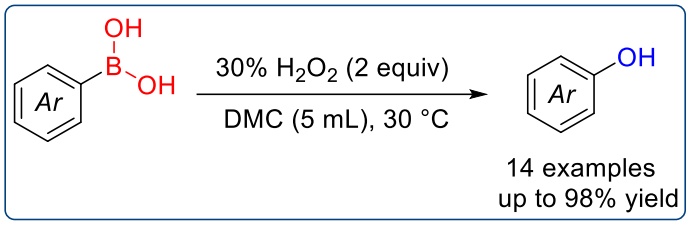
Scheme 5A.6

Wei et al. reported a metal-free benzoxazole based covalent organic frameworks (LZU-190) and employed as a photocatalyst for the convertion of arylboronic acids to phenols under visible light irradiation in the presence of *N*,*N*-diisopropylethylamine as a sacrificial electron donor and molecular oxygen as an oxidant in a mixture of CH_3CN and H_2O (Scheme 5A.7).[30]



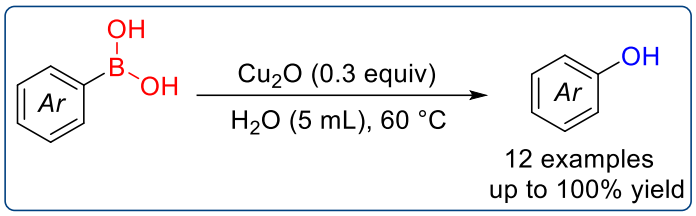
Scheme 5A.7

Nagarkar and co-workers have introduced a protocol for the *ipso*-hydroxylation of arylboronic acids to aryl alcohols using hydrogen peroxide as an oxidizing agent in dimethyl carbonate (DMC) solvent at 30 °C. Also, this methodology is applicable to heteroaromatic boronic acids and offers the corresponding phenols with excellent yields (Scheme 5A.8).[31]



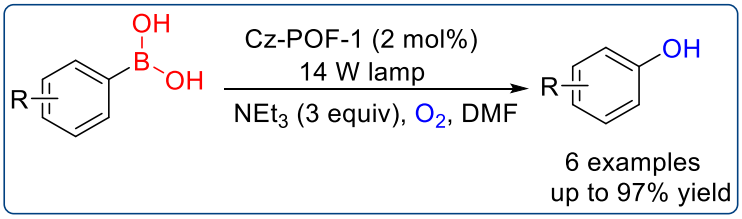
Scheme 5A.8

Chetia et al. prepared the octahedral Cu_2O nanoparticles of size 7.6 nm in biogenic way using Alston plant extracts without using toxic chemicals. Later, it is employed in the *ipso*-hydroxylation of arylboronic acids to phenols in water at 60 °C. This protocol is free of hazardous oxidizing agents and catalyst is recyclable up to 5 times without loss in activity (Scheme 5A.9).[32]



Scheme 5A.9

Zhang and co-workers invented a new metal-free photocatalyst consists of carbazolic porous organic frameworks (Cz-POF-1) and hired as a photocatalyst for the *ipso*-hydroxylation of arylboronic acids to phenols in the presence of triethylamine as a sacrificial electron donor using 14 W compact fluorescent lamp and molecular oxygen in DMF at room temperature (Scheme 5A.10).[33]



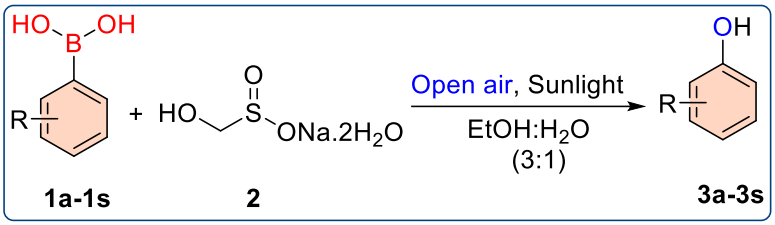
Scheme 5A.10

Based on review of the literature, phenols are mainly prepared from aryl halides and arylboronic acids, but both processes require harsh reaction conditions, expensive reagents, hazardous oxidizing reagents in excess quantities, special reaction setup, long reaction times and transition metal catalysts. There is a necessity to develop green and environment friendly oxidation

methods with functional group tolerance to circumvent the problems associated with the existed methods.

5A.2. Present study

In light of the importance of the phenols in organic synthesis and the associated challenges for their production, we planned to develop a transition metal-free and green protocol by employing arylboronic acids as substrates, rongalite as an electron source and molecular oxygen as an oxidizing agent under sunlight. Based on our previous experience with rongalite, we assumed that rongalite will donate electron to the molecular oxygen to form superoxide radical anion, which is responsible for the oxidative hydroxylation of arylboronic acids to phenols under sunlight. Also, we performed density-functional theory (DFT) calculations for mechanistic study. A graphical abstract is shown in Scheme 5A.11.



Scheme 5A.11. Rongalite-induced aerobic *ipso*-hydroxylation of arylboronic acids under Sunlight

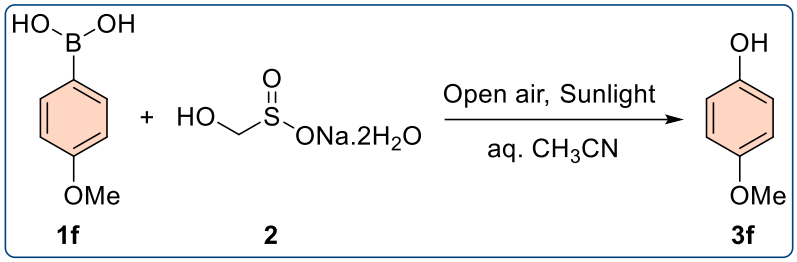
5A.2.1. Results and discussion

In order to test our hypothesis, a reaction was conducted between 4-methoxyphenylboronic acid **1f** as a model substrate and rongalite **2** in the presence of molecular oxygen as an oxidant in aq. CH_3CN under sunlight to transform into the corresponding phenol **3f**. To our delight the formation of **3f** in 60% was observed in aq. CH_3CN under sunlight (Table 5A.1, entry 1). Then, to know the role of components i.e., rongalite, molecular oxygen and sunlight, we have performed some control experiments and the results were shown in Table 5A.1.

Initially, reaction was conducted in absence of rongalite and observed no phenol formation (Table 5A.1, entry 2). Next, reaction was conducted under nitrogen atmosphere to avoid presence of atmospheric oxygen then trace amounts of 4-methoxyphenol **3f** was formed, this may be due to the dissolved oxygen present in water (Table 5A.1, entry 3). Finally, reaction was run under dark conditions to avoid sunlight exposure to reaction mixture, here also we got only

trace amounts of 4-methoxyphenol **3f** (Table 5A.1, entry 4). These results clearly demonstrate that the rongalite, oxygen and sunlight all are essential components for the *ipso*-hydroxylation of arylboronic acids to aryl alcohols.

Table 5A.1. Optimization of reaction conditions[a]



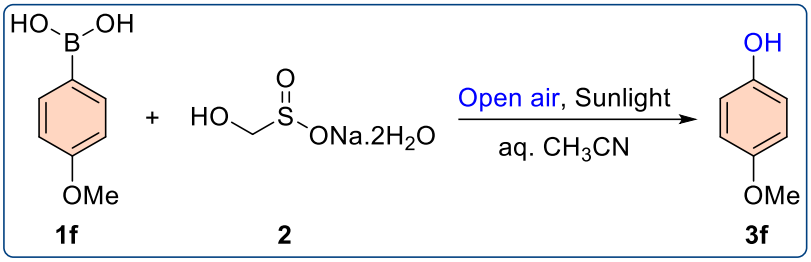
Entry	Rongalite	Air	Sunlight	Time (h)	Yield[b] (%)
1	+	+	+	8	60
2	–	+	+	8	n.r.
3	+	–	+	8	trace
4	+	+	–	8	trace

[a]Reaction conditions: **1f** (0.5 mmol), rongalite **2** (2 equiv, 1.0 mmol), air and sunlight in aq. CH_3CN for 8 h. [b]Yield of isolated product. n.r. = no reaction.

Further, attention has been paid to optimize the reaction conditions under sunlight to improve the yield of the product. All the reactions were performed in mixture of solvents at room temperature with 2.0 equiv of rongalite under sunlight in open air condition (Table 5A.2). Among the solvent mixtures tested, CH_3CN:H_2O (3:1) and EtOH:H_2O (3:1) were afforded desired product in good yields (Table 5A.2, entries 7 and 8), however other combinations resulted in less yield and longer reaction times, this may be attributed to the solubility issues associated with organic substrates (Table 5A.2, entry 9). Further, increase in amount of rongalite did not improve the yield (Table 5A.2, entry 10).

It is worth noting that the reaction time was decreased to 3h when we use oxygen balloon, which indicates the necessity of oxygen (Table 5A.2, entry 11). Moreover, we have examined with other sulfur-containing reducing agents for *in situ* generation of superoxide radical anion for *ipso*-hydroxylation. Thiourea dioxide gave desired product with less yield in longer time, whereas sodium dithionite gave inferior results. This data indicates that rongalite is the best among the other sulfur-containing radical initiators (Table 5A.2, entries 12 and 13).

Table 5A.2. Screening of reaction conditions for the *ipso*-hydroxylation of arylboronic acids[a]



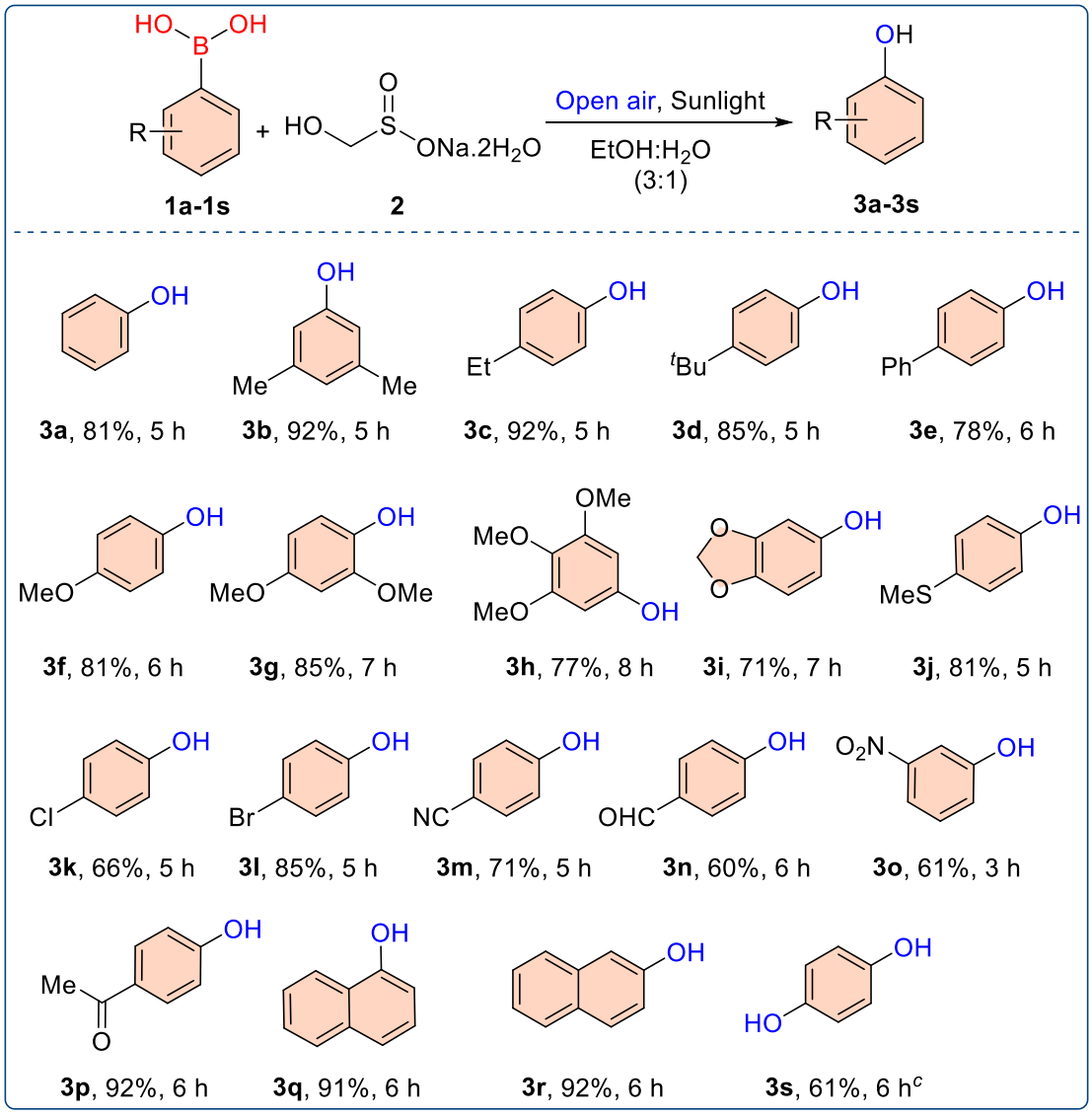
Entry	Solvent	Reagent (equiv)	Time (h)	Yield[b] (%)
1	aq. dioxane	Rongalite (2)	20	55
2	aq. CH_3CN	Rongalite (2)	8	74
3	aq. DMSO	Rongalite (2)	18	35
4	aq. MeOH	Rongalite (2)	8	74
5	aq. THF	Rongalite (2)	15	69
6	aq. DMF	Rongalite (2)	18	65
7	CH_3CN:H_2O (3:1)	Rongalite (2)	6	75
8	**EtOH:H_2O (3:1)**	**Rongalite (2)**	**6**	**81**
9	EtOH:H_2O (1:1)	Rongalite (2)	10	60
10	EtOH:H_2O (3:1)	Rongalite (3)	6	81
11	EtOH:H_2O (3:1)	Rongalite (2)	3	81[c]
12	EtOH:H_2O (3:1)	Thiourea dioxide (2)	72	41
13	EtOH:H_2O (3:1)	Sodium dithionite (2)	72	trace

[a]Reaction conditions: **1f** (0.50 mmol), reagent (2 equiv, 1.0 mmol), air and sunlight.
[b]Yield of isolated product. [c]Reaction was conducted in presence of oxygen balloon.

With optimized reaction conditions (Table 5A.2, entry 8) in hand, the applicability of the reaction condition was explored by using various substituted arylboronic acids/pinacol esters and the results were summarized in Table 5A.3 and 5A.4. Electron-donating groups i.e., ethyl, methyl and phenyl substituted arylboronic acids underwent aerobic *ipso*-hydroxylation in good yields (71-92%) within the period of 5-8 h under sunlight (Table 5A.3, **3a-3j**). Notably, electron-withdrawing groups such as –nitro, –formyl, –cyano and –ketone substituted arylboronic acids did not affect the product yield (Table 5A.3, **3m-3p**). Interestingly, chloro and bromo substituted arylboronic acids also hydroxylated efficiently with the aforementioned conditions without undergoing dehalogenation reaction (Table 5A.3, **3k** and **3l**). 1-naphthylboronic acid and 2-naphthylboronic acid are also subjected to *ipso*-hydroxylation to give corresponding naphthols in 91% and 92% yields respectively (Table 5A.3, **3q-3r**).

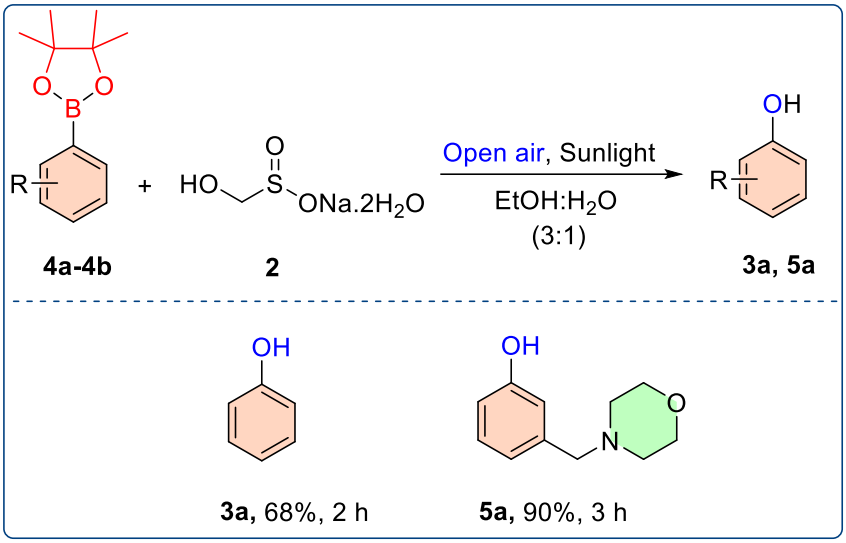
Further, we have applied same optimized reaction conditions to 1,4-phenylenediboronic acid, which readily gave hydroquinone by oxidative *ipso*-hydroxylation at C-1 and C-4 position (Table 5A.3, **3s**). Next, the scope of this methodology has been extended to phenylboronic acid pinacol esters, which are derivatives of phenylboronic acids and obtained desired products in good yields within 2-3 hours (Table 5A.4).

Table 5A.3. Substrate scope of the *ipso*-hydroxylation of arylboronic acids by rongalite under sunlight in open air[a,b]

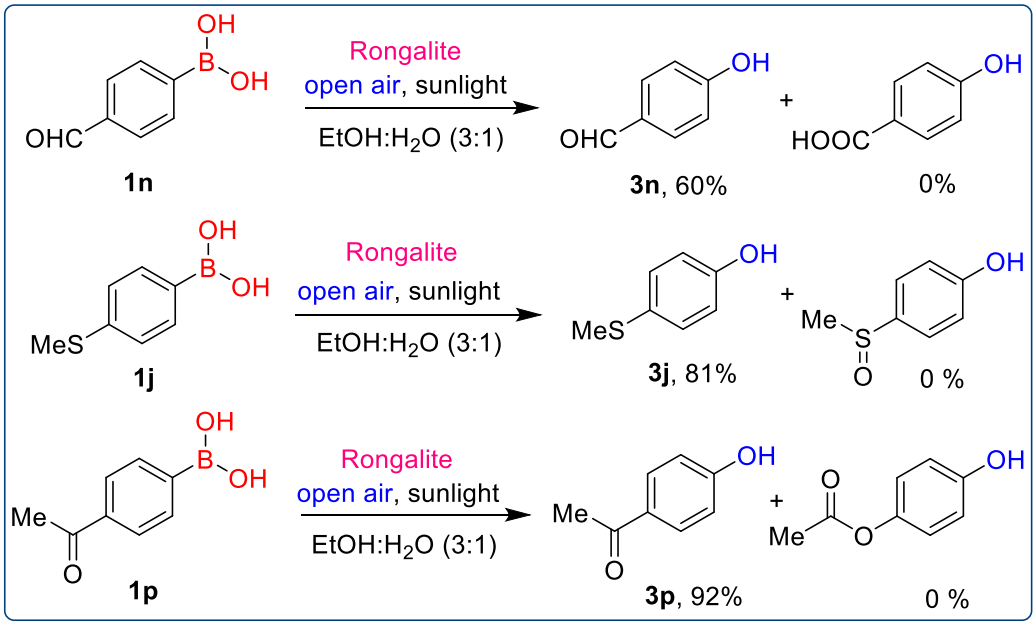


[a]Reaction conditions: arylboronic acid **1** (0.5 mmol), rongalite **2** (2 equiv, 1.0 mmol), air and sunlight in 1 mL of $EtOH:H_2O$ (3:1). [b]Yield of isolated product. [c]4 equiv of rongalite was used.

Table 5A.4. Rongalite mediated hydroxylation of phenylboronic acid pinacol esters[a,b]



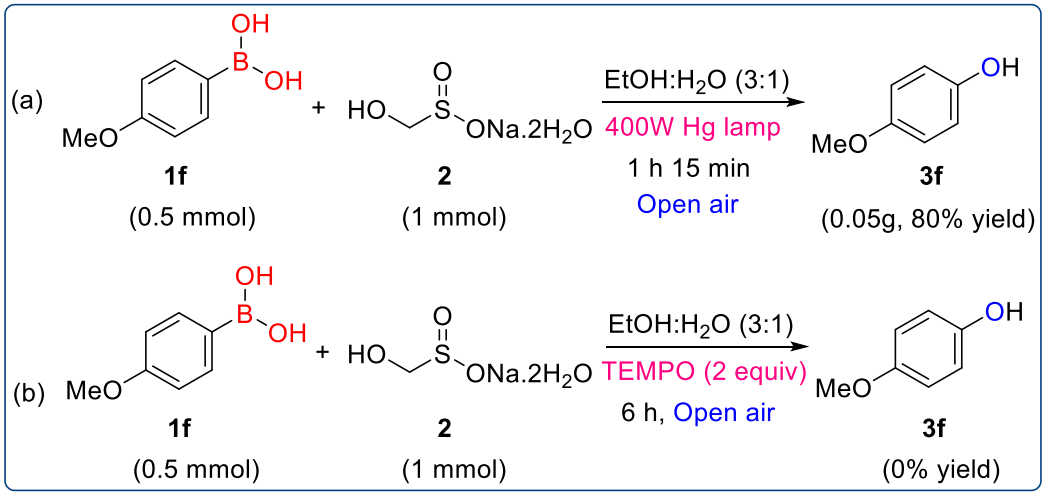
[a]Reaction conditions: substrate **4** (0.5 mmol), rongalite **2** (2 equiv, 1.0 mmol), air and sunlight in 1 mL of EtOH:H_2O (3:1). [b]Yield of isolated product.



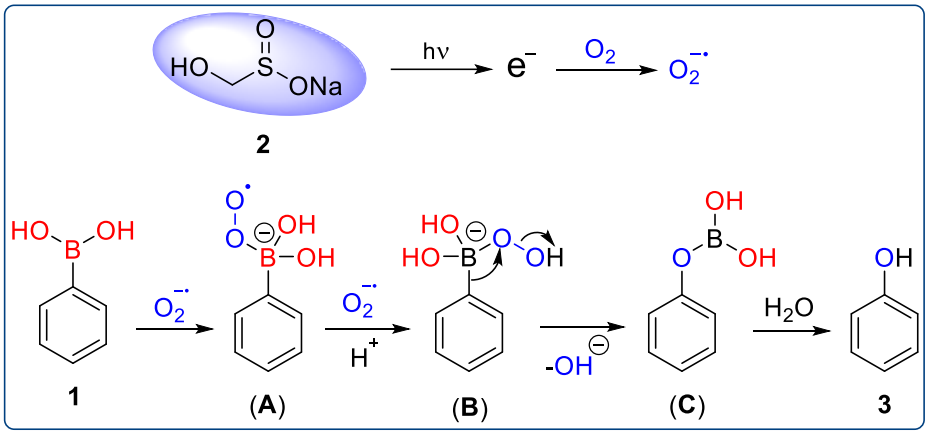
Scheme 5A.12. Chemoselectivity of the proposed method

Considering the importance of multifaceted reactivity of rongalite, we turned our interest to explore chemoselectivity of rongalite and results were summarized in Scheme 5A.12. With the above optimal reaction conditions of oxidative *ipso*-hydroxylation of arylboronic acids, oxidative susceptible functional groups i.e., aldehyde/ketone (Baeyer Villiger oxidation)[34] and sulfide (can convert into sulfoxide and sulfone)[35] remained intact even at prolonged time (Scheme 5A.12).

To gain more insight into the reaction mechanism, we have conducted some controlled experiments. Initially, we conducted the same model reaction under 400W Hg immersion lamp and observed that the reaction was completed within 1 h 15 min (Scheme 5A.13a). It clearly indicates that the ultraviolet light is responsible for moving the reaction under sunlight irradiation. Later, we conducted the same model reaction with radical scavenger (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) and observed that the reaction was completely inhibited (Scheme 5A.13b).



Scheme 5A.13. Control experiments



Scheme 5A.14. Plausible reaction mechanism.

Based on the controlled experiments and previous reports,[36,37] we proposed a possible reaction mechanism involving radical pathway (Scheme 5A.14) and has been validated using density functional theory calculations (Figure 5A.2). Initially, rongalite releases electron on irradiation by sunlight, which is trapped by molecular oxygen to form superoxide radical anion. Later,

superoxide radical anion attacks on the electrophilic boron atom of the phenylboronic acid **1** to form tetrahedral intermediate (**B**). Subsequently, phenyl group in tetrahedral intermediate (**B**) undergoes Baeyer-Villiger type of migration onto peroxy oxygen atom and followed by hydrolysis to afford the desired phenols **3**.

5A.2.2. Density functional theory (DFT) calculations

To gain insight into the reaction mechanism, density functional theory (DFT) calculations were performed. Geometries of reactants, transition structures (TSs), and intermediates were fully optimized using UB3LYP/6-311+G(d,p) level of theory.[38,39] Calculated relative energy profile shown in Figure 5A.2 along with important geometry.

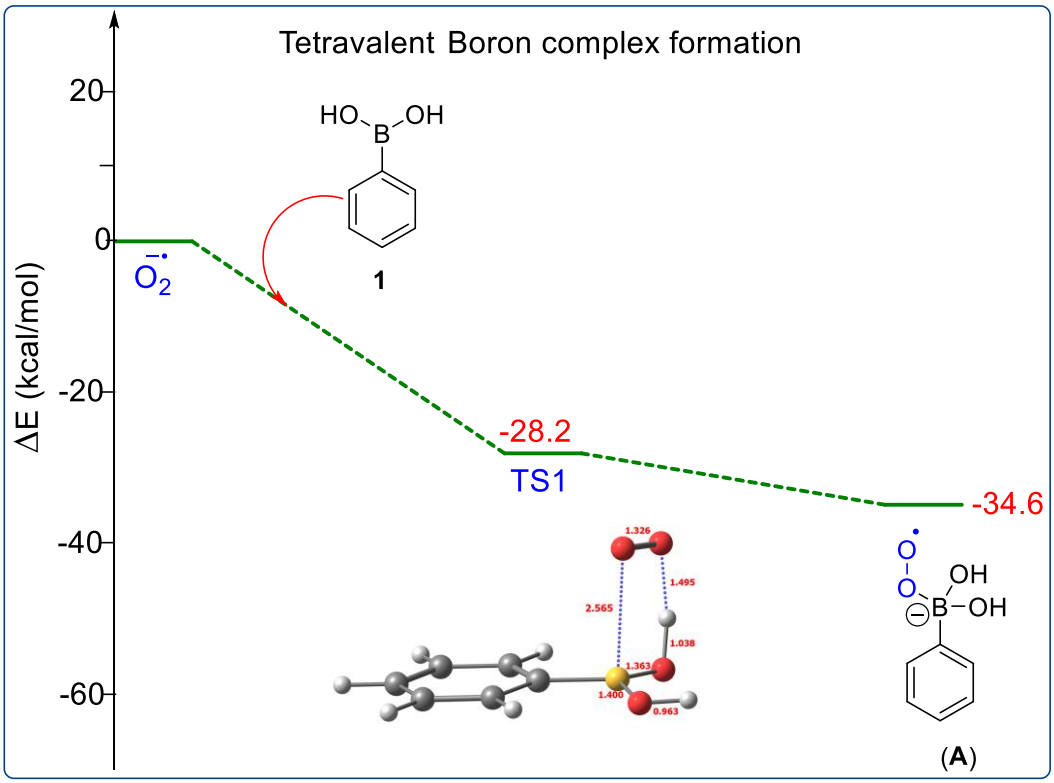


Figure 5A.2. Relative energy profile of tetravalent boron intermediate formation. (Color key: White = Hydrogen, Yellow = Boron, Grey = Carbon and Red = Oxygen).

Formation of superoxide radical anion described elsewhere.[40] Close analysis of relative energy of formation of transition state (TS1) is -28.2 kcal/mol, which clearly indicates that the superoxide radical anion readily reacts with phenylboronic acid to form the intermediate (**A)** (Figure 5A.2). It is also interesting to note from the optimized geometry of TS1 that phenylboronic acid forms hydrogen bond interaction with the incoming super oxide radical anion. Therefore, it is worth to

mention that the low energy barrier of this reaction may be attributed to the additional stabilization of TS1 arises due to the formation of hydrogen bond. Furthermore, it can also be noted that relative energy of formation of tetravalent boron radical anion intermediate (**A**) is less when compared to that of TS1 and reactant. Boron anion radical intermediate readily abstracts the proton to form tetravalent boron anion intermediate as shown in following Figure 5A.3.

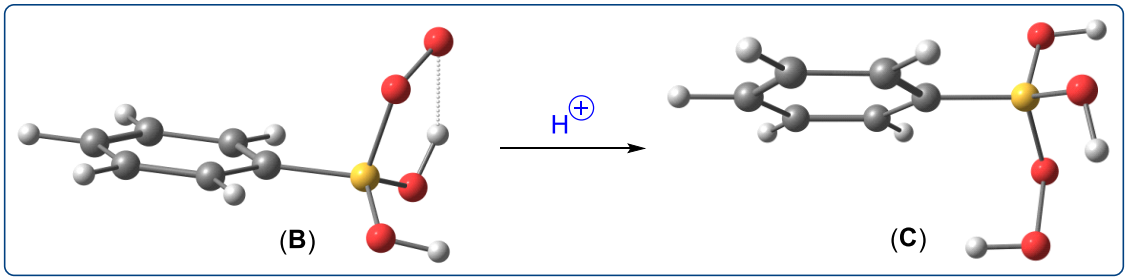


Figure 5A.3. Formation of tetravalent boron anion intermediate.

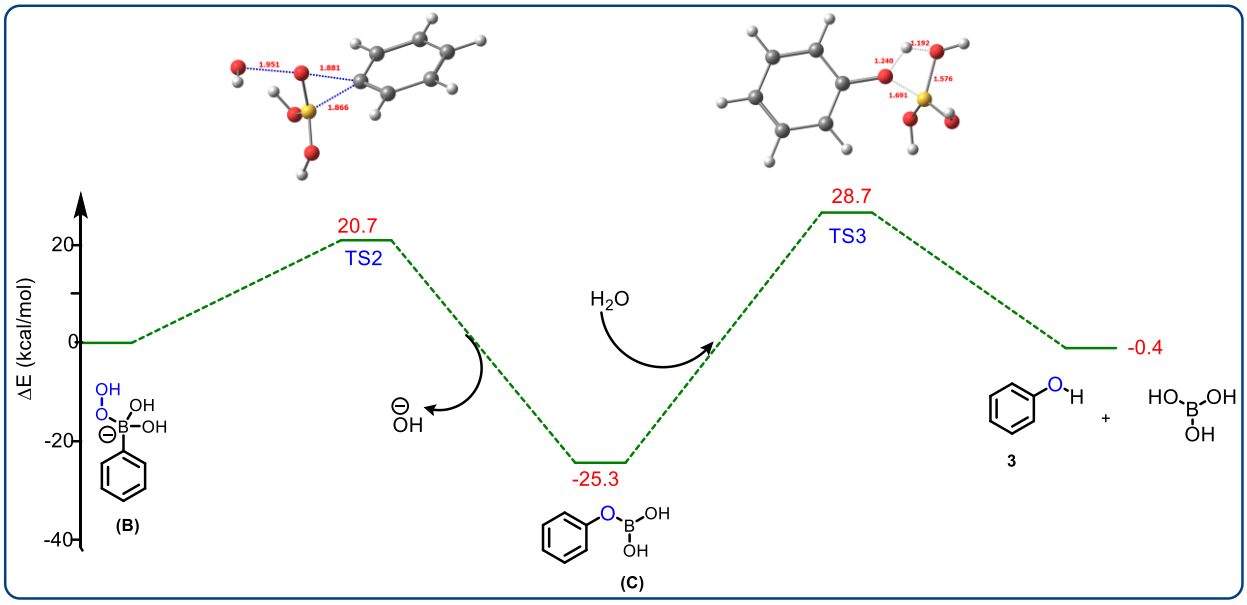


Figure 5A.4. Relative energy profile of formation of phenol from tetravalent boron anion intermediate (**B**).

It is interesting to note that the protonation of boron anion radical intermediate (**B**) stabilizes enormously. Typically, calculated energy difference of these intermediates is 517.8 kcal/mol. The large energy difference is clear evidence of occurrence of reaction at room temperature condition. The relative energy profile of formation of phenol from protonated tetravalent boron anion intermediate (**B**) is shown in Figure 5A.4. Calculated relative energy profile clearly indicates the formation of TS3 corresponding to the hydrolysis of phenoxy boronic acid

intermediate **C** requires more energy when compared with TS2 (phenyl group migration from B to O). The isolated products obtained in the reaction are energetically and marginally stable, when compared with the protonated tetravalent boron anion intermediate (**B)**. The calculated data clearly reinforces the experimental findings *viz*. incorporation of oxygen atom into the product from the molecular oxygen, reaction time, temperature, and the product yield (due to the low energy barrier).

5A.3. Conclusions

We have developed a green protocol using rongalite:molecular oxygen reagent system, which generates superoxide radical anion *in situ* facilitates the *ipso*-hydroxylation of arylboronic acids to their corresponding phenols in good yields with relatively short reaction times. Additionally, this protocol enables the synthesis of wide range of phenols up to 92% yields. Notably, this protocol is chemoselective and functional groups which are sensitive to oxidation are well tolerated. Further, DFT calculations were performed to gain insight into the reaction mechanism.

5A.4. Experimental section

5A.4.1. General information

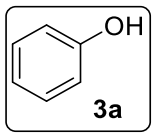
All chemicals and solvents were purchased from Alfa Aesar, Spectrochem, SRL, Finar and used as received. The reactions were monitored by analytical TLC on 200 µm aluminum-foil-backed silica gel plates. Column chromatography was performed using 100-200 mesh silica gel. Bruker Avance 400 MHz spectrometer was used to record ^{1}H NMR spectra and used $CDCl_3$ and DMSO-d_6 as solvents and TMS as an internal standard. The multiplicities were described using the following acronyms: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Coupling constants, *J* were reported in Hertz unit (Hz). Bruker Avance 100 MHz spectrometer was used to record $^{13}C\{^{1}H\}$ NMR spectra, and they were fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to the center line of a triplet at 77.16 ppm of chloroform-*d* (a multiplet at 39.52 ppm of DMSO-d_6). A Stuart SMP30 apparatus was used to determine the melting points and are uncorrected. FT-IR spectra were recorded on a Perkin Elmer spectrometer. HRMS were analyzed with Agilent Q-TOF 6230. The ^{1}H NMR and ^{13}C NMRs of all phenols were compared with literature reports.

5A.4.2. General procedure

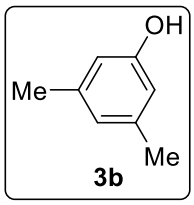
To a clean and dry round bottom flask, phenylboronic acid/pinacol esters (0.5 mmol), sodium hydroxymethanesulfinate dihydrate (2 equiv, 1.0 mmol) and 1 mL of EtOH:H_2O (3:1) solvent mixture were added. The resulting mixture was stirred under sunlight irradiation in open air. The reaction progress was monitored by TLC. After completion of reaction, solvent mixture was evaporated under vacuum, the crude product was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried on anhydrous Na_2SO_4, solvent was evaporated under vacuum. The residue was purified by column chromatography using silica gel as a stationary phase and ethyl acetate/hexanes as an eluent.

5A.5. Characterization data of 3a-3s & 5a

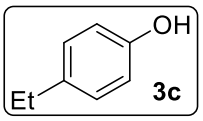
phenol (3a).[41] Colorless liquid; Yield (31 mg, 65%); The title compound is prepared according to the general procedure described as above; FT-IR (KBr, cm^{-1}) 3421, 2923, 1455; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.33 – 7.26 (m, 2H), 6.99 (t, J = 7.6 Hz, 1H), 6.90 (d, J = 7.6 Hz, 2H), 4.91 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 155.4, 129.8, 120.9, 115.5.



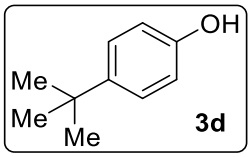
3,5-dimethylphenol (3b).[42] White crystalline solid; Yield (42 mg, 69%); The title compound is prepared according to the general procedure described as above; FT-IR (KBr, cm^{-1}) 3276, 3036, 2919, 2854, 1619, 1473, 1312, 1151, 832, 683; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.51 (s, 1H), 6.39 (s, 2H), 4.56 (s, 1H), 2.19 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 155.4, 139.6, 122.6, 113.1, 21.3.



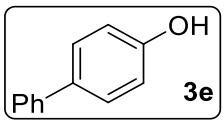
4-ethylphenol (3c).[41] White solid; Yield (48 mg, 78%); The title compound is prepared according to the general procedure described as above; FT-IR (KBr, cm^{-1}) 3317, 2964, 2929, 2871, 1613, 1514, 1451, 1237, 829; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.97 (d, J = 8.4 Hz, 2H), 6.67 (d, J = 8.4 Hz, 2H), 5.23 (s, 1H), 2.49 (q, J = 7.6 Hz, 2H), 1.11 (t, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 153.3, 136.6, 129.0, 115.3, 28.0, 15.9.



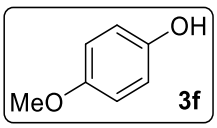
4-(*tert*-butyl) phenol (3d).[43] White crystalline solid; Yield (52 mg, 69%); The title compound is prepared according to the general procedure described as above; FT-IR (KBr, cm^{-1}) 3247, 2960, 2928, 2868, 1613, 1514, 453, 1362, 828, 546; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.18 (d, J = 8.8 Hz, 2H), 6.70 (d, J = 8.8 Hz, 2H), 4.69 (s, 1H), 1.22 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 153.1, 143.5, 126.5, 114.8, 34.1, 31.5.



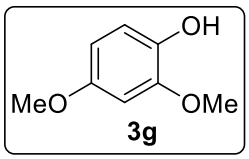
[1,1'-biphenyl]-4-ol (3e).[41] White solid; Yield (78 mg, 92%); The title compound is prepared according to the general procedure described as above; FT-IR (KBr, cm^{-1}) 3386, 2923, 1487, 1374, 832, 757, 685; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.46 (d, J = 7.6 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.33 (t, J = 7.6 Hz, 2H), 7.23 (t, J = 7.6 Hz, 1H), 6.83 (d, J = 8.4 Hz, 2H), 4.89 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ (ppm): 157.0, 141.0, 132.2, 128.7, 128.0, 126.5, 126.4, 115.9.



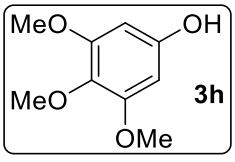
4-methoxyphenol (3f).[43] White solid; Yield (50 mg, 81%); The title compound is prepared according to the general procedure described as above; FT-IR (KBr, cm^{-1}) 3368, 3012, 2951, 2834, 1607, 1510, 1448, 1231, 1032, 824, 733, 513; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.72 – 6.67 (m, 4H), 5.42 (s, 1H), 3.68 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 153.7, 149.5, 116.1, 114.9, 55.9.



2,4-dimethoxyphenol (3g).[44] Brown liquid; Yield (65 mg, 85%); The title compound is prepared according to the general procedure described as above; FT-IR (KBr, cm^{-1}) 3436, 2936, 2837, 1610, 1511, 1433, 1349, 1292, 1129, 851, 764; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.65 (d, J = 8.8 Hz, 1H), 6.40 (d, J = 2.8 Hz, 1H), 6.28 (dd, J = 8.8, 2.8 Hz, 1H), 5.39 (s, 1H), 3.74 (s, 3H), 3.73 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 150.3, 149.8, 143.0, 112.5, 105.9, 100.6, 56.6, 55.8.

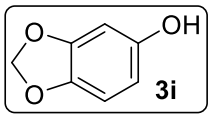


3,4,5-trimethoxyphenol (3h).[45] White crystalline solid; Yield (71 mg, 77%); The title compound is prepared according to the general procedure described as above; FT-IR (KBr, cm^{-1}) 3268, 2925, 2849, 1611, 1485, 1429, 1223, 1126, 776; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.11 (s, 2H), 5.04 (s, 1H), 3.83 (s,



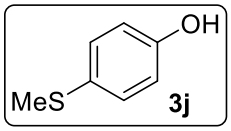
6H), 3.80 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 153.7, 152.6, 131.7, 93.0, 61.1, 56.0.

benzo[d][1,3]dioxol-5-ol (3i).[46] Colorless liquid; Yield (49 mg, 71%); The title compound is



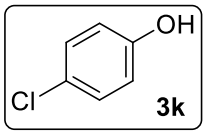
prepared according to the general procedure described as above; FT-IR (KBr, cm^{-1}) 3373, 2891, 1632, 1503, 1489, 1473, 1187, 1030, 1005, 813, 766; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.58 (d, J = 8.4 Hz, 1H), 6.35 (d, J = 2.4 Hz, 1H), 6.18 (dd, J = 8.4, 2.4 Hz, 1H), 5.83 (s, 2H), 4.28 (s, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ (ppm): 152.4, 147.9, 140.3, 108.0, 106.7, 100.7, 98.3.

4-(methylthio)phenol (3j).[43] White crystalline solid; Yield (57 mg, 81%); The title compound is



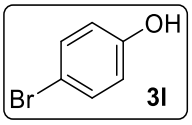
prepared according to the general procedure described as above; FT-IR (KBr, cm^{-1}) 3494, 2919, 1599, 1494, 1305, 821; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.15 (d, J = 8.8 Hz, 2H), 6.72 (d, J = 8.8 Hz, 2H), 2.36 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 154.2, 130.5, 128.8, 116.1, 18.1.

4-chlorophenol (3k).[41] Colorless liquid; Yield (42 mg, 66%); The title compound is prepared



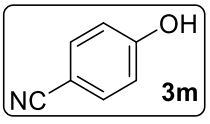
according to the general procedure described as above; FT-IR (KBr, cm^{-1}) 3351, 2927, 1591, 1493, 1234, 825, 643; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.11 (d, J = 8.8 Hz, 2H), 6.69 (d, J = 8.8 Hz, 2H), 5.18 (s, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 154.0, 129.6, 125.7, 116.7.

4-bromophenol (3l).[42] Colorless liquid; Yield (73 mg, 85%); The title compound is prepared



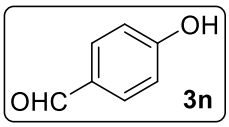
according to the general procedure described as above; FT-IR (KBr, cm^{-1}) 3374, 2926, 1587, 1489, 1238, 823, 606, 502; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.36 (d, J = 8.8 Hz, 2H), 6.75 (d, J = 8.8 Hz, 2H), 5.32 (s, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 154.5, 132.6, 117.3, 113.0.

4-hydroxybenzonitrile (3m).[41] Pale orange solid; Yield (42 mg, 71%); The title compound is

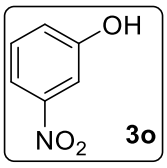


prepared according to the general procedure described as above; FT-IR (KBr, cm^{-1}) 3279, 2924, 2853, 2232, 1586, 1509, 1438, 1166, 837, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.47 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ (ppm): 161.6, 133.9, 119.8, 116.5, 101.9.

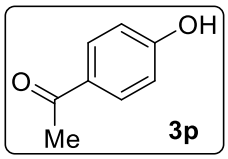
4-hydroxybenzaldehyde (3n).[41] White crystalline solid; Yield (37 mg, 60%); The title compound is prepared according to the general procedure described as above; FT-IR (KBr, cm^{-1}) 3207, 2924, 2853, 1670, 1599, 1517, 1453, 1384, 857, 833, 787, 703, 602; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.79 (s, 1H), 7.75 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 6.63 (s, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 195.4, 168.4, 136.9, 133.5, 120.8.



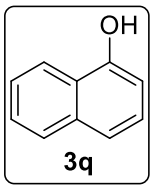
3-nitrophenol (3o).[41] Pale yellow crystalline solid; Yield (42 mg, 61%); The title compound is prepared according to the general procedure described as above; FT-IR (KBr, cm^{-1}) 3390, 2924, 2853, 1528, 1351, 816, 738; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.73 (d, J = 8.4 Hz, 1H), 7.63 (s, 1H), 7.33 (t, J = 8.4 Hz, 1H), 7.11 (d, J = 7.2 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ (ppm): 158.3, 149.0, 129.8, 122.2, 114.1, 110.3.



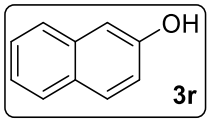
1-(4-hydroxyphenyl)ethanone (3p).[43] White crystalline solid; Yield (63 mg, 92%); The title compound is prepared according to the general procedure described as above; FT-IR (KBr, cm^{-1}) 3306, 2923, 2852, 1662, 1603, 1596, 1522, 1511, 1358, 847, 816, 668; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.27 (s, 1H), 7.94 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 2.61 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 199.2, 161.8, 131.3, 129.3, 115.7, 26.3.



naphthalen-1-ol (3q).[41] White crystalline solid; Yield (66 mg, 91%); The title compound is prepared according to the general procedure described as above; FT-IR (KBr, cm^{-1}) 3262, 2923, 2852, 1597, 1579, 1386, 789, 765; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.08 – 8.03 (m, 1H), 7.70 – 7.64 (m, 1H), 7.38 – 7.32 (m, 2H), 7.30 (d, J = 8.4 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 6.61 (d, J = 7.6 Hz, 1H), 5.54 (s, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 151.6, 134.8, 127.7, 126.5, 125.9, 125.3, 124.5, 121.7, 120.6, 108.7.

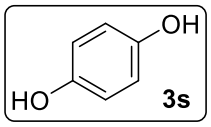


naphthalen-2-ol (3r).[41] White crystalline solid; Yield (66 mg, 92%); The title compound is prepared according to the general procedure described as above; FT-IR (KBr, cm^{-1}) 3254, 3051, 2924, 1630, 1512, 1466, 1216, 843, 813, 741; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.69 – 7.61 (m, 2H), 7.55 (d, J = 8.4 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H),

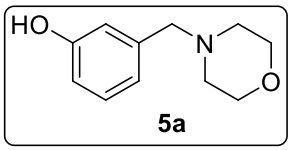


7.22 (t, *J* = 7.6 Hz, 1H), 7.03 (s, 1H), 7.02 – 6.98 (m, 1H), 5.45 (s, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ (ppm): 155.2, 134.9, 129.3, 128.3, 127.7, 126.2, 126.1, 122.8, 118.7, 109.2.

hydroquinone (3s).[41] White solid; Yield (34 mg, 61%); The title compound is prepared according to the general procedure described as above; FT-IR (KBr, cm^{-1}) 3419, 2924, 2853, 1101; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.62 (s, 2H), 6.57 (s, 4H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ (ppm): 150.0, 116.0.



3-(morpholinomethyl)phenol (5a).[47] White solid; Yield (87 mg, 90%); The title compound is prepared according to the general procedure described as above; FT-IR (KBr, cm^{-1}) 3419, 2928, 1588, 1486, 1451, 1349, 1295, 1111, 908, 780; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.09 (t, *J* = 7.6 Hz, 1H), 6.80 – 6.74 (m, 2H), 6.65 (d, *J* = 8.0 Hz, 1H), 3.66 (t, *J* = 4.0 Hz, 4H), 3.40 (s, 2H), 2.42 (s, 4H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 156.2, 138.5, 129.5, 121.5, 116.4, 114.7, 66.7, 63.2, 53.5.



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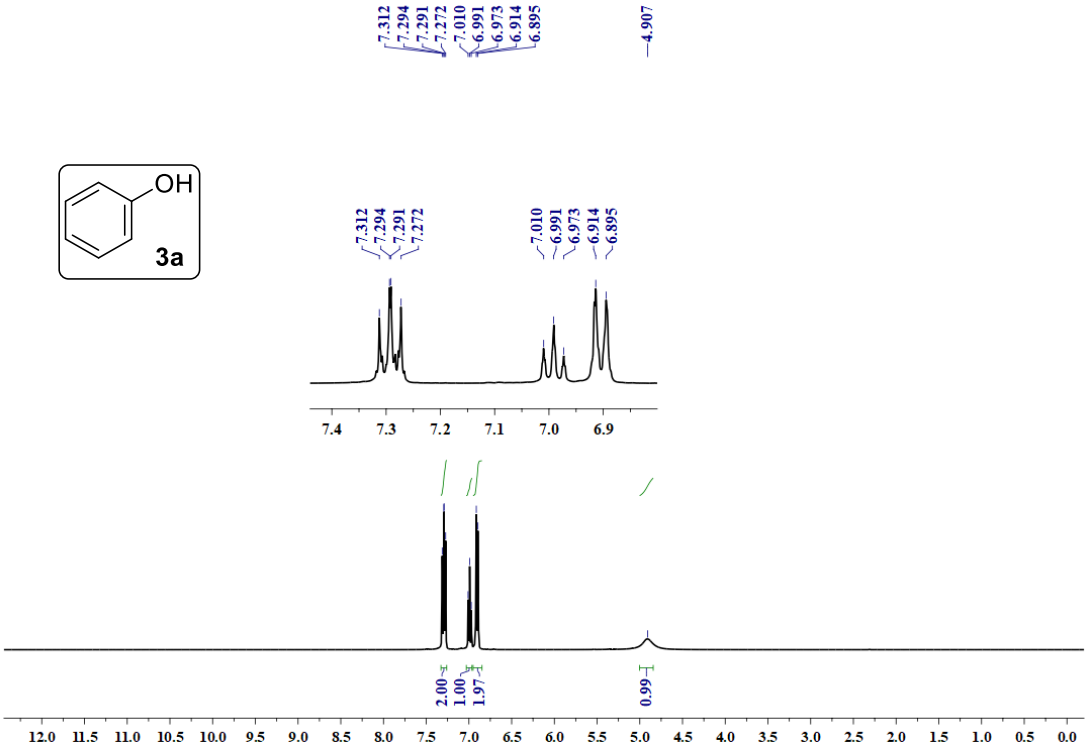
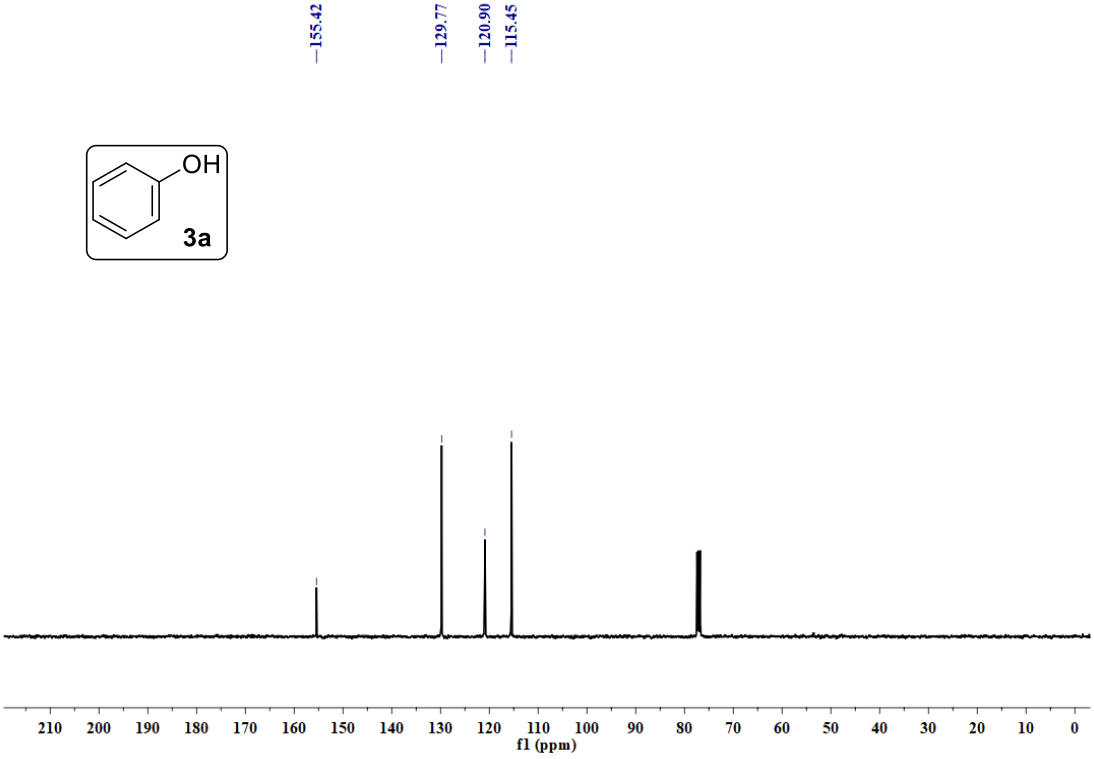
5A.7. Selected NMR (^{1}H & ^{13}C) and HRMS spectra

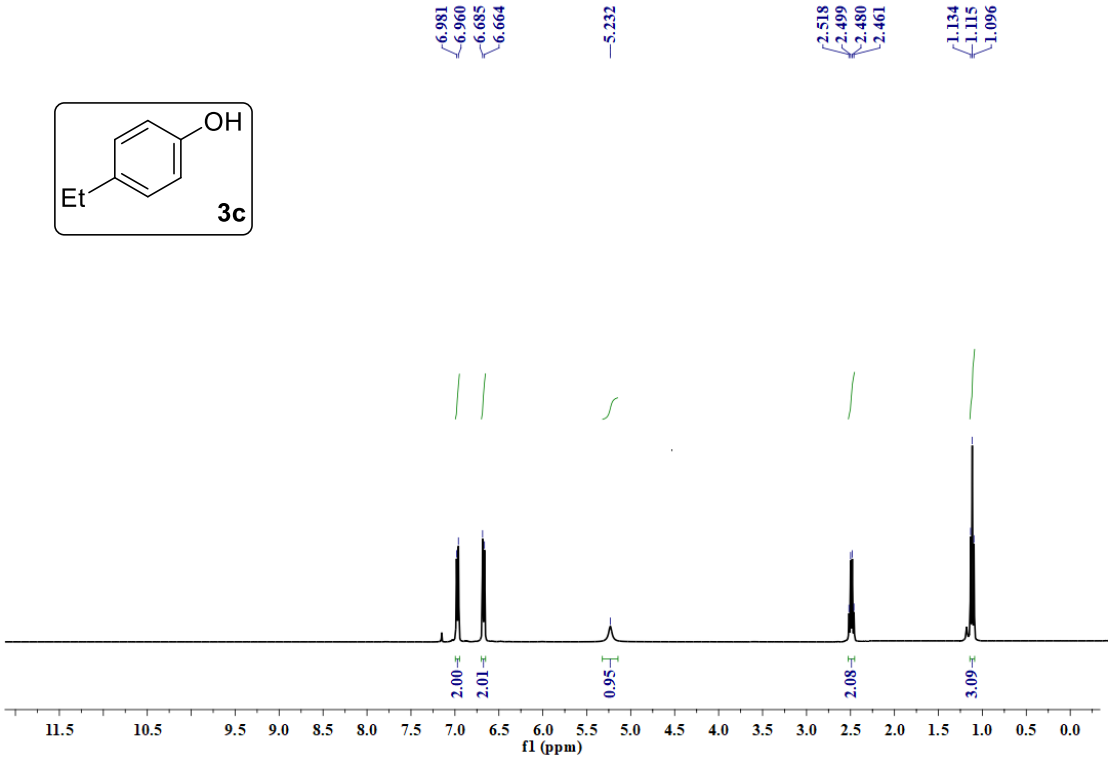
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of phenol (3a)



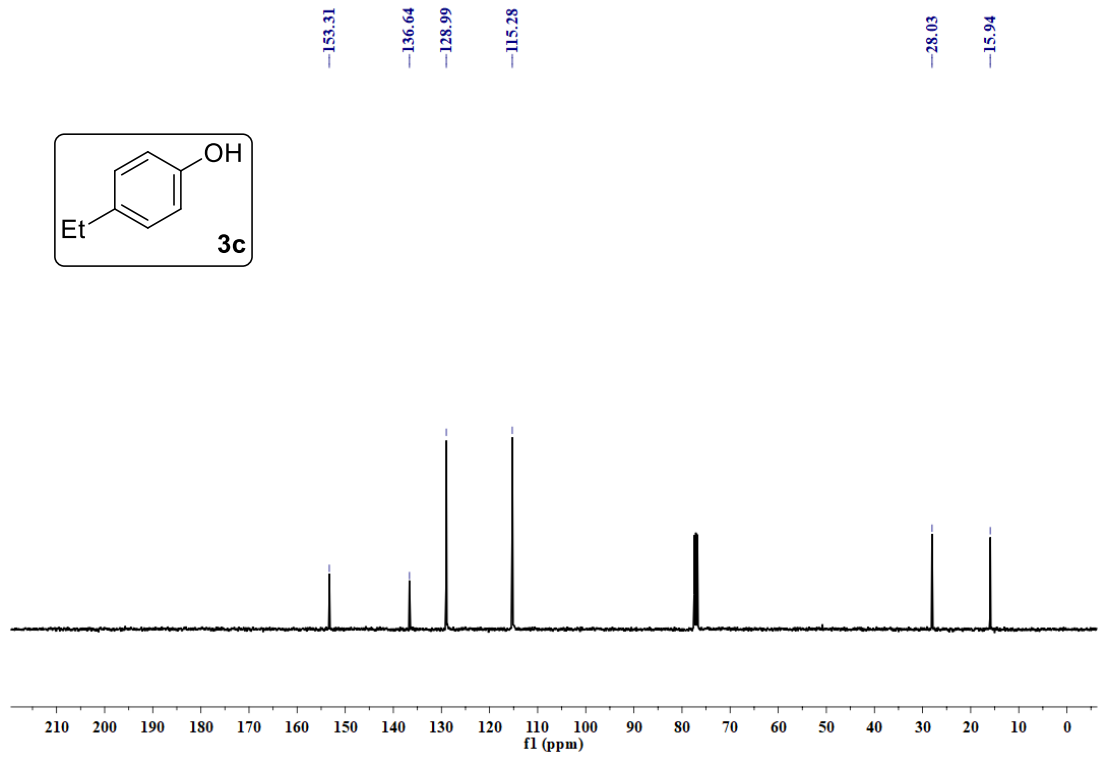
$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of phenol (3a)



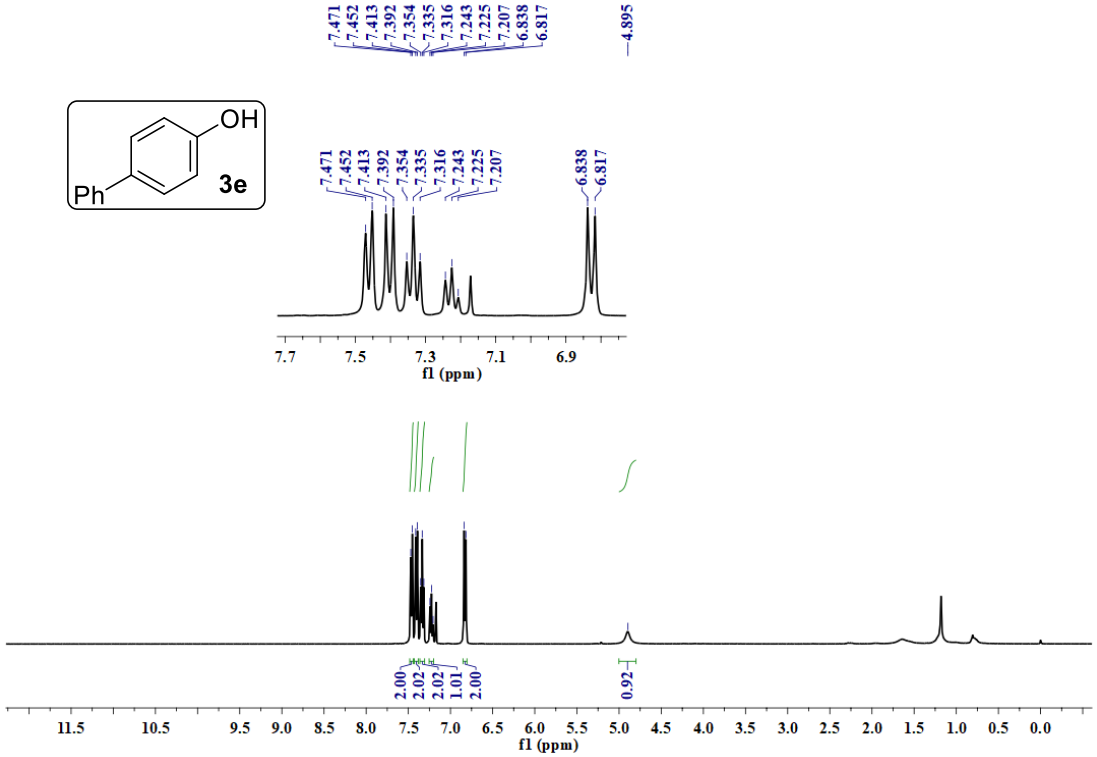
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 4-ethylphenol (3c)



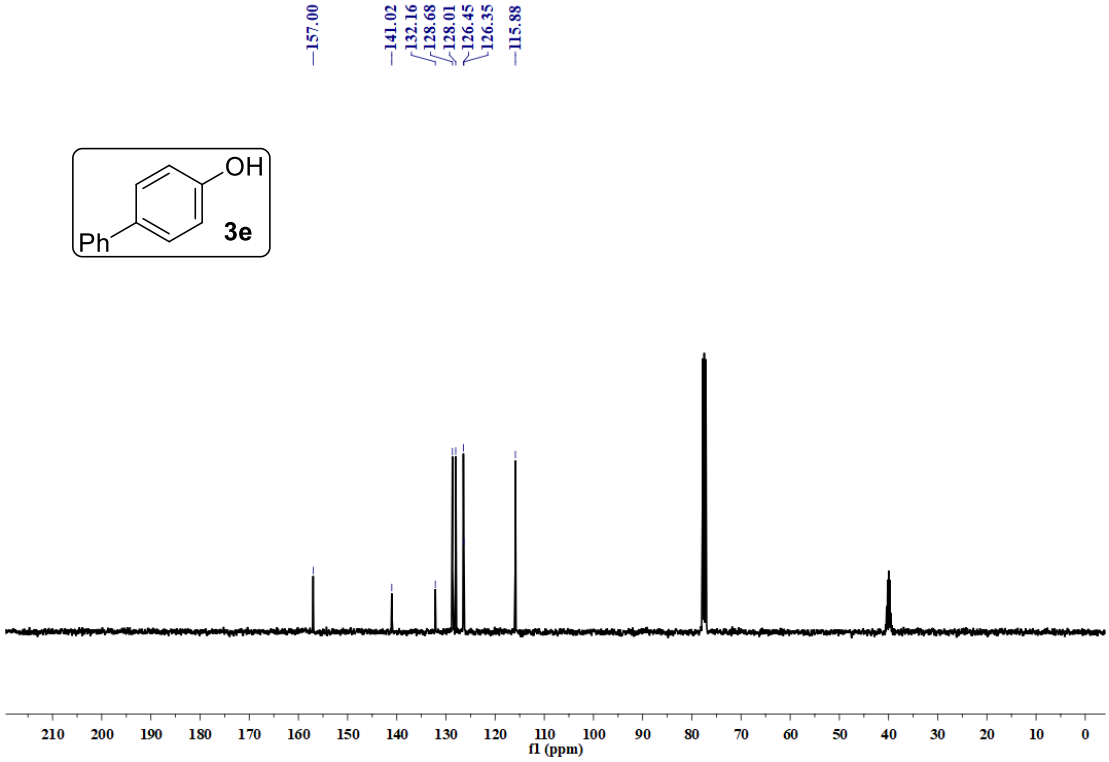
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of 4-ethylphenol (3c)



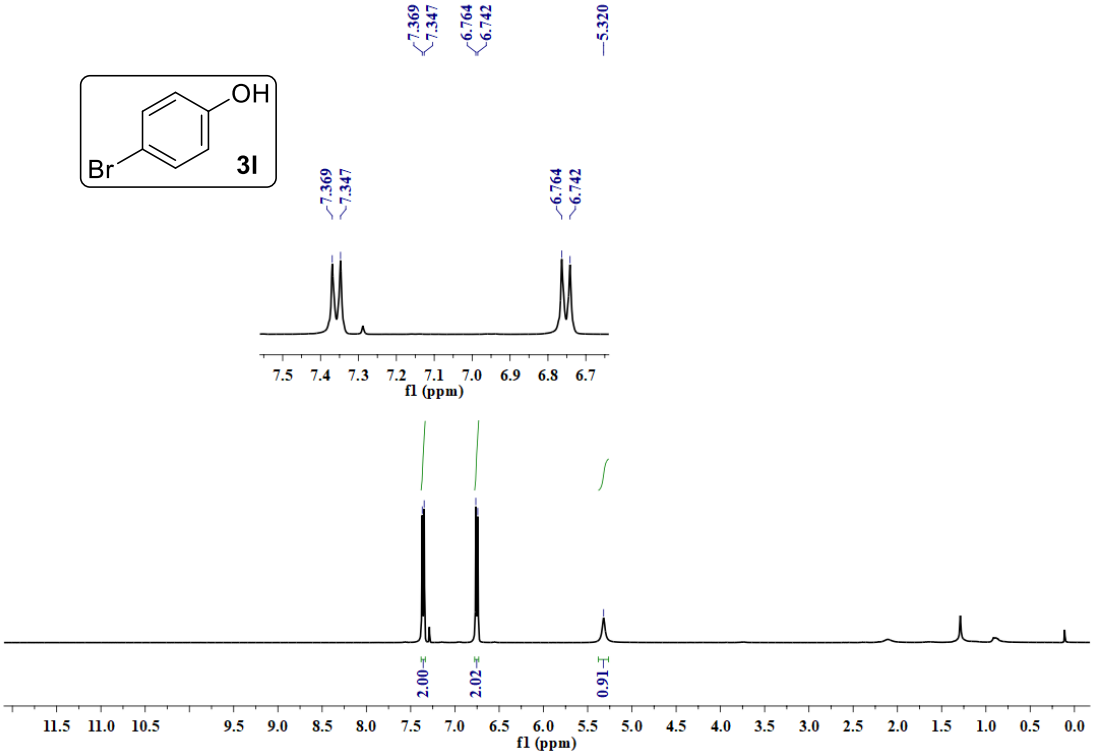
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of [1,1'-biphenyl]-4-ol (3e)



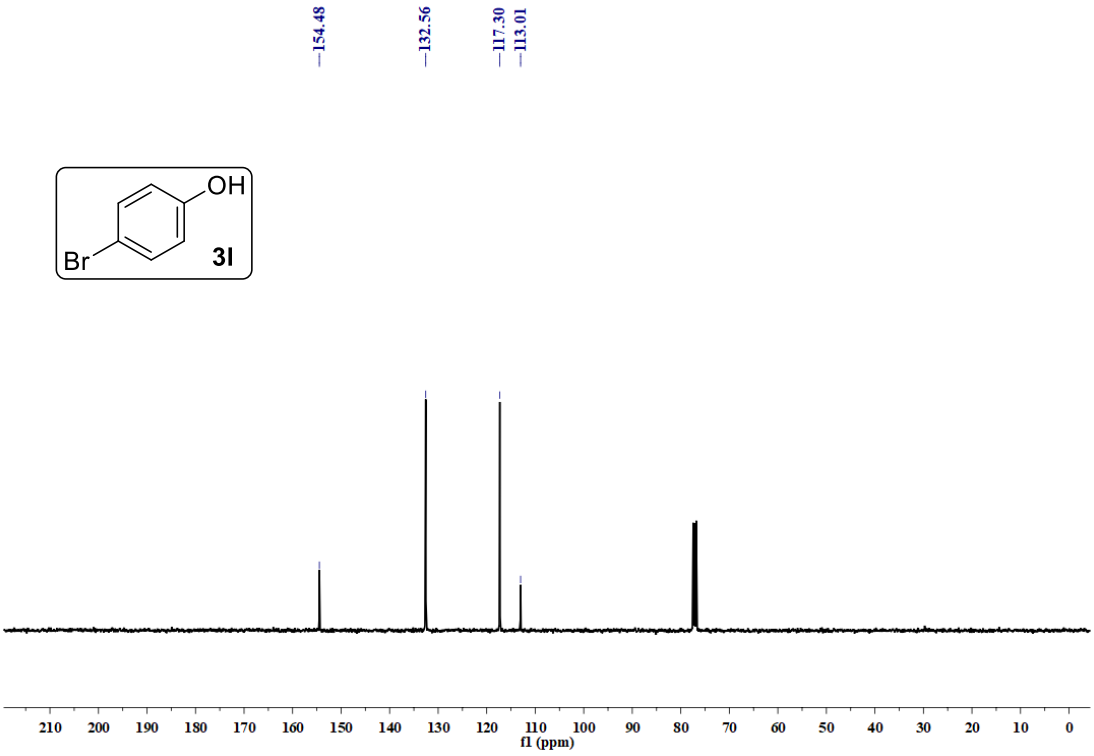
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$+DMSO-d_6) spectrum of [1,1'-biphenyl]-4-ol (3e)



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 4-bromophenol (3l)

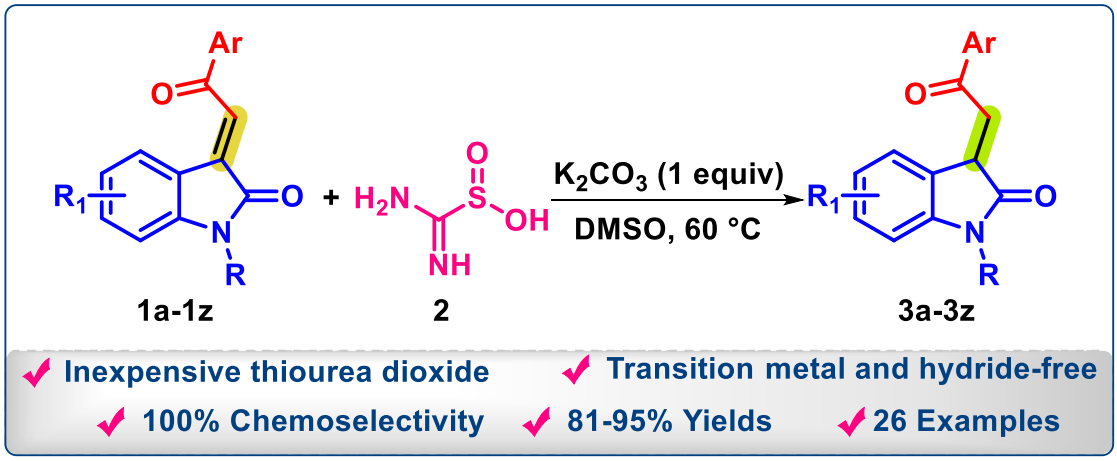


^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of 4-bromophenol (3l)



CHAPTER-VB

Chemoselective Reduction of 3-Phenacylidene-2-oxindoles Using Thiourea Dioxide



5B.1. Introduction

Chemoselective reduction is one of the most prominent methods in organic synthesis and it plays a major role in the synthesis of many natural products, fine chemicals and pharmaceuticals.[1,2] Among chemoselective reductions, the selective reduction of activated olefins captured the attention of researchers owing its enormous applications in the total synthesis of complex molecules.[3-5] Many biosynthetic pathways rely on the selective reduction of activated alkenes and allows the synthesis of fatty acids by enolate reductases in the living microorganisms.[6]

From the past decade, the transition metals such as Ni,[7-8] Co,[9] Cu,[10-11] Pd,[12] Ir,[13-15] Rh,[16] and Ru[17-18] catalyzed chemoselective reductions are developed for the synthesis of saturated carbonyl compounds from the corresponding *α,β*-unsaturated carbonyl compounds. Albeit, aforementioned methodologies are limited due to high cost, generates the toxic waste and also the minor amounts of transition metals are associated with the products, which restrict their usage in pharmaceutical industry. Based on the environmental and economical concern, transition metal-free strategies are need to be developed for the chemoselective reduction of activated alkenes.

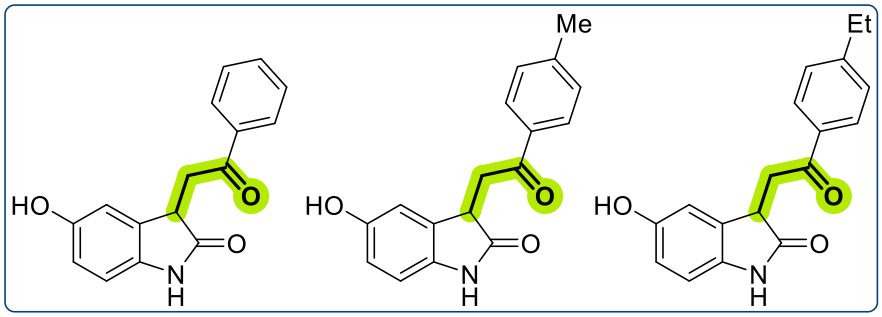


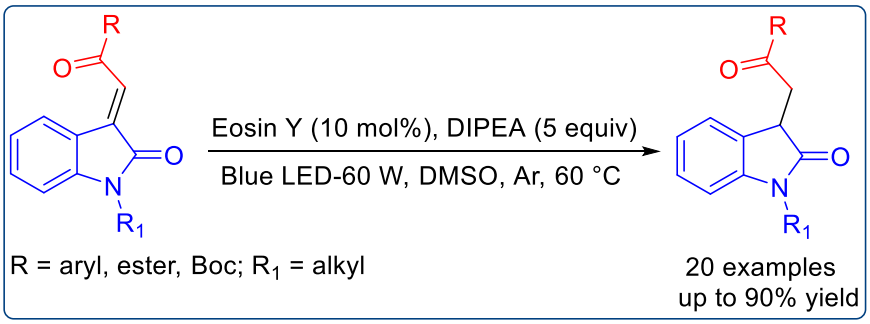
Figure 5B.1. 3-Phenacyl-2-oxindoles with antioxidant properties

In addition, among the chemoselective reduction of activated olefins, reduction of isatin-derived *α,β*-unsaturated carbonyl compounds are becoming popular due to their antioxidant and pro-oxidant properties. The reduced products i.e., 3-phenacyl-2-oxindoles showed higher DPPH radical scavenging activity and also the presence of 3-phenacyl substitution aid these compounds to exert greater lipid peroxidation-inhibitory activity. Apart from this, there is a good balance between their antioxidant properties and cytotoxicity. These properties made them to consider as novel lead candidates for antioxidant therapeutics (Figure 5B.1).[19]

In addition to biological activities of the 3-phenacyl-2-oxindoles, they also serve as crucial building blocks for the synthesis of 2-arylquinoline-4-carboxylates,[20] 3-spirocyclopentene-2-oxindoles.[21] corresponding bromo and ester compounds,[22] spirocyclic oxindoles,[23] oxindole dimers,[24] and spirocyclopentane-2-oxindoles.[25]

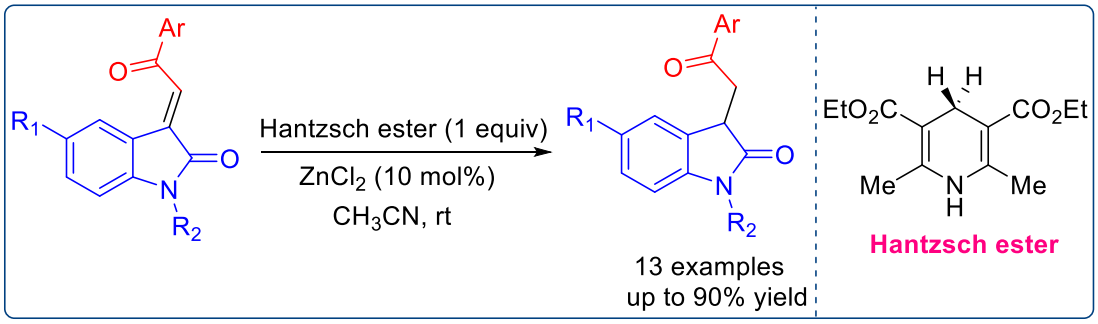
5B.1.1. Previous reports for the synthesis of 3-phenacyl-2-indolinones

Bhat and co-workers developed a protocol for the synthesis of 3-phenacyl-2-indolinones under visible light irradiation using Eosin Y as a photocatalyst and *N*,*N*-diisopropylethylamine (DIPEA) as a sacrificial electron donor in DMSO under argon atmosphere at 60 °C. This methodology avoids the use of transition-metals, external reducing agents and achieved 3-phenacyl-2-indolinones up to 90% yield (Scheme 5B.1).[22]



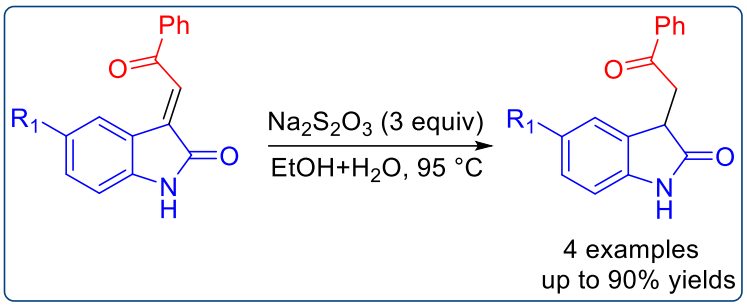
Scheme 5B.1

Murthy Gandikota et al. introduced a chemoselective strategy for the reduction of 3-phenacylidene-2-oxindoles using Hantzsch ester as a reducing agent in the presence of catalytic amount of zinc chloride under argon atmosphere in acetonitrile solvent at room temperature to produce the 3-phenacyl-2-oxindoles. This protocol offers the synthesis of 3-phenacyl-2-oxindoles in 82-90% yield (Scheme 5B.2).[26]



Scheme 5B.2

Popp and co-workers reported a sodium hyposulfite mediated chemoselective reduction of 3-phenacylidene-2-oxindoles to obtain 3-phenacyl-2-oxindoles in a mixture of ethanol (EtOH) and water (H_2O) at 95 °C. This approach produces the 3-phenacyl-2-oxindoles in 74-90% yields (Scheme 5B.3).[27]

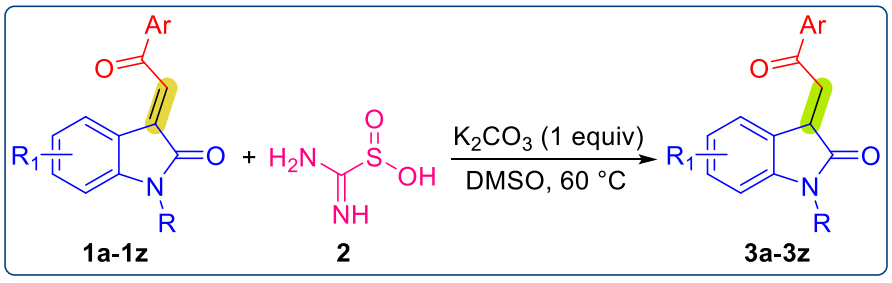


Scheme 5B.3

Based on the literature survey, we observed that only three reports are available for the chemoselective reduction of 3-phenacylidene-2-oxindoles to 3-phenacyl-2-oxindoles and these protocols inherently possess some disadvantages such as use of catalysts, additives and narrow substrate scope. To address the limitations associated with the existed methods, we aim to develop an environmentally benign method for the synthesis of 3-phenacyl-2-oxindoles using electron-donating property of thiourea dioxide.

5B.2. Present study

Considering the importance of 3-phenacyl-2-oxindoles, we were planned to develop a chemoselective protocol using 3-phenacylidene-2-oxindoles as starting materials by employing thiourea dioxide as a hydride-free reducing agent. Thiourea dioxide is a sulfur containing reducing agent and it is a source of sulfinate anion, which is capable of donate electrons to the electron-deficient alkene present in 3-phenacylidene-2-oxindoles and allows the synthesis of wide range of 3-phenacyl-2-oxindoles in 81-95% yields (Scheme 5B.4).

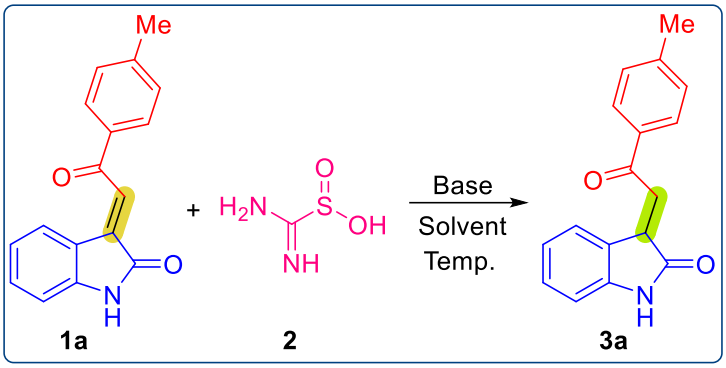


Scheme 5B.4. Chemoselective reduction of 3-phenacylidene-2-oxindoles using thiourea dioxide

5B.2.1. Results and discussion

We have commenced our investigation, by taking 3-(4-methylphenacylidene)-2-indolinone **1a** (1 mmol) as a model substrate, and treated with thiourea dioxide **2** (2 mmol) and K_2CO_3 (1 mmol)

Table 5B.1. Optimization of the reaction conditions[a]



Entry	Solvent (8:2 v/v)	Reagent	Base	Temp. (°C)	Time (min)	Yield (%)[b]
1	EtOH+H_2O	Thiourea dioxide	K_2CO_3	rt	24 h	10
2	EtOH+H_2O	Thiourea dioxide	K_2CO_3	60	30	55
3	MeOH+H_2O	Thiourea dioxide	K_2CO_3	60	30	60
4	*i*-PrOH+H_2O	Thiourea dioxide	K_2CO_3	60	30	59
5	CH_3CN+H_2O	Thiourea dioxide	K_2CO_3	60	30	62
6	THF+H_2O	Thiourea dioxide	K_2CO_3	60	30	30
7	DMF	Thiourea dioxide	K_2CO_3	60	10	85
8	**DMSO**	**Thiourea dioxide**	**K_2CO_3**	**60**	**10**	**95**
9	DMSO	Thiourea dioxide	Cs_2CO_3	60	10	75
10	DMSO	Thiourea dioxide	NEt_3	60	10	61
11	DMSO	Thiourea dioxide	DBU	60	10	72
12	DMSO	Thiourea dioxide	K_2CO_3	60	15	82[c]
13	DMSO	Thiourea dioxide	K_2CO_3	60	10	95[d]
14	DMSO	Thiourea dioxide	K_2CO_3	70	10	95
15	DMSO	Thiourea dioxide	K_2CO_3	50	15	92
16	DMSO	Rongalite	K_2CO_3	60	10	68
17	DMSO	Sodium dithionite	K_2CO_3	60	10	72

[a]Reaction conditions: 3-(4-methylphenacylidene)-2-indolinone **1a** (1 mmol), reagent (2 mmol) and base (1 mmol) in variable reaction media at different temperatures. [b]Yield of isolated product. [c]Thiourea dioxide (1.5 mmol) was used. [d]Thiourea dioxide (2.5 mmol) was used. rt = room temperature.

in EtOH+H_2O (8:2 v/v) at room temperature resulted in the formation of **3a** in 10% yield (Table 5B.1, entry 1). The structure of **3a** was confirmed by ^1H, ^{13}C NMR and HRMS spectral analysis.

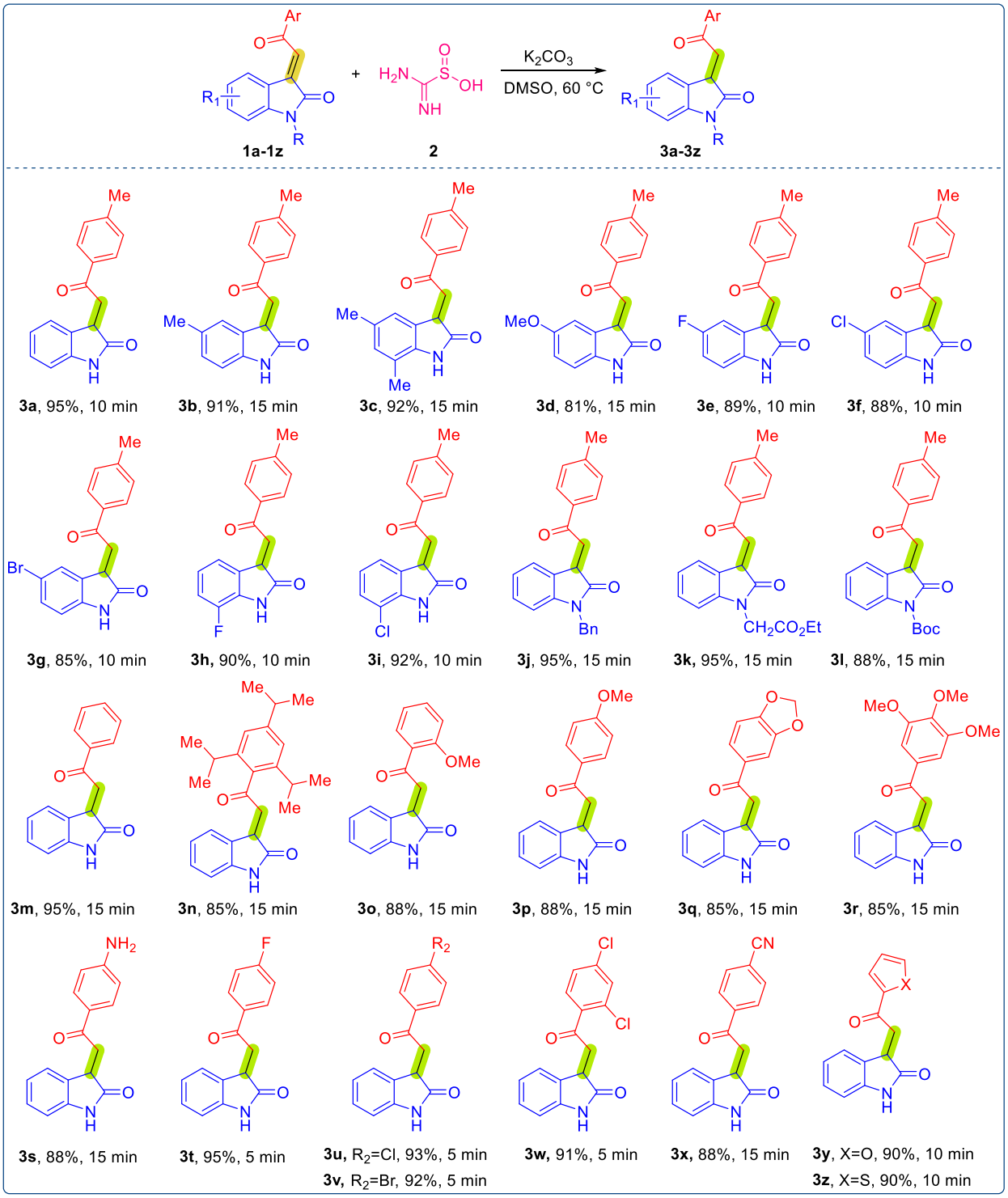
We are pleased to observe that the yield of **3a** was improved to 55%, when the temperature was raised to 60 °C (Table 5B.1, entry 2). Later, screening of reaction was continued in other polar protic solvents such as aq. MeOH and aq. *i*-PrOH and found moderate yields, respectively (Table 5B.1, entries 3-4). Further, reaction was examined in polar aprotic solvents such as aq. CH_3CN, aq. THF, DMF and DMSO. Among all the tested solvents, DMSO was found to be an optimal solvent and resulted the desired product in 95% yield (Table 5B.1, entries 5-8).

Then, we tested the reaction with different organic and inorganic bases and got low yields (Table 5B.1, entries 9-11). In addition, variants in temperature and the equiv of thiourea dioxide were found to be not useful (Table 5B.1, entries 12-15). Further, the model reaction was also examined with other sulfur containing reducing agents such as rongalite and sodium dithionite and observed inferior results (Table 5B.1, entries 16-17). Thus, the optimal reaction conditions are as follows: 3-(4-methylphenacylidene)-2-indolinone **1a** (1 mmol), thiourea dioxide **2** (2 mmol) and K_2CO_3 (1 mmol) in 2 mL of DMSO at 60 °C (Table 5B.1, entry 8).

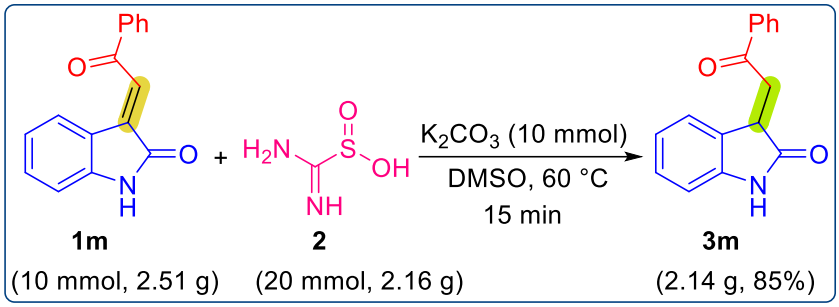
To demonstrate the versatility of this developed methodology, an array of isatin-chalcones were subjected to the optimized reaction conditions and the results are summarized in Tables 5B.2. The electron-donating groups such as methyl, methoxy and $–NH_2$ substituted isatin-chalcones were smoothly reacted with thiourea dioxide and delivered **3b**-**3d** and **3n**-**3s** in 81-92% yields (Table 5B.2). Isatin-chalcones bearing halogens (–F, –Cl, and –Br) also offered the respective reduced products **3e-3i** and **3t**-**3w** in 85-95% yields (Table 5B.2). Also, the reaction was viable with isatin-chalcone containing electron withdrawing group like –CN to produce the corresponding product **3x** in 88% yield (Table 5B.2). Moreover, *N*-protected isatin-chalcones effortlessly involved in the reaction and pleasingly, the ester and Boc protecting groups were intact with thiourea dioxide and furnished the respective 3-phenacyl-2-indolinones **3j**-**3l** in 88-95% yields (Table 5B.2). It is worth noting that the isatin-chalcones, which were formed by heteroaromatic acetophenones gave the reduced products **3y** and **3z** in 90% yield (Table 5B.2).

To check the synthetic potential of our protocol, we have carried out a scale-up experiment by taking 3-phenacylidene-2-indolinone **1m** (10 mmol, 2.51 g), thiourea dioxide **2** (20 mmol, 2.16 g), K_2CO_3 (10 mmol, 1.38 g) and DMSO (15 mL) at 60 °C. The reaction was completed within 15 min and furnished the reduced product i.e., 3-phenacyl-2-indolinone **3m** in 85% yield (Scheme 5B.5).

Table 5B.2. Scope of thiourea dioxide-induced chemoselective reduction of isatin-chalcones[a,b]

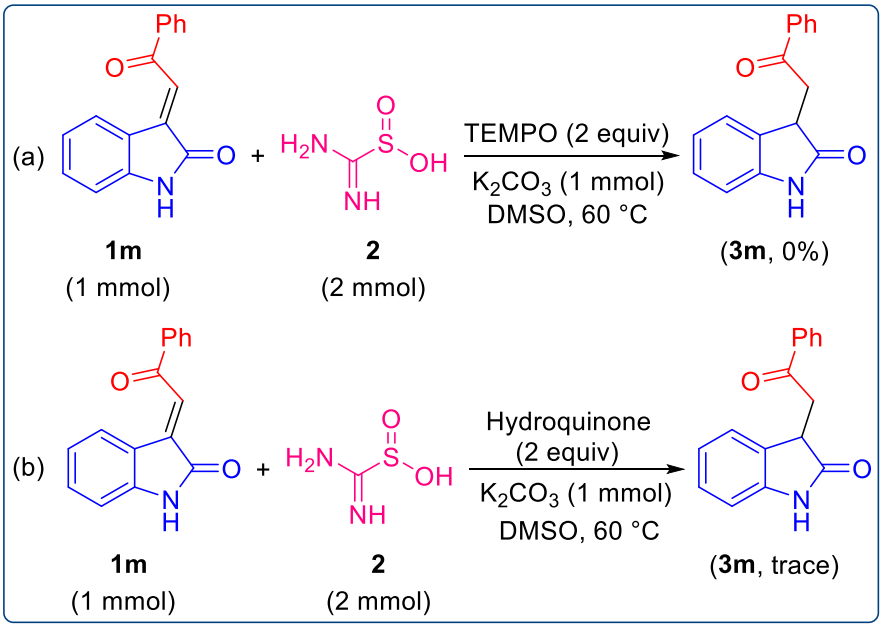


[a]Reaction conditions: isatin-chalcone **1** (1 mmol), thiourea dioxide **2** (2 mmol) and K_2CO_3 (1 mmol) in 2 mL of DMSO at 60 °C. [b]Yield of isolated product.



Scheme 5B.5. Gram-scale synthesis

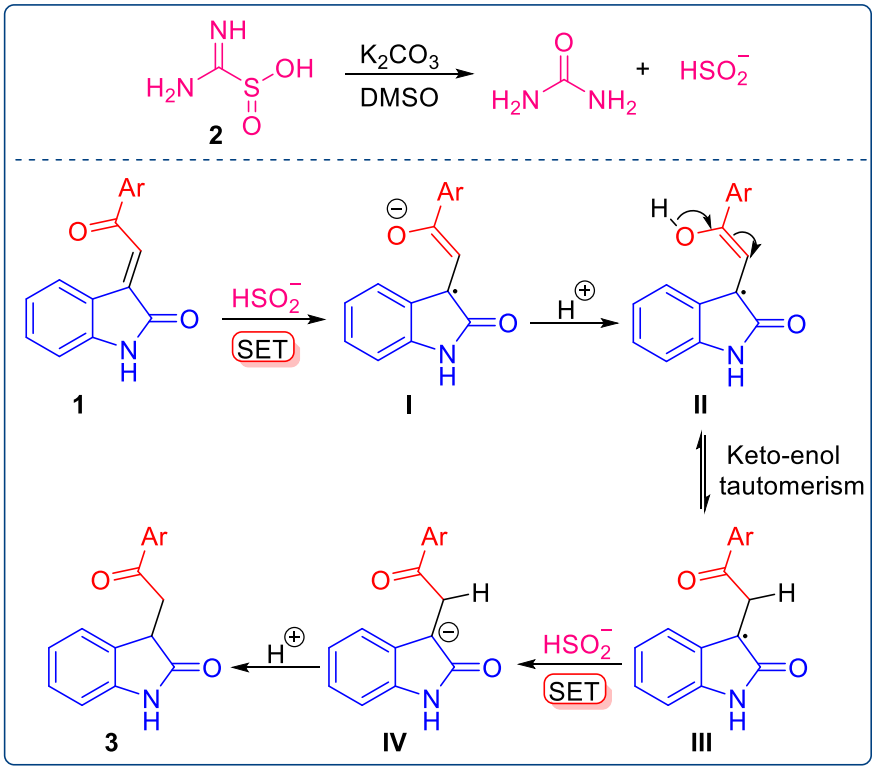
In order to unveil the pathway of the reaction mechanism, we have conducted some control experiments with radical scavengers such as TEMPO and hydroquinone (Scheme 5B.6). Initially, 3-phenacylidene-2-indolinone **1m** (1 mmol, 0.251 g) was treated with thiourea dioxide **2** (2 mmol, 0.216 g), K_2CO_3 (1 mmol, 0.138 g) and TEMPO (2 equiv) in DMSO (2 mL) at 60 °C. The desired product i.e., 3-phenacyl-2-indolinone **3m** was not observed even after long durations and the starting material **1m** was completely remained in the reaction mixture (Scheme 5B.6a). Later, we have performed another experiment with hydroquinone as a radical scavenger and observed the trace amounts of **3m** (Scheme 5B.6b). These two experiments are clearly indicating that the reaction is undergoing through radical mechanism.



Scheme 5B.6. Control experiments

Based on the controlled experiments and existing literature,[22,28-29] a plausible reaction mechanism was proposed in Scheme 5B.7. Initially, thiourea dioxide dissociates into urea and

sulfinate anion under basic condition. Later on, a single-electron transfer (SET) takes place from the sulfinate anion to 3-phenacylidene-2-indolinone **1** to form the intermediate radical anion **I**. Further, abstraction of proton and subsequent keto-enol tautomerism generates the intermediate radical **III**. Furthermore, another single-electron transfer occurs at intermediate radical **III** from the sulfinate anion to produce the intermediate anion **IV**, which is later undergoes the protonation to deliver the desired product **3**.



Scheme 5B.7. Plausible reaction mechanism

5B.3. Conclusion

We have developed a novel protocol for the chemoselective reduction of 3-phenacylidene-2-oxindoles to 3-phenacyl-2-oxindoles using thiourea dioxide as a hydride-free reducing agent *via* single-electron transfer pathway. Thiourea dioxide produces the sulfinate anion *in situ*, which is responsible for the reduction of activated alkene present in isatin-chalcone and allows rapid access to a wide range of 3-phenacyl-2-oxindoles in 81-95% yields. The key features of this synthetic approach include, use of inexpensive and industrial reagent thiourea dioxide, 100% chemoselectivity, short reaction times and mild reaction conditions.

5B.4. Experimental section

5B.4.1. General information

All chemicals and solvents were purchased from Alfa Aesar, Spectrochem, SRL, Finar and used as received. Thin layer chromatography was performed on 200 µm aluminum-foil backed silica gel plates and the column chromatography was performed using 100-200 mesh silica gel (Merk). Bruker Avance 400 MHz spectrometer was used to record ^{1}H NMR spectra and used $CDCl_3$ and DMSO-d_6 as solvents and TMS as an internal standard. The multiplicities were described using the following acronyms: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, and m = multiplet. Coupling constants, *J* were reported in Hertz unit (Hz). Bruker Avance 100 MHz spectrometer was used to record $^{13}C\{^{1}H\}$ NMR spectra, and they were fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to the center line of a triplet at 77.16 ppm of chloroform-*d* (a multiplet at 39.52 ppm of DMSO-d_6). A Stuart SMP30 apparatus was used to determine the melting points and are uncorrected. FT-IR spectra were recorded on a Perkin Elmer spectrometer. HRMS were analyzed with Agilent Q-TOF 6230.

5B.4.2. General procedure for the synthesis of 3-hydroxy-3-phenacyl-2-oxindoles[30]

An oven dried 50 mL reaction flask was charged with appropriate isatin (10 mmol), appropriate acetphenone (10 mmol, 1 equiv) and EtOH (10 mL). To this, catalytic amount of diethylamine was added and allowed to reflux until the completion of reaction and also observed the color change from red to colorless. Later, water was added to the reaction mixture and the resultant solid was filtered off under vacuum and the product was air dried.

5B.4.3. General procedure for the synthesis of 3-phenacylidene-2-oxindoles (1a-1z)[30]

An oven dried 25 mL reaction flask was charged with appropriate 3-hydroxy-3-phenacyl-2-oxindole (5 mmol), 0.5 mL of Conc. HCl and 8.5 mL of CH_3COOH and allowed to stir at 95 °C until the completion of reaction, and observed the color change from colorless to red. After that, water was added to the reaction mixture and the resultant solid was filtered off under vacuum and the product was air dried.

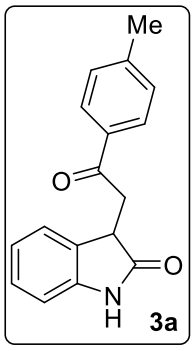
5B.4.4. General procedure (A) for the synthesis of 3-phenacyl-2-oxindoles (3a-3z)

An oven dried 10 mL reaction flask was charged with appropriate 3-phenacylidene-2-oxindole **1** (1 mmol), thiourea dioxide **2** (2 mmol, 2 equiv), K_2CO_3 (1 mmol, 1 equiv) and DMSO (2 mL),

stirred at 60 °C for the appropriate time (5-15 min). The reaction was monitored by TLC using hexanes and ethyl acetate as an eluent. After the reaction has finised, water was added to the reaction mixture and the organic compound was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried on Na_2SO_4 and evaporated to give a residue that was purified on silica gel by column chromatography using hexanes and ethyl acetate as an eluent.

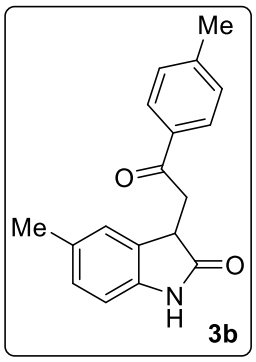
5B.5. Characterization data of products 3a-3z

3-(2-oxo-2-(*p*-tolyl)ethyl)indolin-2-one (3a). White solid; Yield (126 mg, 95%); mp 162-163 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3435, 3061, 2976, 1641, 1557, 815; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.76 (s, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 7.12 (t, J = 7.6 Hz, 2H), 6.89 – 6.81 (m, 2H), 4.02 (dd, J = 8.8, 3.2 Hz, 1H), 3.72 (dd, J = 17.6, 3.2 Hz, 1H), 3.35 (dd, J = 17.6, 8.8 Hz, 1H), 2.33 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 196.5, 180.4, 144.4, 141.6, 133.9, 129.8, 129.4, 128.3, 128.0, 124.6, 122.4, 109.8, 41.7, 39.7, 21.7; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{17}H_{15}NNaO_2$ 288.1000; found 288.0997.



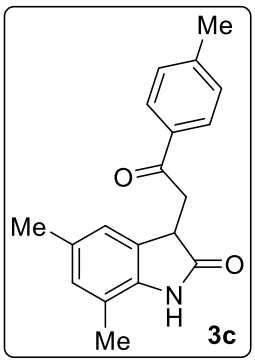
3a

5-methyl-3-(2-oxo-2-(*p*-tolyl)ethyl)indolin-2-one (3b). White crystalline solid; Yield (127 mg, 91%); mp 206-207 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3410, 3062, 2976, 1640, 1557, 814; ^1H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ (ppm): 10.22 (s, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 6.95 – 6.90 (m, 2H), 6.72 (d, J = 8.4 Hz, 1H), 3.80 (dd, J = 8.0, 3.6 Hz, 1H), 3.70 (dd, J = 18.4, 3.6 Hz, 1H), 3.40 (dd, J = 18.4, 8.0 Hz, 1H), 2.38 (s, 3H), 2.19 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ (ppm): 196.7, 179.3, 144.1, 140.7, 134.1, 130.5, 130.1, 129.5, 128.3, 128.0, 124.7, 109.3, 41.7, 39.3, 21.7, 21.2; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{18}H_{17}NNaO_2$ 302.1157; found 302.1152.



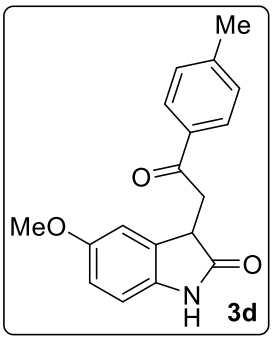
3b

5,7-dimethyl-3-(2-oxo-2-(*p*-tolyl)ethyl)indolin-2-one (3c). White solid; Yield (135 mg, 92%);



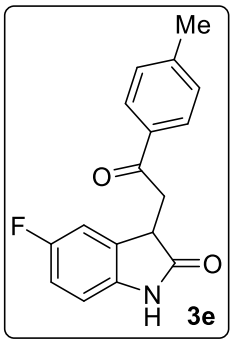
mp 228-229 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3417, 3075, 2976, 1642, 1558, 817; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.99 (s, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 7.6 Hz, 2H), 6.79 (s, 1H), 6.75 (s, 1H), 4.03 (dd, J = 8.8, 2.8 Hz, 1H), 3.70 (dd, J = 17.6, 3.2 Hz, 1H), 3.33 (dd, J = 17.6, 9.2 Hz, 1H), 2.34 (s, 3H), 2.18 (s, 3H), 2.15 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 196.6, 180.7, 144.3, 137.9, 134.0, 131.9, 129.8, 129.6, 129.4, 128.3, 122.7, 118.7, 42.1, 39.9, 21.7, 21.0, 16.4; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{19}H_{19}NNaO_2$ 316.1313; found 316.1309.

5-methoxy-3-(2-oxo-2-(*p*-tolyl)ethyl)indolin-2-one (3d).[19] White crystalline solid; Yield (120



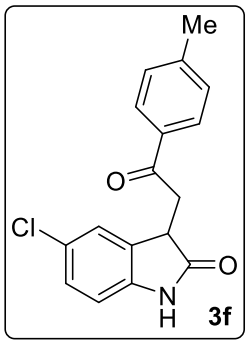
mg, 81%); mp 160-161 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3389, 3082, 2962, 1657, 1563, 881; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.09 (s, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 6.85 (d, J = 1.6 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.73 (dd, J = 8.4, 2.4 Hz, 1H), 4.07 (dd, J = 8.8, 2.8 Hz, 1H), 3.79 (dd, J = 17.6, 2.8 Hz, 1H), 3.72 (s, 3H), 3.42 (dd, J = 18.4, 9.2 Hz, 1H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 196.5, 180.2, 155.8, 144.4, 134.9, 133.9, 131.2, 129.4, 128.3, 112.7, 111.9, 110.1, 55.8, 42.2, 39.8, 21.7.

5-fluoro-3-(2-oxo-2-(*p*-tolyl)ethyl)indolin-2-one (3e). White crystalline solid; Yield (126 mg,

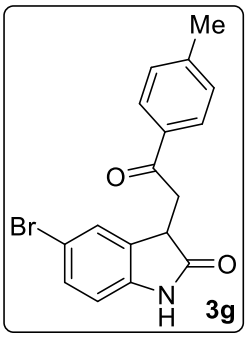


89%); mp 201-202 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3497, 3084, 2980, 1646, 1557, 811; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.43 (s, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.08 (dd, J = 8.4, 2.4 Hz, 1H), 7.01 – 6.94 (m, 1H), 6.82 (dd, J = 8.4, 4.4 Hz, 1H), 3.91 – 3.82 (m, 2H), 3.58 (dd, J = 17.6, 5.6 Hz, 1H), 2.38 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ (ppm): 197.1, 179.2, 158.2 (d, $^1J_{C\text{-}F}$ = 234.0 Hz), 144.4, 139.7 (d, $^4J_{C\text{-}F}$ = 1.7 Hz), 134.1, 132.4 (d, $^3J_{C\text{-}F}$ = 8.6 Hz), 129.8, 128.6, 113.9 (d, $^2J_{C\text{-}F}$ = 23.0 Hz), 111.9 (d, $^2J_{C\text{-}F}$ = 24.6 Hz), 110.0 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 42.3 (d, $^4J_{C\text{-}F}$ = 1.6 Hz), 38.5, 21.6; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{17}H_{14}FNNaO_2$ 306.0906; found 306.0903.

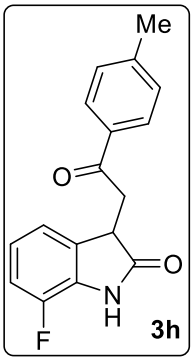
5-chloro-3-(2-oxo-2-(*p*-tolyl)ethyl)indolin-2-one (3f). White solid; Yield (132 mg, 88%); mp 201-202 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3432, 3082, 2980, 1644, 1556, 808; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.54 (s, 1H), 7.87 (d, J = 8.0 Hz, 2H), 7.38 (s, 1H), 7.36 – 7.30 (m, 3H), 6.80 (d, J = 8.4 Hz, 1H), 3.92 (dd, J = 18.4, 4.0 Hz, 1H), 3.85 – 3.81 (m, 1H), 3.60 (dd, J = 18.4, 6.4 Hz, 1H), 2.38 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ (ppm): 197.1, 178.9, 144.4, 142.9, 134.1, 133.1, 130.5, 129.8, 128.6, 126.8, 113.2, 111.4, 41.9, 38.5, 21.6; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{17}H_{14}ClNNaO_2$ 322.0611; found 322.0603.



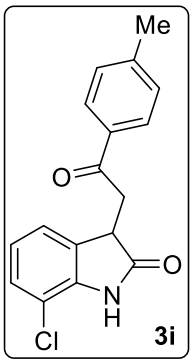
5-bromo-3-(2-oxo-2-(*p*-tolyl)ethyl)indolin-2-one (3g). White solid; Yield (146 mg, 85%); mp 251-252 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3418, 3076, 2978, 1642, 1556, 1076; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.53 (s, 1H), 7.87 (d, J = 8.0 Hz, 2H), 7.38 – 7.16 (m, 4H), 6.87 – 6.78 (m, 1H), 3.91 (dd, J = 18.4, 3.6 Hz, 1H), 3.86 – 3.80 (m, 1H), 3.60 (dd, J = 18.8, 6.4 Hz, 1H), 2.38 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ (ppm): 197.1, 179.0, 144.4, 142.5, 134.1, 132.7, 129.8, 128.6, 127.6, 125.5, 124.1, 110.8, 41.9, 38.5, 21.6; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{15}BrNO_2$ 344.0286; found 344.0279.



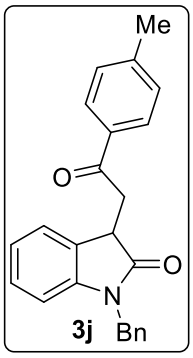
7-fluoro-3-(2-oxo-2-(*p*-tolyl)ethyl)indolin-2-one (3h). Off-white solid; Yield (128 mg, 90%); mp 186-187 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3482, 3065, 2980, 1643, 1557, 810; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.60 (s, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 6.95 – 6.81 (m, 3H), 4.04 (dd, J = 8.4, 2.4 Hz, 1H), 3.75 (dd, J = 18.4, 2.8 Hz, 1H), 3.39 (dd, J = 18.0, 8.8 Hz, 1H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 196.2, 179.3, 147.0 (d, $^1J_{C\text{-}F}$ = 242 Hz), 144.5, 133.7, 132.4 (d, $^3J_{C\text{-}F}$ = 3.3 Hz), 129.4, 128.8 (d, $^2J_{C\text{-}F}$ = 12 Hz), 128.3, 123.0 (d, $^3J_{C\text{-}F}$ = 5.8 Hz), 120.3 (d, $^4J_{C\text{-}F}$ = 3.3 Hz), 115.2 (d, $^2J_{C\text{-}F}$ = 17.0 Hz), 42.0 (d, $^4J_{C\text{-}F}$ = 2.4 Hz), 39.7, 21.7; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{17}H_{14}FNNaO_2$ 306.0906; found 306.0902.



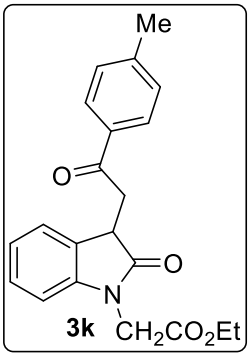
7-chloro-3-(2-oxo-2-(*p*-tolyl)ethyl)indolin-2-one (3i). White crystalline solid; Yield (138 mg, 92%); mp 183-184 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3430, 3084, 2980, 1646, 1556, 802; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.32 (s, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 1H), 7.04 (d, J = 7.6 Hz, 1H), 6.83 (t, J = 8.0 Hz, 1H), 4.08 (dd, J = 9.2, 2.8 Hz, 1H), 3.74 (dd, J = 18.4, 3.2 Hz, 1H), 3.37 (dd, J = 18.4, 9.2 Hz, 1H), 2.34 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 196.1, 178.6, 144.6, 139.2, 133.7, 131.0, 129.4, 128.3, 128.0, 123.3, 122.9, 114.8, 42.6, 39.7, 21.7; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{17}H_{14}ClNNaO_2$ 322.0611; found 322.0603.



1-benzyl-3-(2-oxo-2-(*p*-tolyl)ethyl)indolin-2-one (3j). White solid; Yield (169 mg, 95%); mp 143-144 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3430, 3082, 2981, 1640, 1553, 882; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.93 (d, J = 8.0 Hz, 2H), 7.41 – 7.27 (m, 8H), 7.17 (t, J = 8.0 Hz, 1H), 6.97 (t, J = 7.2 Hz, 1H), 6.76 (d, J = 7.6 Hz, 1H), 5.05 – 4.96 (m, 2H), 4.20 (dd, J = 9.2, 3.2 Hz, 1H), 3.89 (dd, J = 18.0, 2.8 Hz, 1H), 3.47 (dd, J = 18.0, 8.8 Hz, 1H), 2.44 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 196.5, 177.9, 144.3, 143.4, 135.9, 133.9, 129.4, 129.2, 128.8, 128.3, 127.9, 127.6, 127.3, 124.5, 122.5, 109.0, 43.9, 41.3, 39.9, 21.7; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{24}H_{21}NNaO_2$ 378.1470; found 378.1469.

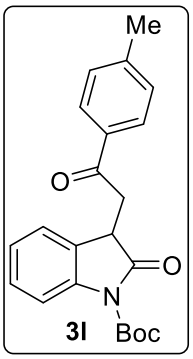


ethyl 2-(2-oxo-3-(2-oxo-2-(*p*-tolyl)ethyl)indolin-1-yl)acetate (3k). White solid; Yield (167 mg, 95%); mp 104-105 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3430, 3081, 2980, 1746, 1708, 1646, 1553, 820; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.81 (d, J = 8.0 Hz, 2H), 7.21 – 7.13 (m, 4H), 6.92 (t, J = 7.6 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 4.50 – 4.38 (m, 2H), 4.16 (q, J = 7.2 Hz, 2H), 4.11 (dd, J = 9.6, 3.2 Hz, 1H), 3.73 (dd, J = 18.4, 3.2 Hz, 1H), 3.32 (dd, J = 18.0, 9.6 Hz, 1H), 2.33 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz,



$CDCl_3$) δ (ppm): 196.5, 177.9, 167.7, 144.4, 142.9, 133.9, 129.4, 129.0, 128.3, 128.1, 124.8, 122.9, 108.0, 61.8, 41.6, 41.1, 40.1, 21.7, 14.2; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{21}H_{21}NNaO_4$ 374.1368; found 374.1362.

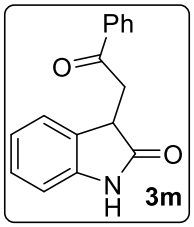
***tert*-butyl 2-oxo-3-(2-oxo-2-(*p*-tolyl)ethyl)indoline-1-carboxylate (3l)**. Off-white solid; Yield



3l

(161 mg, 88%); mp 122-123 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3400, 3082, 2980, 1754, 1681, 1553; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.80 – 7.75 (m, 3H), 7.23 – 7.17 (m, 3H), 7.13 (d, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 4.10 (dd, *J* = 8.0, 2.8 Hz, 1H), 3.75 (dd, *J* = 18.0, 3.2 Hz, 1H), 3.43 (dd, *J* = 18.4, 8.4 Hz, 1H), 2.33 (s, 3H), 1.59 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 195.9, 176.3, 149.3, 144.5, 140.2, 133.7, 129.4, 128.3, 128.2, 127.9, 124.4, 123.9, 114.9, 84.3, 41.8, 40.4, 28.1, 21.7; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{22}H_{23}NNaO_4$ 388.1525; found 388.1523.

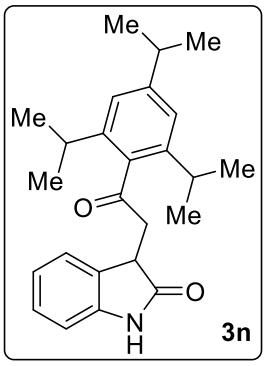
3-(2-oxo-2-phenylethyl)indolin-2-one (3m).[26] White crystalline solid; Yield (119 mg, 95%); mp



3m

177-178 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3436, 3074, 2980, 1644, 1556, 810; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.74 (s, 1H), 7.94 – 7.83 (m, 2H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.16 – 7.09 (m, 2H), 6.88 (t, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 4.03 (dd, *J* = 8.8, 2.8 Hz, 1H), 3.76 (dd, *J* = 18.4, 3.2 Hz, 1H), 3.39 (dd, *J* = 18.4, 8.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 196.9, 180.3, 141.6, 136.3, 133.5, 129.7, 128.7, 128.2, 128.1, 124.6, 122.5, 109.8, 41.7, 39.9.

3-(2-oxo-2-(2,4,6-triisopropylphenyl)ethyl)indolin-2-one (3n). White crystalline solid; Yield

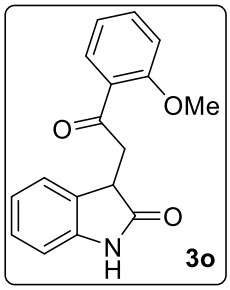


3n

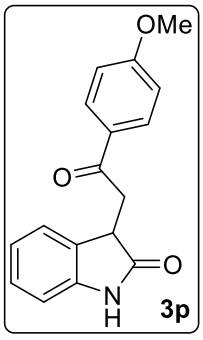
(160 mg, 85%); mp 153-154 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3427, 3062, 2977, 1644, 1553, 874; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.69 (s, 1H), 7.22 (d, *J* = 7.2 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 6.94 (t, *J* = 7.2 Hz, 1H), 6.91 (s, 2H), 6.84 (d, *J* = 7.6 Hz, 1H), 3.94 (dd, *J* = 8.0, 2.8 Hz, 1H), 3.45 (dd, *J* = 19.2, 3.2 Hz, 1H), 3.12 (dd, *J* = 19.6, 8.4 Hz, 1H), 2.80 (sept, *J* = 6.8 Hz, 1H), 2.60 (sept, *J* = 6.8 Hz, 2H), 1.17 (d,

J = 6.8 Hz, 12H), 1.07 (d, *J* = 6.8 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 207.6, 179.9, 149.9, 143.9, 141.8, 136.4, 129.3, 128.1, 124.4, 122.2, 121.1, 109.9, 47.1, 41.6, 34.3, 30.8, 23.9; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{25}H_{31}NNaO_2$ 400.2252; found 400.2253.

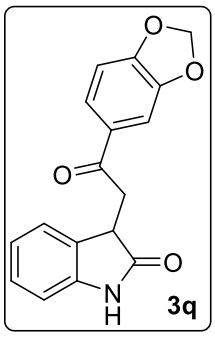
3-(2-(2-methoxyphenyl)-2-oxoethyl)indolin-2-one (3o). White crystalline solid; Yield (124 mg, 88%); mp 167-168 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3427, 3091, 2978, 1661, 1557, 880; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.38 (s, 1H), 7.61 – 7.52 (m, 2H), 7.22 – 7.11 (m, 3H), 7.02 (t, *J* = 7.2 Hz, 1H), 6.87 (t, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 3.90 (s, 3H), 3.79 (dd, *J* = 7.2, 4.0 Hz, 1H), 3.69 (dd, *J* = 18.8, 4.4 Hz, 1H), 3.40 (dd, *J* = 18.4, 7.2 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 198.4, 180.5, 159.1, 141.6, 134.2, 130.7, 130.2, 127.8, 127.1, 124.5, 122.3, 120.7, 111.6, 109.6, 55.5, 44.9, 42.2; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{17}H_{15}NNaO_3$ 304.0950; found 304.0949.



3-(2-(4-methoxyphenyl)-2-oxoethyl)indolin-2-one (3p). White crystalline solid; Yield (124 mg, 88%); mp 166-167 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3430, 3065, 2978, 1664, 1557, 817; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.64 (s, 1H), 7.89 (d, *J* = 8.8 Hz, 2H), 7.16 – 7.08 (m, 2H), 6.92 – 6.80 (m, 4H), 4.02 (dd, *J* = 8.8, 2.8 Hz, 1H), 3.79 (s, 3H), 3.70 (dd, *J* = 18.0, 3.2 Hz, 1H), 3.34 (dd, *J* = 18.0, 9.2 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 195.3, 180.4, 163.8, 141.5, 130.5, 129.9, 129.5, 128.0, 124.7, 122.4, 113.9, 109.7, 55.5, 41.8, 39.5; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{17}H_{15}NNaO_3$ 304.0950; found 304.0949.

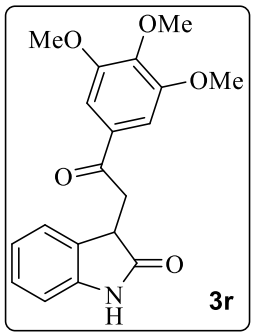


3-(2-(benzo[d][1,3]dioxol-5-yl)-2-oxoethyl)indolin-2-one (3q). White solid; Yield (125 mg, 85%); mp 209-210 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3391, 3062, 2983, 1646, 1557, 803; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.41 (s, 1H), 7.64 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.45 (d, *J* = 1.6 Hz, 1H), 7.14 (t, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.89 – 6.81 (m, 2H), 6.14 (s, 2H), 3.80 (dd, *J* = 6.4, 4.0 Hz, 1H), 3.75 (dd, *J* = 18.4, 4.0 Hz, 1H), 3.49 (dd, *J* = 18.0, 6.8



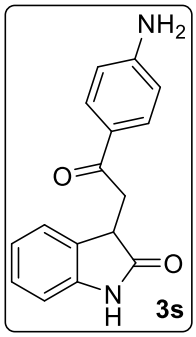
Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 195.7, 179.3, 152.1, 148.3, 143.4, 131.4, 130.4, 127.9, 125.0, 123.9, 121.5, 109.6, 108.6, 107.9, 102.5, 41.8, 38.7; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{17}H_{13}NNaO_4$ 318.0742; found 318.0742.

3-(2-oxo-2-(3,4,5-trimethoxyphenyl)ethyl)indolin-2-one (3r). White crystalline solid; Yield



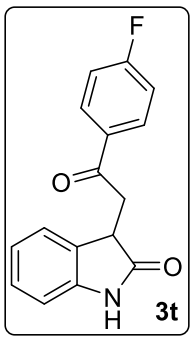
(145 mg, 85%); mp 240-241 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3432, 3065, 2980, 1644, 1556, 882; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.44 (s, 1H), 7.29 (s, 2H), 7.18 – 7.13 (m, 2H), 6.90 – 6.83 (m, 2H), 3.86 – 3.80 (m, 8H), 3.74 (s, 3H), 3.62 (dd, *J* = 19.2, 8.0 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 196.6, 179.3, 153.2, 143.5, 142.5, 131.9, 130.5, 127.9, 124.0, 121.5, 109.6, 106.1, 60.6, 56.5, 41.7, 38.9; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{19}H_{19}NNaO_5$ 364.1161; found 364.1154.

3-(2-(4-aminophenyl)-2-oxoethyl)indolin-2-one (3s). Pale yellow solid; Yield (117 mg, 88%);



mp 236-237 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3398, 3092, 2977, 1641, 1556, 815; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.37 (s, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.13 (t, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 6.88 – 6.80 (m, 2H), 6.56 (d, *J* = 8.8 Hz, 2H), 6.07 (s, 2H), 3.78 (dd, *J* = 7.2, 3.6 Hz, 1H), 3.59 (dd, *J* = 18.0, 4.0 Hz, 1H), 3.32 (dd, *J* = 18.0, 7.6 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 194.4, 179.6, 154.3, 143.4, 130.9, 130.8, 127.8, 124.5, 124.0, 121.4, 112.9, 109.5, 41.9, 38.1; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{16}H_{14}N_2NaO_2$ 289.0953; found 289.0948.

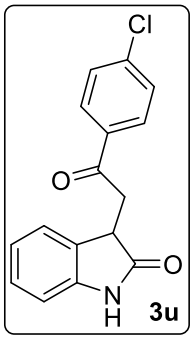
3-(2-(4-fluorophenyl)-2-oxoethyl)indolin-2-one (3t). White solid; Yield (128 mg, 95%); mp



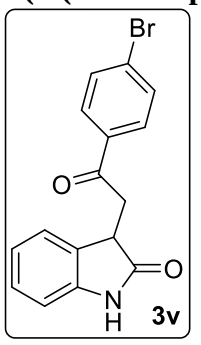
159-160 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3407, 3084, 2974, 1640, 1557, 815; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.69 (s, 1H), 8.05 – 7.97 (m, 2H), 7.20 (t, *J* = 7.6 Hz, 2H), 7.14 (t, *J* = 8.4 Hz, 2H), 6.97 (t, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.09 (dd, *J* = 8.4, 2.8 Hz, 1H), 3.80 (dd, *J* = 18.0, 3.2 Hz, 1H), 3.44 (dd, *J* = 18.4, 8.8 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 195.3,

180.1, 166.0 (d, $^{1}J_{C\text{-}F}$ = 254 Hz), 141.5, 132.8 (d, $^{4}J_{C\text{-}F}$ = 2.9 Hz), 130.8 (d, $^{3}J_{C\text{-}F}$ = 9.3 Hz), 129.6, 128.2, 124.6, 122.5, 115.9 (d, $^{2}J_{C\text{-}F}$ = 21.8 Hz), 109.8, 41.6, 39.7; HRMS (ESI) *m/z*: $[M+Na]^{+}$ calcd for $C_{16}H_{12}FNNaO_2$ 292.0750; found 292.0742.

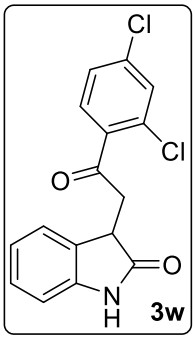
3-(2-(4-chlorophenyl)-2-oxoethyl)indolin-2-one (3u).[26] White crystalline solid; Yield (133 mg, 93%); mp 186-187 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3423, 3065, 2982, 1641, 1552, 881; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.43 (s, 1H), 8.00 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.15 (t, *J* = 7.2 Hz, 2H), 6.89 – 6.83 (m, 2H), 3.87 – 3.80 (m, 2H), 3.57 (dd, *J* = 19.2, 7.6 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 196.8, 179.1, 143.4, 138.9, 135.3, 130.4, 130.2, 129.3, 127.9, 124.0, 121.5, 109.6, 41.7, 38.9.



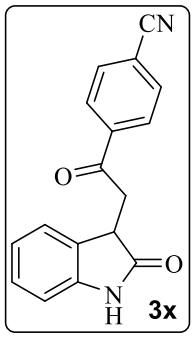
3-(2-(4-bromophenyl)-2-oxoethyl)indolin-2-one (3v).[26] White solid; Yield (151 mg, 92%); mp 188-189 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3418, 3062, 2978, 1642, 1556, 814; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.62 (s, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.15 – 7.09 (m, 2H), 6.89 (t, *J* = 7.2 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 4.00 (dd, *J* = 8.8, 3.2 Hz, 1H), 3.71 (dd, *J* = 18.4, 3.2 Hz, 1H), 3.35 (dd, *J* = 18.0, 8.8 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 195.9, 179.9, 141.5, 135.0, 132.1, 129.7, 129.5, 128.8, 128.2, 124.5, 122.5, 109.8, 41.6, 39.7.



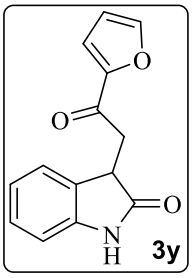
3-(2-(2,4-dichlorophenyl)-2-oxoethyl)indolin-2-one (3w). Off-white solid; Yield (145 mg, 91%); mp 103-104 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3462, 3091, 2985, 1646, 1552, 819; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.45 (s, 1H), 7.78 – 7.71 (m, 2H), 7.58 – 7.52 (m, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 6.91 (t, *J* = 7.2 Hz, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 3.88 – 3.82 (m, 1H), 3.72 (dd, *J* = 18.8, 4.4 Hz, 1H), 3.46 (dd, *J* = 18.4, 6.8 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 198.5, 179.6, 141.5, 137.9, 136.4, 132.4, 130.7, 130.6, 129.0, 128.3, 127.5, 124.4, 122.6, 109.9, 43.7, 41.9; HRMS (ESI) *m/z*: $[M+Na]^{+}$ calcd for $C_{16}H_{11}Cl_2NNaO_2$ 342.0065; found 342.0058.



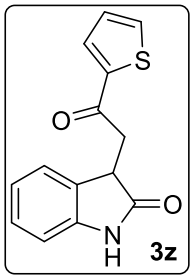
4-(2-(2-oxoindolin-3-yl)acetyl)benzonitrile (3x). White solid; Yield (121 mg, 88%); mp 210-211 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3430, 3084, 2978, 2234, 1646, 1557, 820; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.45 (s, 1H), 8.13 (d, J = 8.4 Hz, 2H), 8.02 (d, J = 8.4 Hz, 2H), 7.19 – 7.13 (m, 2H), 6.90 – 6.83 (m, 2H), 3.93 – 3.84 (m, 2H), 3.69 – 3.60 (m, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 197.4, 179.0, 143.4, 139.7, 133.3, 130.1, 129.2, 128.1, 124.1, 121.6, 118.6, 115.9, 109.6, 41.7, 39.3; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{17}H_{12}N_2NaO_2$ 299.0796; found 299.0790.



3-(2-(furan-2-yl)-2-oxoethyl)indolin-2-one (3y). White solid; Yield (108 mg, 90%); mp 169-170 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3423, 3072, 2978, 1641, 1557, 815; ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ (ppm): 9.73 (s, 1H), 7.63 – 7.59 (m, 1H), 7.23 (d, J = 3.6 Hz, 1H), 7.19 – 7.14 (m, 2H), 6.94 – 6.88 (m, 2H), 6.56 (dd, J = 3.6, 1.6 Hz, 1H), 3.99 (dd, J = 8.8, 3.6 Hz, 1H), 3.63 (dd, J = 18.0, 3.6 Hz, 1H), 3.26 (dd, J = 18.0, 8.8 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCL_3$+DMSO-d_6) δ (ppm): 186.1, 179.3, 152.2, 146.7, 142.4, 129.4, 127.9, 124.3, 121.8, 117.5, 112.4, 109.8, 41.3, 39.3; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{11}NNaO_3$ 264.0637; found 264.0635.



3-(2-oxo-2-(thiophen-2-yl)ethyl)indolin-2-one (3z). White crystalline solid; Yield (116 mg, 90%); mp 154-155 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3411, 3062, 2975, 1690, 1652, 1556, 814; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.70 (s, 1H), 7.74 (dd, J = 4.0, 1.2 Hz, 1H), 7.66 (dd, J = 4.8, 0.8 Hz, 1H), 7.25 – 7.17 (m, 2H), 7.13 (dd, J = 4.8, 4.0 Hz, 1H), 6.97 (t, J = 7.6 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 4.08 (dd, J = 9.2, 3.2 Hz, 1H), 3.76 (dd, J = 18.0, 3.6 Hz, 1H), 3.39 (dd, J = 17.6, 8.8 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 189.8, 179.9, 143.4, 141.5, 134.1, 132.4, 129.4, 128.3, 128.2, 124.7, 122.5, 109.8, 41.7, 40.2; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{11}NNaO_2S$ 280.0408; found 280.0407.



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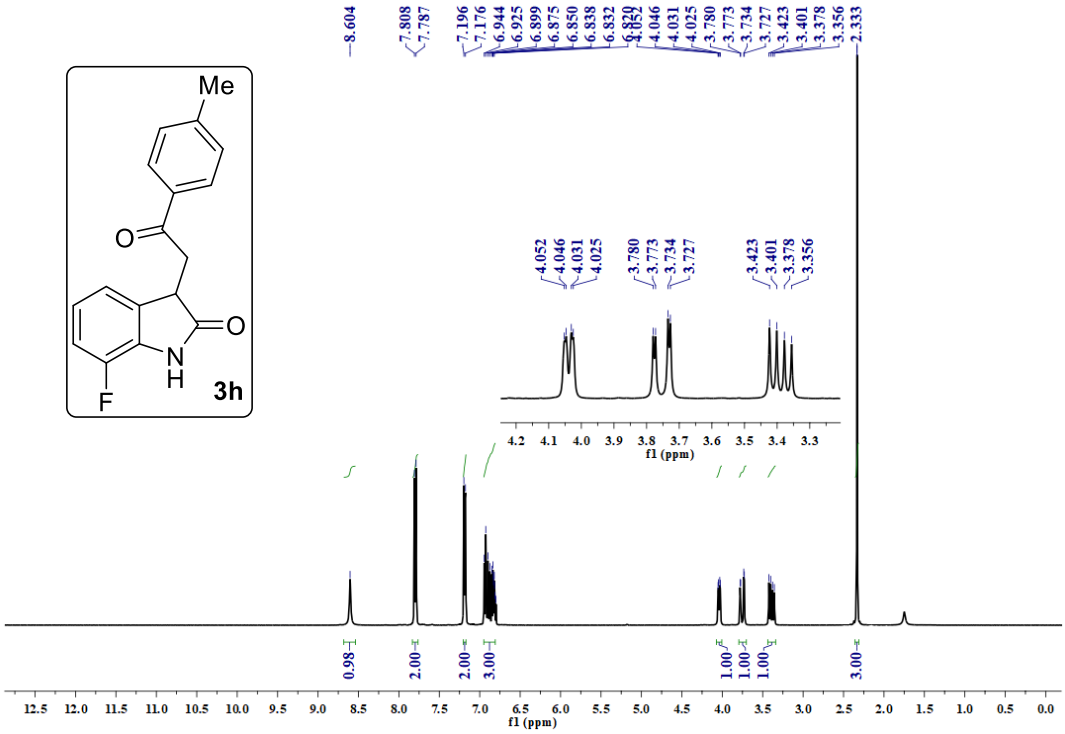
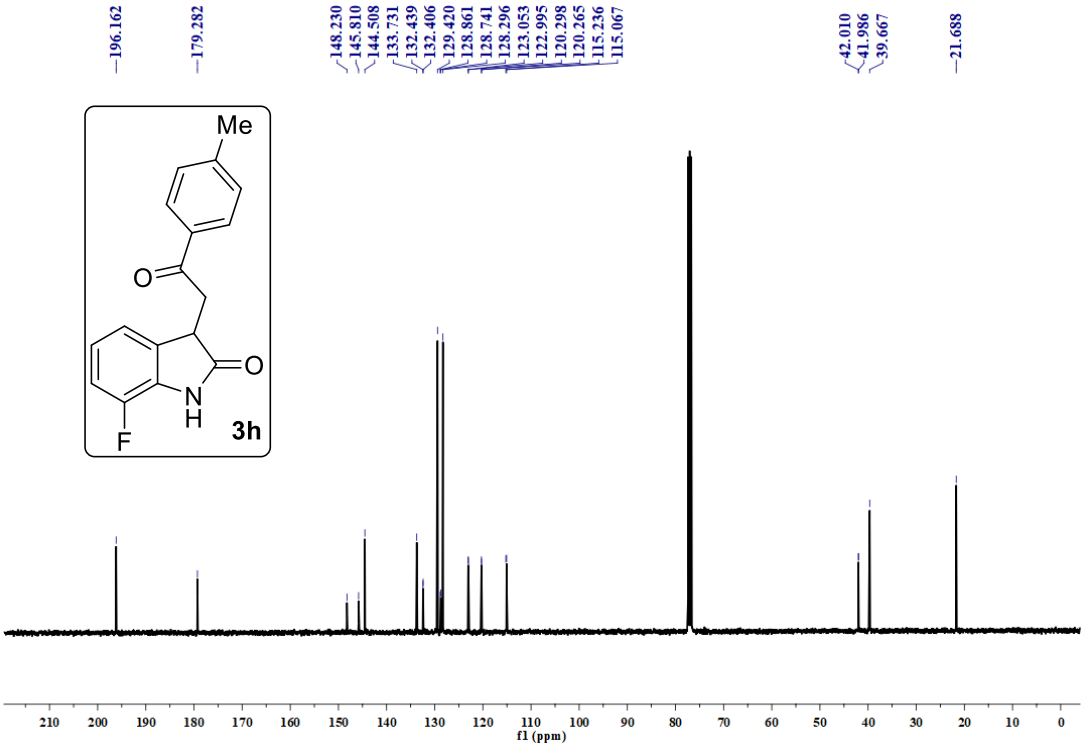
5B.7. Selected HRMS and NMR (^{1}H & ^{13}C) spectra

^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 7-fluoro-3-(2-oxo-2-(*p*-tolyl)ethyl)indolin-2-one (3h)

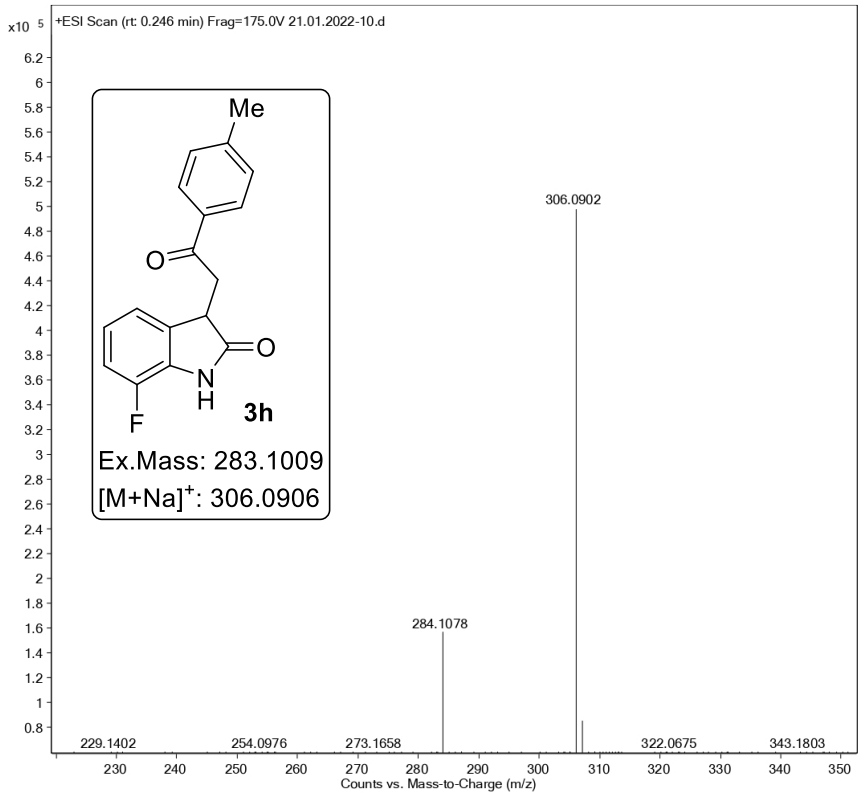


^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of 7-fluoro-3-(2-oxo-2-(*p*-tolyl)ethyl)indolin-2-one (3h)

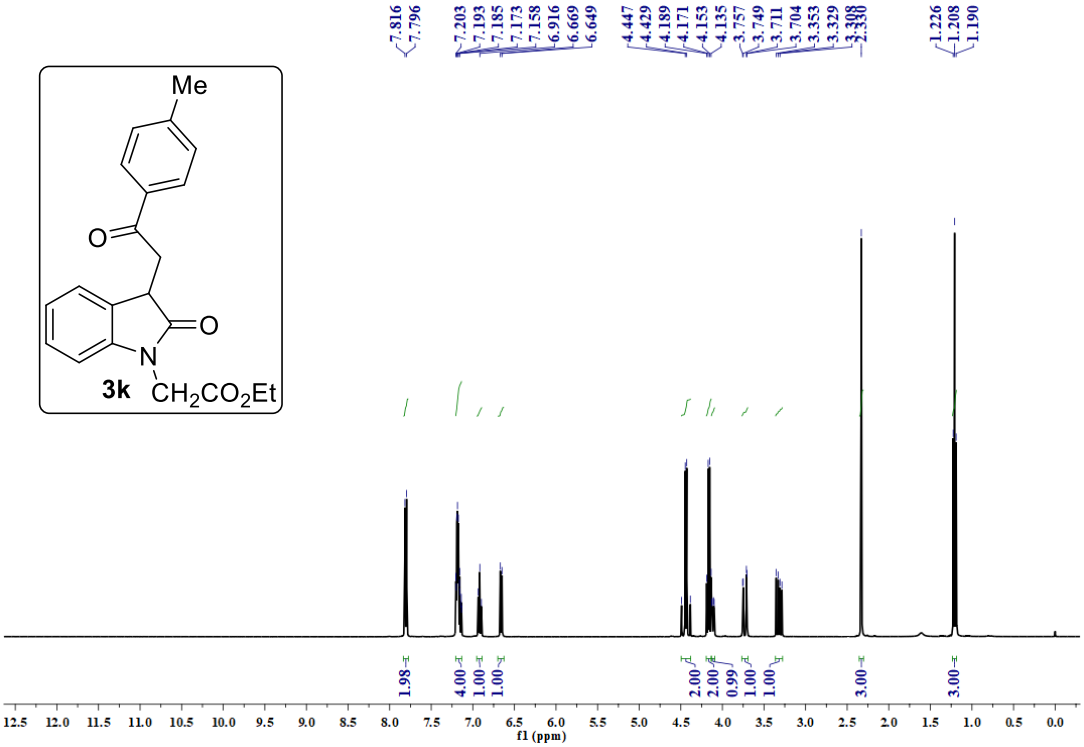


HRMS of 7-fluoro-3-(2-oxo-2-(*p*-tolyl)ethyl)indolin-2-one (3h)

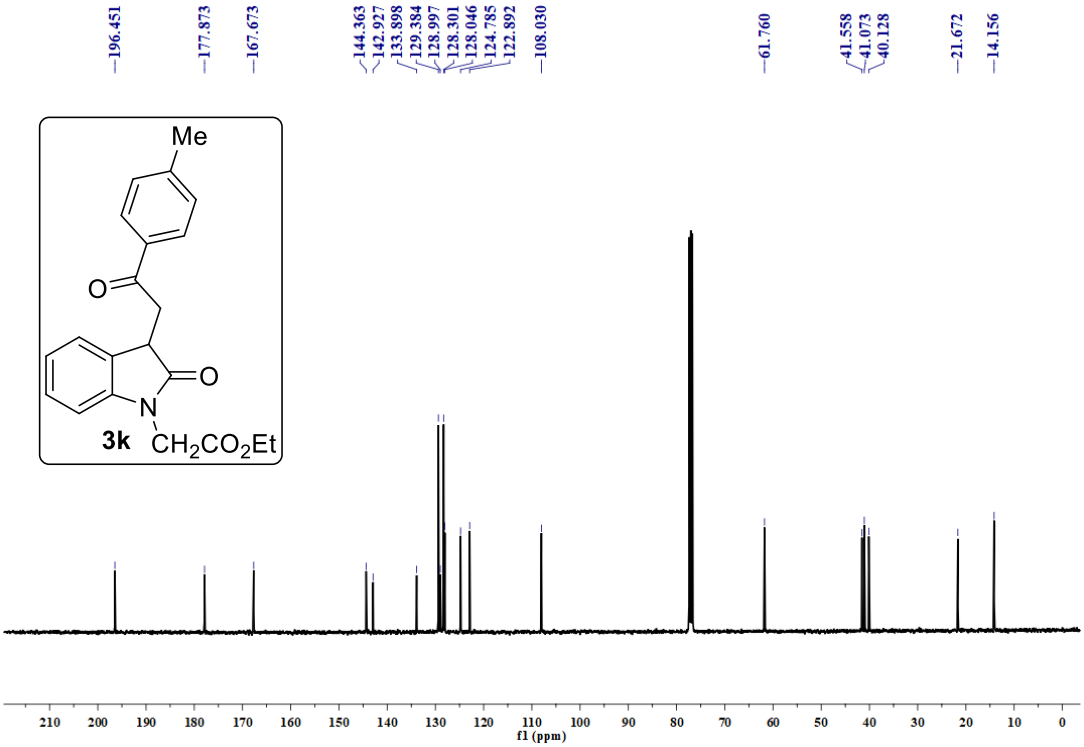
Sample Name	7F4CH3CHL	**Position**	P1-B1	**Instrument Name**	Instrument 1
User Name		**Inj Vol**	2	**InjPosition**	
Sample Type	Sample	**IRM Calibration Status**	Success	**Data Filename**	21.01.2022-10.d
ACQ Method	NITW-W.m	**Comment**		**Acquired Time**	21-Jan-22 11:57:35 AM



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of ethyl 2-(2-oxo-3-(2-oxo-2-(*p*-tolyl)ethyl)indolin-1-yl)acetate (3k)

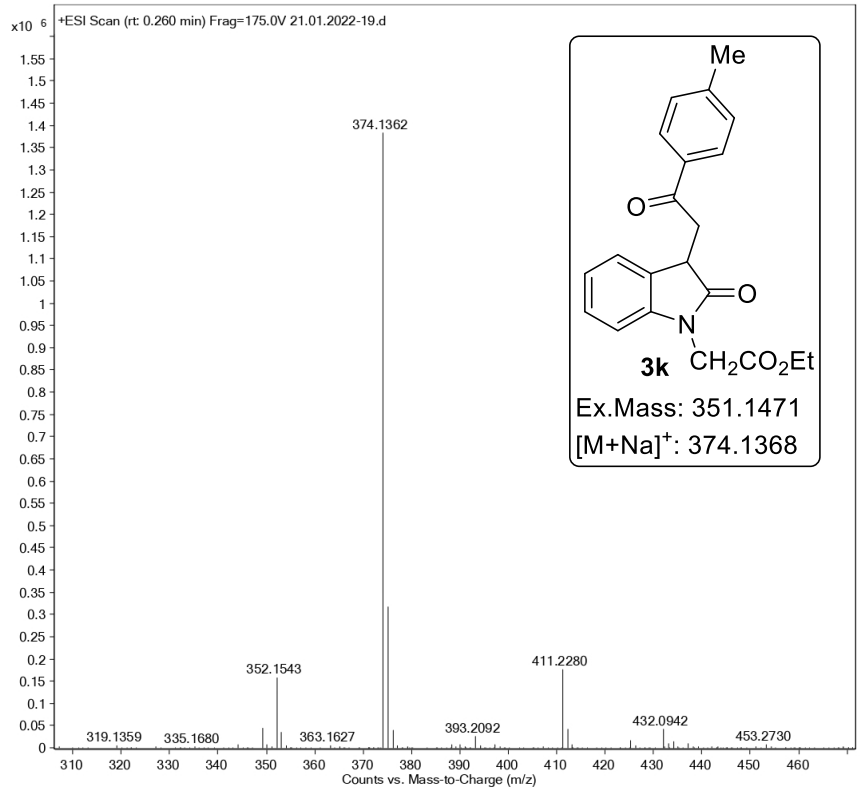


^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of ethyl 2-(2-oxo-3-(2-oxo-2-(*p*-tolyl)ethyl)indolin-1-yl)acetate (3k)

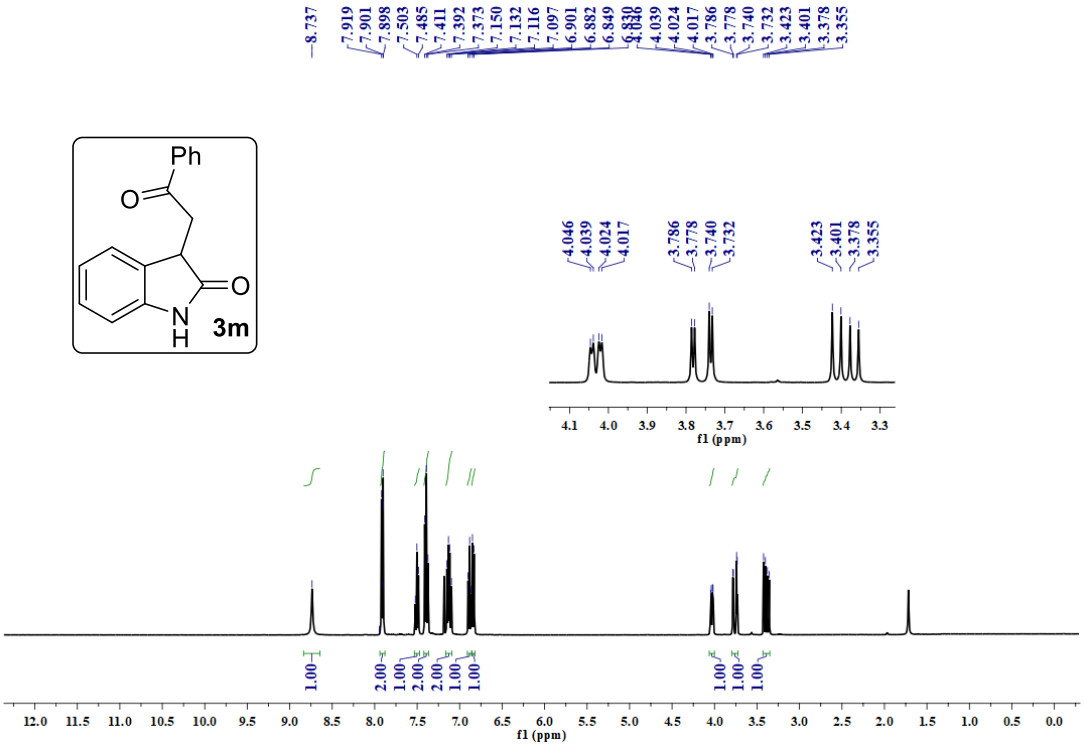


HRMS of ethyl 2-(2-oxo-3-(2-oxo-2-(*p*-tolyl)ethyl)indolin-1-yl)acetate (3k)

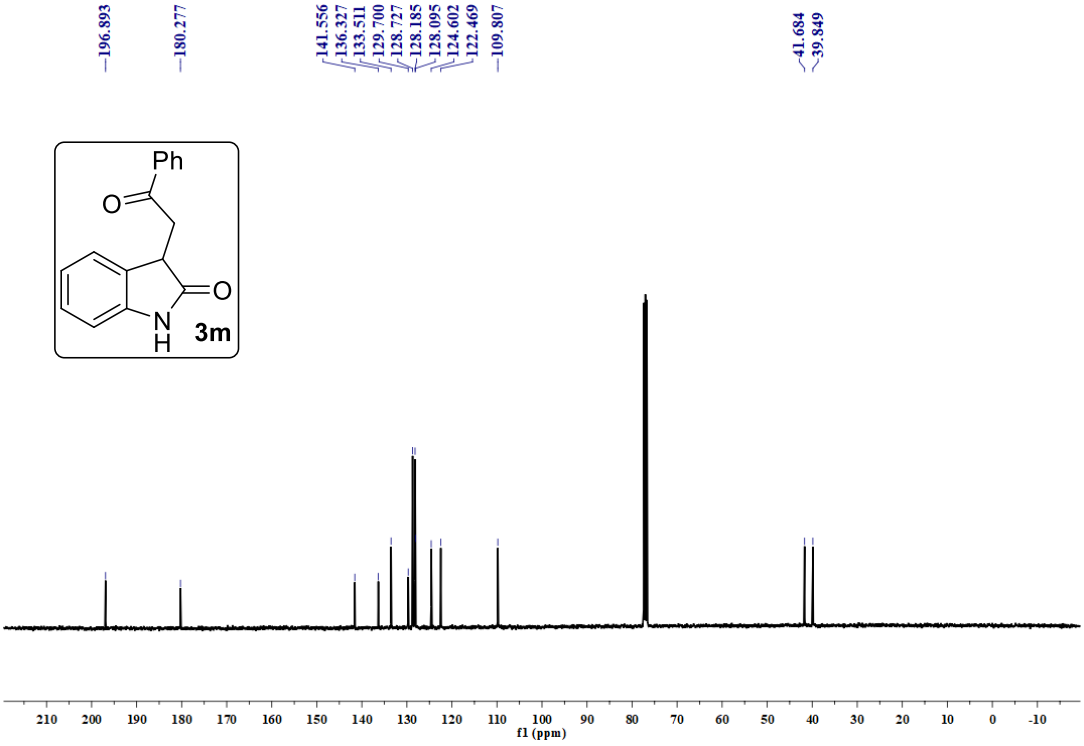
Sample Name	NCH2CO2ET4CH3CHL	**Position**	P1-C1	**Instrument Name**	Instrument 1
User Name		**Inj Vol**	2	**InjPosition**	
Sample Type	Sample	**IRM Calibration Status**	Success	**Data Filename**	21.01.2022-19.d
ACQ Method	NITW-W.m	**Comment**		**Acquired Time**	21-Jan-22 12:33:21 PM



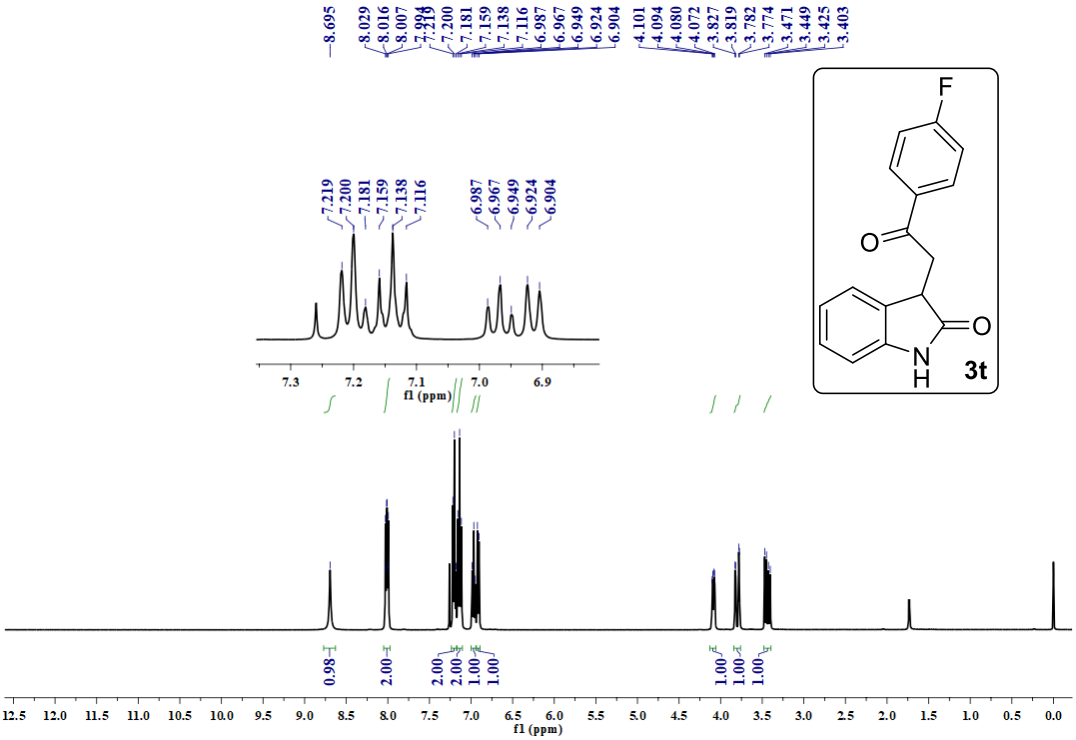
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3-(2-oxo-2-phenylethyl)indolin-2-one (3m)



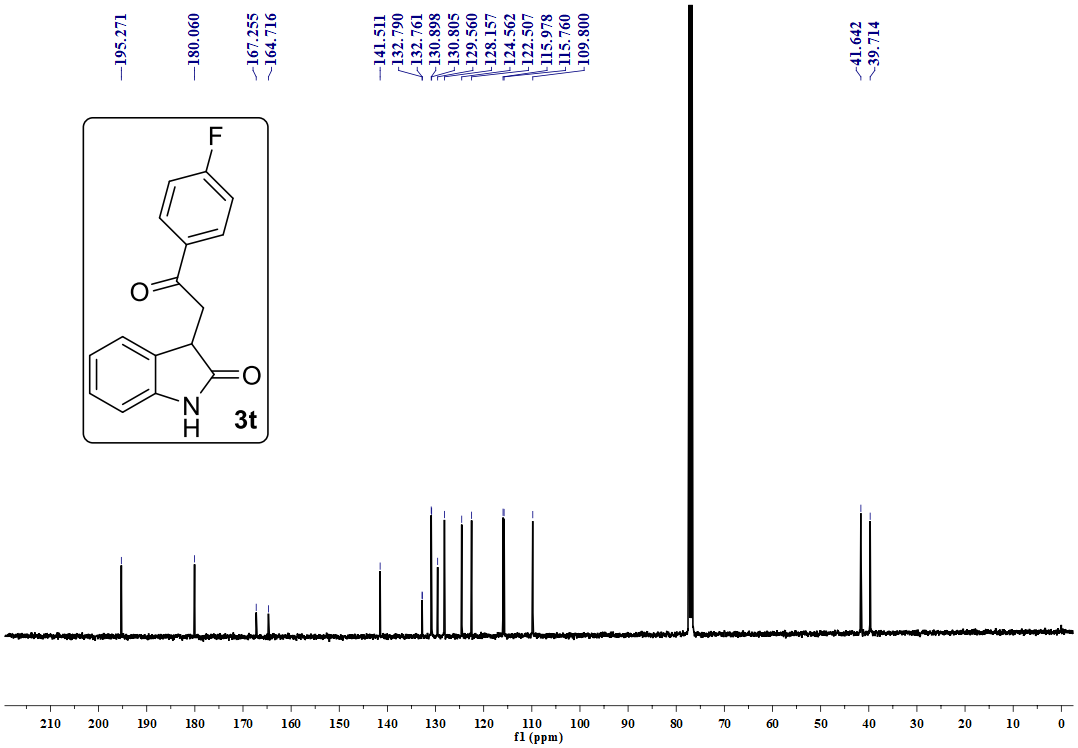
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of 3-(2-oxo-2-phenylethyl)indolin-2-one (3m)



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3-(2-(4-fluorophenyl)-2-oxoethyl)indolin-2-one (3t)

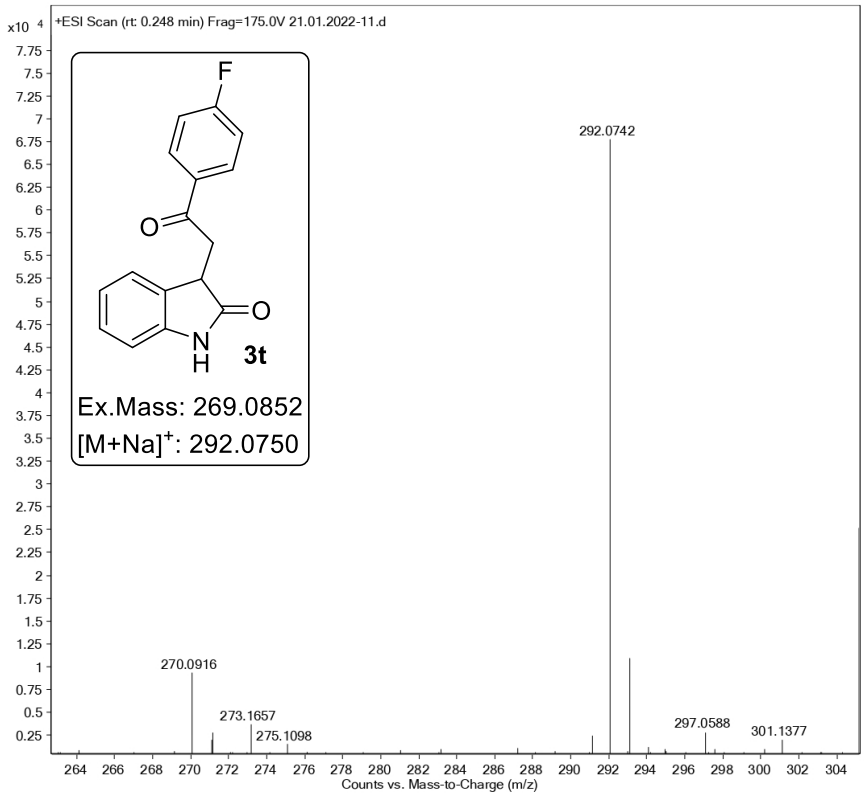


^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of 3-(2-(4-fluorophenyl)-2-oxoethyl)indolin-2-one (3t)



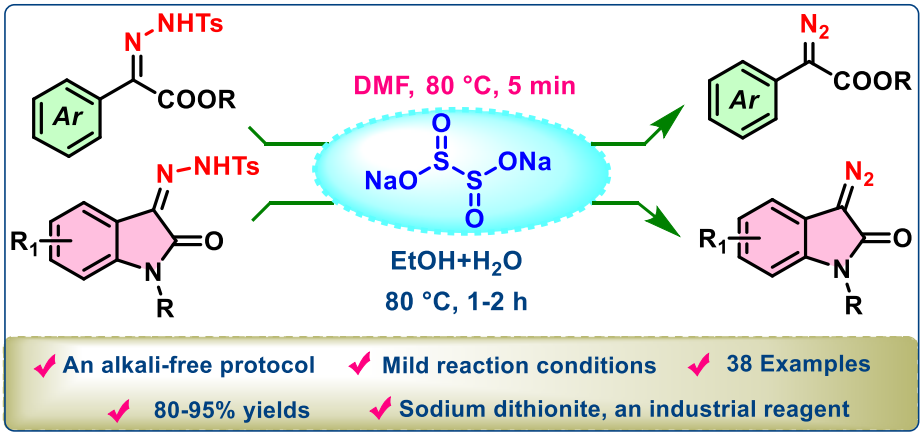
HRMS of 3-(2-(4-fluorophenyl)-2-oxoethyl)indolin-2-one (3t)

Sample Name	I4FCHL	**Position**	P1-B2	**Instrument Name**	Instrument 1
User Name		**Inj Vol**	2	**InjPosition**	
Sample Type	Sample	**IRM Calibration Status**	Success	**Data Filename**	21.01.2022-11.d
ACQ Method	NITW-W.m	**Comment**		**Acquired Time**	21-Jan-22 12:01:33 PM



CHAPTER-VIA

Sodium Dithionite Mediated Synthesis of *α*-Diazo Esters and 3-Diazooxindoles: An Alkali-Free Approach



6A.1. Introduction

Diazo groups are omnipresent in many natural products such as kinamycins A-D,[1] isolated from the bacterium *Streptomyces kanamyceticus* and lomaiviticins A-B,[2] isolated from *Micromonospora lomaivitiensis* and amino acids such as azaserine, *N*-alanylazaserine, thrazarine, 6-diazo-5-oxonorleucine, duazomycin A-B and alazopeptin[3] exhibit potent anticancer and antibiotic activities (Figure 6A.1).

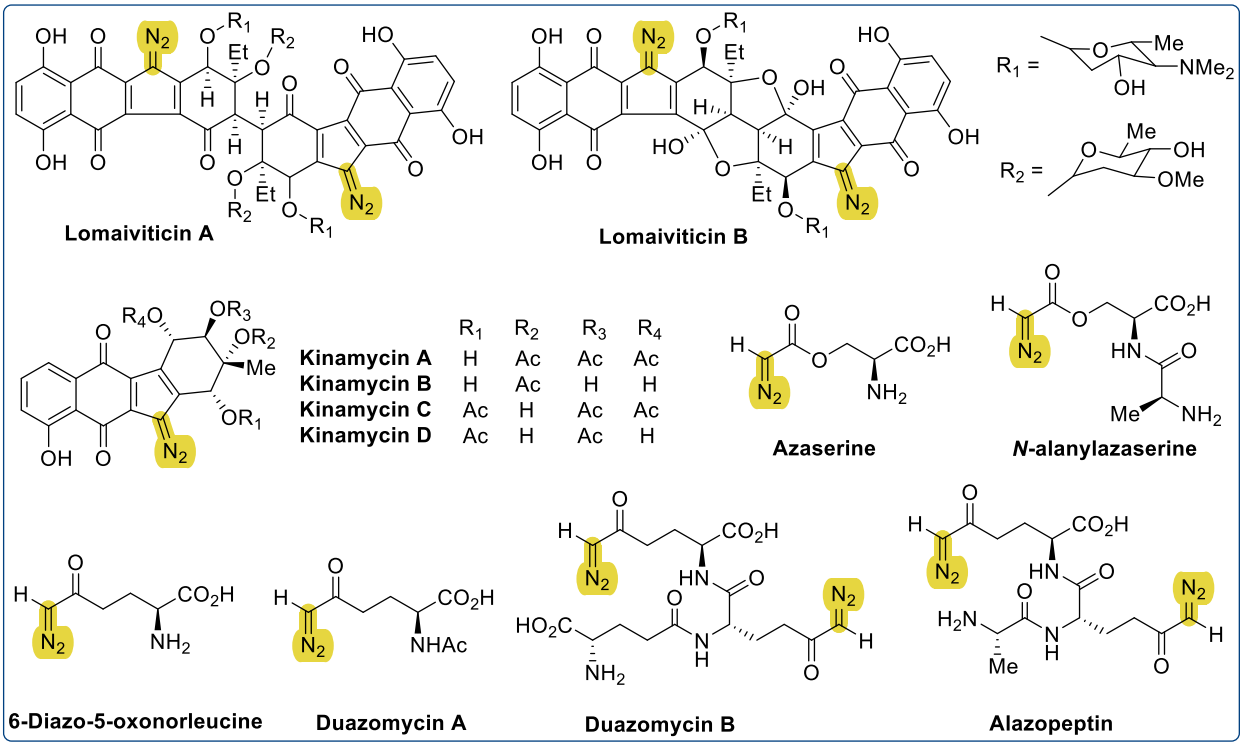
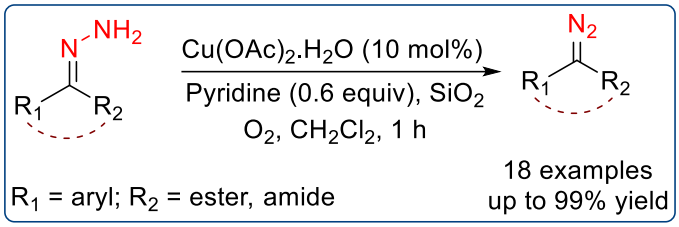


Figure 6A.1. Natural products and amino acids containing diazo moiety

Also, chemical biologists use the diazo compounds for modification and detection of biomolecules.[4] In addition, diazo compounds are widely used in organic synthesis, particularly in carbene chemistry, which include cyclopropanations,[5] X-H insertions[6] (X = C, N, O, S and Si), cycloadditions[7] and are widely used in cross-coupling reactions.[8] Among diazo compounds, *α*-diazo esters and 3-diazo-2-oxindoles received a significant interest of chemists all over the world, owing its applications in the development of multifunctionalized compounds such as spirocyclic compounds,[9a] (–)-spirotryprostatin B,[9b] PPAR agonist MBX-102 acid,[9c] diarylacetates,[9d] *α*-silyl and thioesters,[9e] cyclopropane esters,[9f] spirocyclopropanes,[9g] 3-aryl-2-oxindoles,[9h] tetrasubstituted cyclobutanes,[9i] and 3,3´-disubstituted oxindoles.[9j]

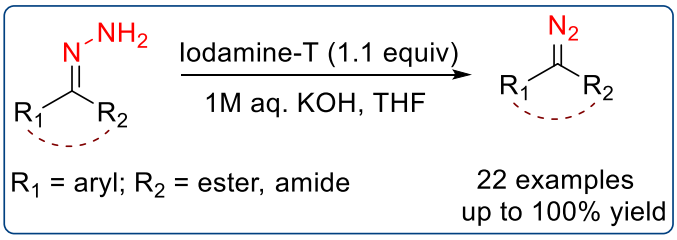
6A.1.1. Previous reports for the synthesis of *α*-diazo esters and 3-diazoindolin-2-ones

Davies and co-workers developed a method for the synthesis of *α*-diazo esters and 3-diazoindolin-2-ones *via* aerobic oxidation of hydrazones in the presence of Cu salt as a catalyst, pyridine as a co-catalyst and SiO_2 as an additive in CH_2Cl_2 solvent at room temperature. This protocol is also applicable to prepare diaryl diazomethanes (Scheme 6A.1).[10]



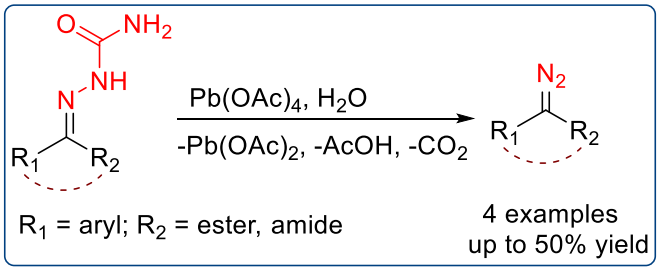
Scheme 6A.1

Nicolle et al. described the preparation of potassium *N*-iodo *p*-toluenesulfonamide (Iodamine-T) from tosylhydrazine and later, it is employed in the oxidation of hydrazones to produce *α*-diazo esters and 3-diazoindolin-2-ones in the presence of 1M aq. KOH in THF solvent at room temperature (Scheme 6A.2).[11]



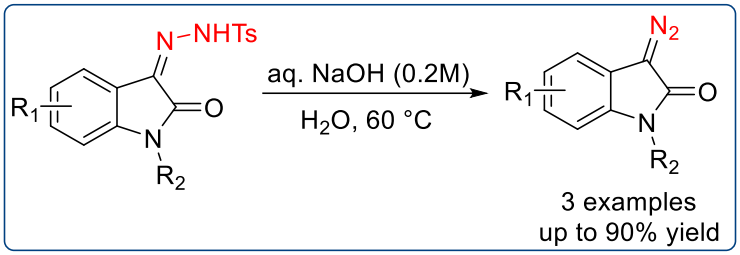
Scheme 6A.2

Meier and co-workers introduced a protocol for the synthesis of *α*-diazo esters and 3-diazoindolin-2-ones from their corresponding semicarbazones with the help of $Pb(OAc)_4$ as an oxidizing agent in the presence of water with the elimination of $Pb(OAc)_2$. acetic acid and carbon dioxide (Scheme 6A.3).[12]



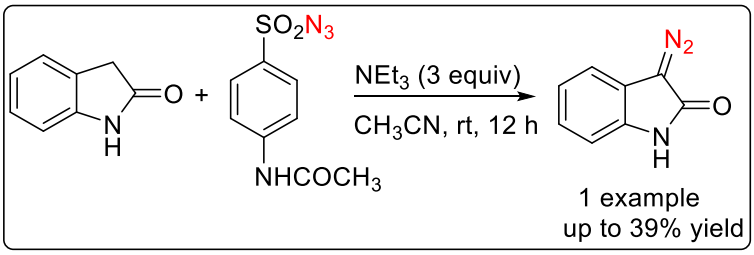
Scheme 6A.3

Varano and co-workers reported a protocol for the synthesis of 3-diazoindolin-2-ones from the respective isatin-3-*p*-tosylhydrazones using 0.2M aq. NaOH at 60 °C. This protocol is similar to the first step of Bamford-Stevens reaction i.e., base induced oxidation of tosylhydrazone to diazo compounds. This methodology allows the synthesis of 3-diazo-2-oxindoles up to 90% yield (Scheme 6A.4).[13]



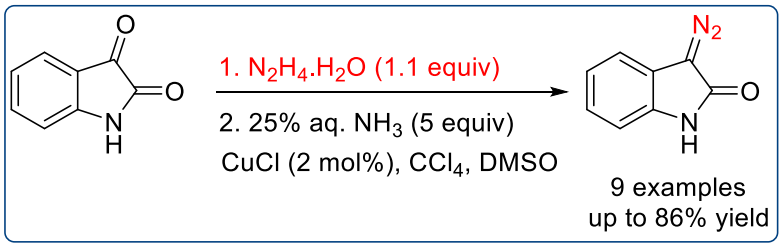
Scheme 6A.4

Shook et al. developed a protocol for the synthesis of 3-diazoindolin-2-one from 2-oxindole using *p*-acetamidobenzenesulfonyl azide as diazo transfer reagent in the presence of NEt_3 in CH_3CN solvent at room temperature for 12 h, offers the 3-diazo-2-oxindole with 39% yield (Scheme 6A.5).[14]



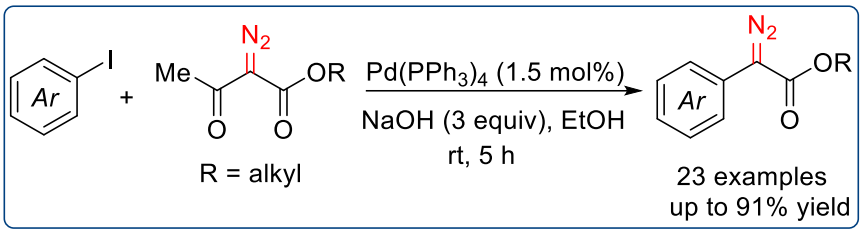
Scheme 6A.5

Nenajdenko and co-workers reported the synthesis of 3-diazoindolin-2-ones from respective isatin hydrazones (which are prepared *in situ* from isatins and hydrazine hydrate) in the presence of CuCl, CCl_4 and aq. NH_3 in DMSO solvent at room temperature. In this protocol, CCl_4 generates *in situ* Cu(II) from Cu(I), which acts as an oxidant and atmospheric oxygen as a co-oxidant (Scheme 6A.6).[15]



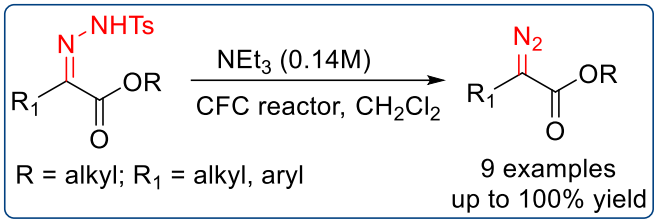
Scheme 6A.6

Ye et al. developed a palladium catalyzed strategy for the synthesis of *α*-diazo esters *via* the deacylative cross-coupling of acyldiazoacetates with aryl iodides in the presence of catalytic amount of $Pd(PPh_3)_4$ and NaOH in ethanol solvent at room temperature for 5 h. This method allows the synthesis of *α*-diazo esters in 42-91% yields (Scheme 6A.7).[16]



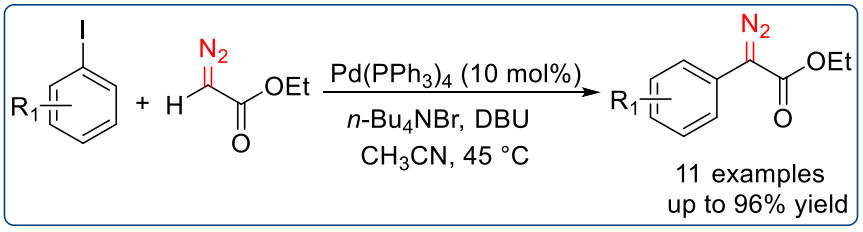
Scheme 6A.7

Hayes and co-workers introduced a protocol for the synthesis of *α*-diazo esters under convection flow coil reactor (CFC) in continuous manner from the respective tosylhydrazones in the presence of NEt_3 in CH_2Cl_2 solvent at 80-100 °C. This method enables the rapid synthesis of *α*-diazo esters in 37-100% yields (Scheme 6A.8).[17]



Scheme 6A.8

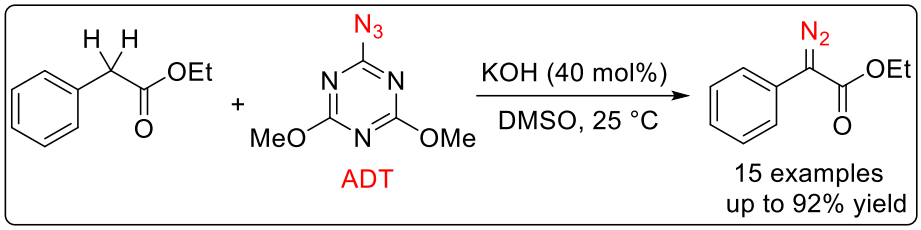
Peng et al. described the synthesis of *α*-diazo esters *via* Pd(0) catalyzed cross-coupling of ethyl diazoacetate with aryl iodides in the presence of DBU as a base and *n*-tetrabutylammonium bromide (*n*-Bu_4NBr) as an additive in CH_3CN solvent at 45 °C. This protocol is also applicable to vinyl iodides (Scheme 6A.9).[18]



Scheme 6A.9

Ma and co-workers synthesized an intrinsically safe and bench-stable azide i.e., 2-azido-4,6-dimethoxy-1,3,5-triazine (ADT). Later, it was employed in the synthesis of *α*-diazo esters *via*

transfer of diazo group to active methylene compounds in the presence of an inorganic base (KOH) in DMSO solvent at 25 °C (Scheme 6A.10).[19]

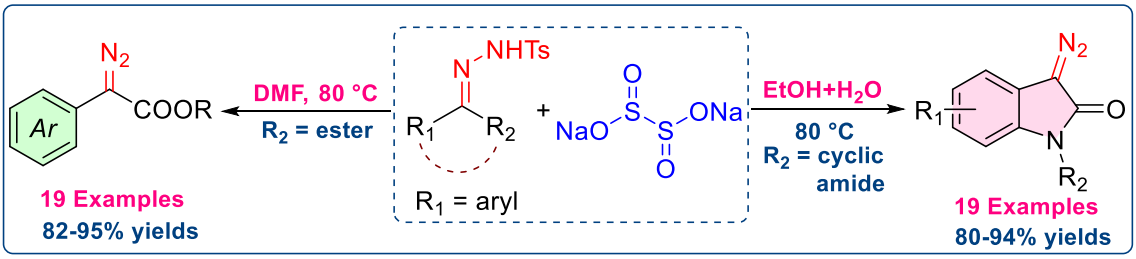


Scheme 6A.10

Based on the literature, we found that the majority of the reported methods require transition metal catalysts, strong bases, potentially explosive azides, special reaction set-up and have limited substrate scope. To address the limitations of existed reports, we aim to develop an environmentally benign protocol to synthesize *α*-diazo esters and 3-diazoindolin-2-ones using sodium dithionite.

6A.2. Present study

Considering the importance of *α*-diazo esters and 3-diazoindolin-2-ones as synthetic precursors, we have developed a protocol by employing tosylhydrazones and sodium dithionite. Here, sodium dithionite functions as a mild base. This protocol allows the rapid synthesis of wide range of *α*-diazo esters and 3-diazooxindoles from respective tosylhydrazones with 80-95% yields. Use of inexpensive and commercially available sodium dithionite, broad substrate scope with functional group tolerance and mild reaction conditions are some of the key features of this methodology. This protocol is also applicable to gram-scale synthesis (Scheme 6A.11).

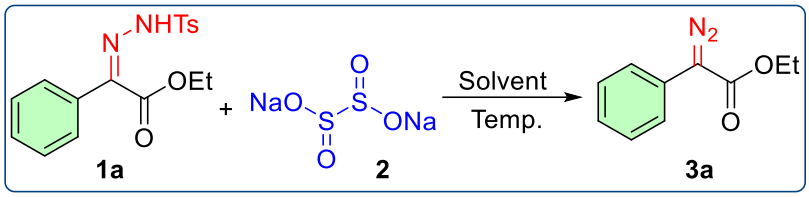


Scheme 6A.11. Synthesis of *α*-diazo esters and 3-diazo-2-oxindoles using sodium dithionite

6A.2.1. Results and discussion

In our initial studies, ethyl-2-phenyl-2-(2-tosylhydrazono)acetate **1a** (1 mmol) was attempted to react with sodium dithionite **2** (1 mmol) in EtOH+H_2O at room temperature and obtained the ethyl 2-diazo-2-phenylacetate **3a** in 60% yield (Table 6A.1, entry 1).

Table 6A.1. Optimization of the reaction conditions[a]



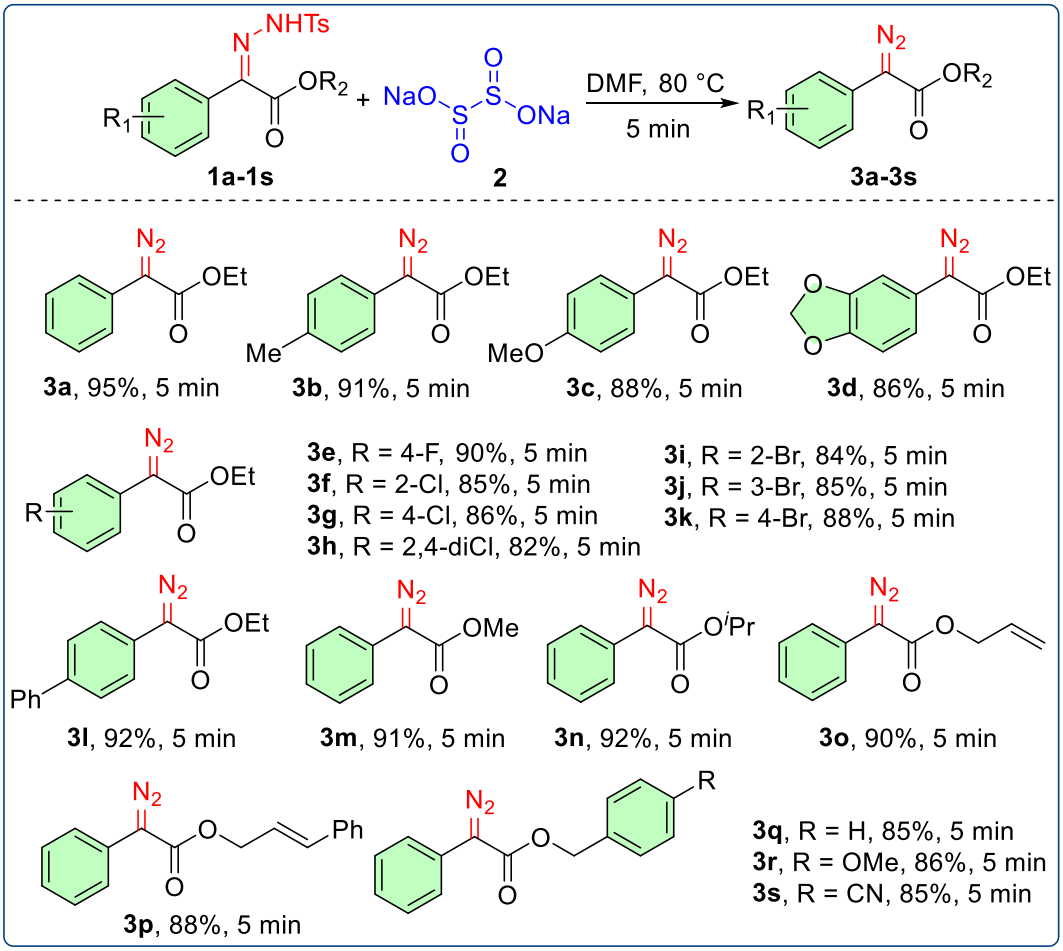
Entry	Solvent (9:1 v/v)	Reagent (equiv)	Temp. (°C)	Time (h)	Yield (%)[b]
1	EtOH+H_2O	Sodium dithionite	rt	24	60
2	EtOH+H_2O	Sodium dithionite	70	1.5	75
3	MeOH+H_2O	Sodium dithionite	70	1	72
4	*i*-PrOH+H_2O	Sodium dithionite	70	1.5	69
5	THF+H_2O	Sodium dithionite	65	5	n.d.
6	CH_3CN+H_2O	Sodium dithionite	70	1	70
7	DMSO	Sodium dithionite	80	10 min	84
8	**DMF**	**Sodium dithionite**	**80**	**5 min**	**95**
9	DMF	Sodium dithionite	80	1	47[c]
10	DMF	Sodium dithionite	70	15 min	90
11	DMF	Sodium dithionite	90	5 min	95
12	DMF	Rongalite	80	1	55
13	DMF	Thiourea dioxide	80	1.5	75

[a]Reaction conditions: ethyl-2-phenyl-2-(2-tosylhydrazono)acetate **1a** (1.0 mmol) and sodium dithionite **2** (1.0 mmol) in variable solvents (2 mL) at different temperatures. [b]Yield of isolated product.[c]0.5 equiv. of sodium dithionite was used. rt = room temperature. n.d. = not detected.

The structure of **3a** was confirmed by ^1H and ^{13}C NMR spectral data. To our delight, the yield of **3a** was improved to 75%, when the reaction was conducted at 70 °C (Table 6A.1, entry 2). With this good result, further screening was carried out with other polar protic solvents such as MeOH+H_2O and *i*-PrOH+H_2O and obtained **3a** in 72% and 69% yields, respectively (Table 6A.1, entries 3-4). Later, tested the reaction in polar aprotic solvents and among them, DMF was found to be superior and furnished the target compound **3a** in 95% yield (Table 6A.1, entries 5-8). Additionally, variants in temperature and equiv of sodium dithionite were not useful to improve the yield of the product **3a** (Table 6A.1, entries 9-11). Also, we tested the reaction with

other sulfur reagents which are analogous to sodium dithionite such as rongalite and thiourea dioxide and got inferior results (Table 6A.1, entries 12-13). Thus, the optimized reaction conditions are as follows: 1.0 mmol of ethyl-2-phenyl-2-(2-tosylhydrazono)acetate **1a**, 1.0 mmol of sodium dithionite **2** in 2 mL of DMF at 80 °C for 5 min (Table 6A.1, entry 8).

Table 6A.2. Substrate scope of 2-phenyl-2-(2-tosylhydrazono)acetates[a,b]

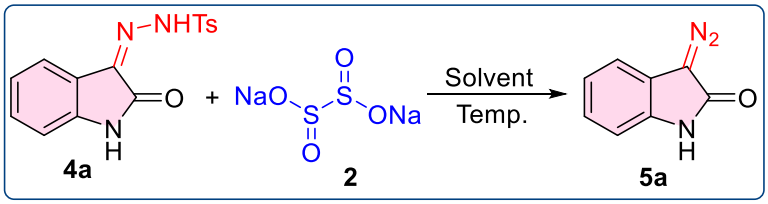


[a]Reaction conditions: 2-phenyl-2-(2-tosylhydrazono)acetates **1** (1.0 mmol) and sodium dithionite **2** (1.0 mmol) in 2 mL of DMF at 80 °C. [b]Yield of isolated product.

With the optimized reaction conditions in hand (Table 6A.1, entry 8), later we tested the scope of this reaction by taking various tosylhydrazones. All the synthesized tosylhydrazones of *α*-keto esters **1a-1s** were readily reacted with sodium dithionite to form the corresponding *α*-diazo esters **3a-3s** in good to excellent yields within 5 min (Table 6A.2). The electron-donating groups such as methyl, methoxy and methylenedioxy substituted tosylhydrazones smoothly reacted with sodium dithionite to furnish **3b-3d** in 86-91% yields (Table 6A.2). Halogens (–F, –Cl and –Br) present on various positions of benzene ring of tosylhydrazones also offered the respective *α*-

diazo esters **3e**-**3k** in 82-90% yields (Table 6A.2). Also, biphenyl tosylhydrazone resulted the diazo compound **3l** in 92% yield. Additionally, tosylhydrazones which were formed by alkyl, allyl and cinnamyl groups were also actively participated in the reaction and afforded the *α*-diazo esters **3m**-**3p** in 88-92% yields (Table 6A.2). Moreover, both electron-donating (–OMe) and electron withdrawing (–CN) groups present on ester part of tosylhydrazones were also efficiently involved in the reaction and produced the corresponding *α*-diazo esters **3r**-**3s** in 85-86% yields (Table 6A.2).

Table 6A.3. Optimization of the reaction conditions[a]



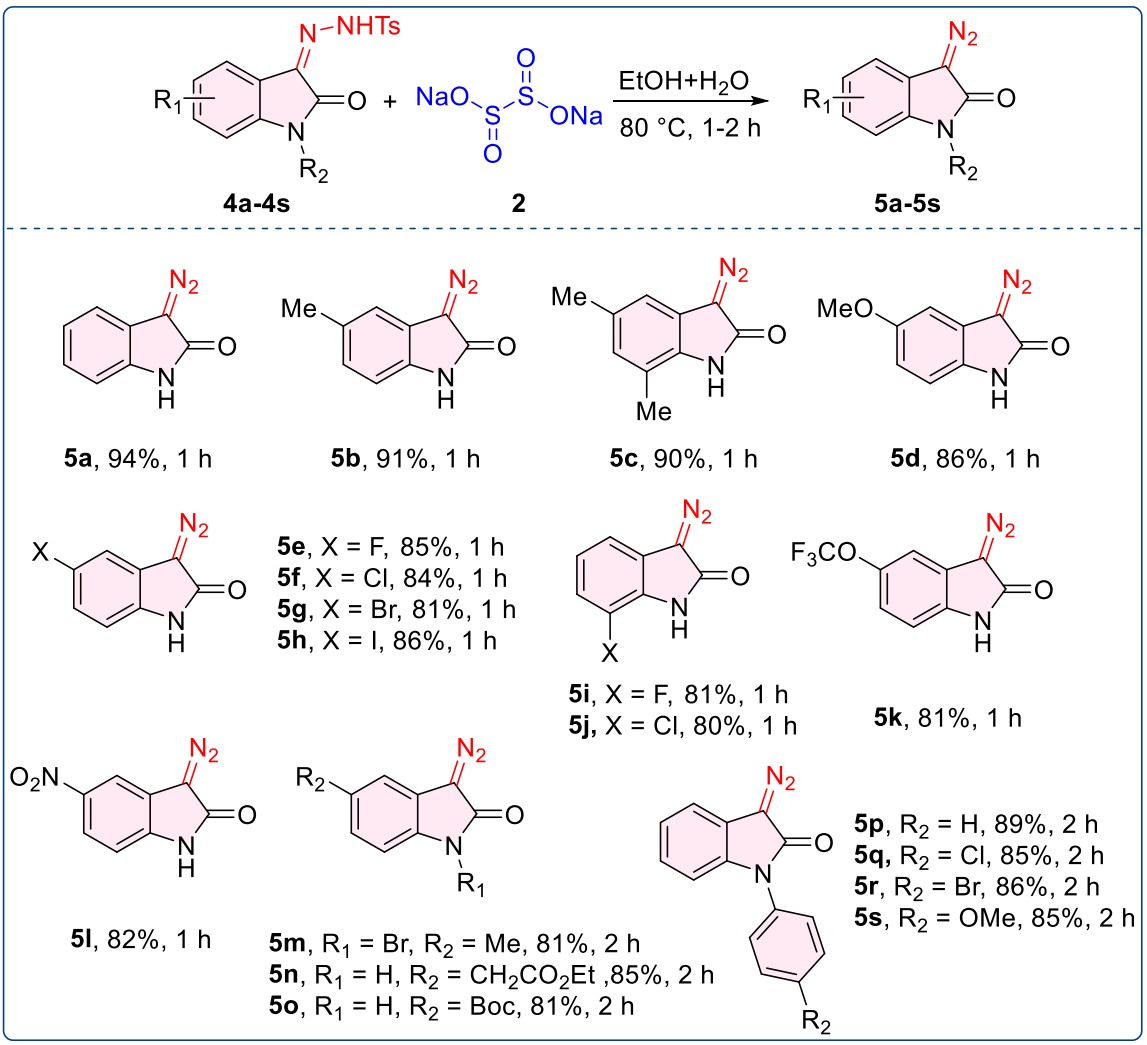
Entry	Solvent (9:1 v/v)	Reagent (equiv)	Temp. (°C)	Time (h)	Yield (%)[b]
1	DMF	Sodium dithionite	80	8	35
2	DMSO	Sodium dithionite	80	3	58
3	CH_3CN+H_2O	Sodium dithionite	80	3	84
4	$THF+H_2O$	Sodium dithionite	65	2	52
5	H_2O	Sodium dithionite	80	16	30
6	$MeOH+H_2O$	Sodium dithionite	80	1.5	78
7	*i*-$PrOH+H_2O$	Sodium dithionite	80	1.5	75
8	**$EtOH+H_2O$**	**Sodium dithionite**	**80**	**1**	**94**
9	$EtOH+H_2O$	Sodium dithionite	70	1.5	91

[a]Reaction conditions: isatin-3-*p*-tosylhyadrazone **4a** (1.0 mmol) and sodium dithionite **2** (1.0 mmol) in variable solvents (2 mL) at different temperatures. [b]Yield of isolated product.

Next, we tested the scope of the optimized reaction conditions on isatin-3-*p*-tosylhyadrazones **4a** and observed the formation of desired product i.e., 3-diazoindolin-2-one **5a** in 35% yield (Table 6A.3, entry 1). In order to improve the yield of the product, we have screened the reaction with other solvents and the results were shown in Table 6A.3. Firstly, reaction was tested with polar aprotic solvents and obtained 52-84% yields (Table 6A.3, entries 2-4). Among the tested polar protic solvents, EtOH was found to be superior and resulted the product **5a** in 94% yield (Table

6A.3, entries 5-8). Additionally, decrease in temperature resulted with inferior result (Table 6A.3, entry 9). Therefore, the optimized reaction conditions are as follows: 1.0 mmol of isatin-3-*p*-tosylhyadrazone **4a** and 1.0 mmol of sodium dithionite **2** in 2 mL of EtOH+H_2O (9:1 v/v) at 80 °C (Table 6A.3, entry 8).

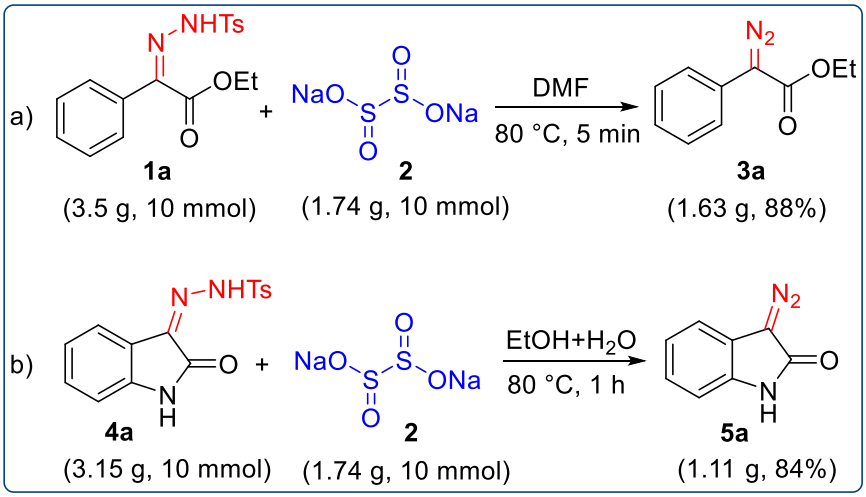
Table 6A.4. Substrate scope of isatin-3-*p*-tosylhyadrazones[a,b]



[a]Reaction conditions: isatin-3-*p*-tosylhyadrazone **4** (1.0 mmol) and sodium dithionite **2** (1.0 mmol) in EtOH+H_2O (2 mL) at 80 °C. [b]Yield of isolated product.

With the optimized reaction conditions in hand (Table 6A.3, entry 8), we turned our attention to study the scope of the reaction with various isatin-3-*p*-tosylhyadrazones (Table 6A.4). The electron-donating groups such as methyl and methoxy substituted isatin-3-*p*-tosylhyadrazones readily reacted with sodium dithionite and furnished **5b**-**5d** in 86-91% yields (Table 6A.4). Also, halogens (–F, –Cl, –Br, and –I) present at different positions of benzene ring of isatin-3-*p*-

tosylhydrazones underwent reaction smoothly with sodium dithionite and afforded the corresponding 3-diazo-2-oxindoles **5e-5j** in 80-86% (Table 6A.4). Moreover, strong electron-withdrawing groups such as trifluoromethoxy (–OCF_3) and nitro (–NO_2) substituted isatin-3-*p*-tosylhyadrazones resulted the respective diazo compounds **5k** and **5l** in 81% and 82% yields, respectively. Additionally, both *N*-alkylated and *N*-arylated isatin-3-*p*-tosylhyadrazones also participated in the reaction and produced the corresponding diazo compounds **5m, 5p-5s** in 81-89% yields (Table 6A.4). Pleasingly, both ester and Boc protecting groups are stable with the sodium dithionite and gave the respective products **5n** and **5o** in 85% and 81% yields, respectively (Table 6A.4).

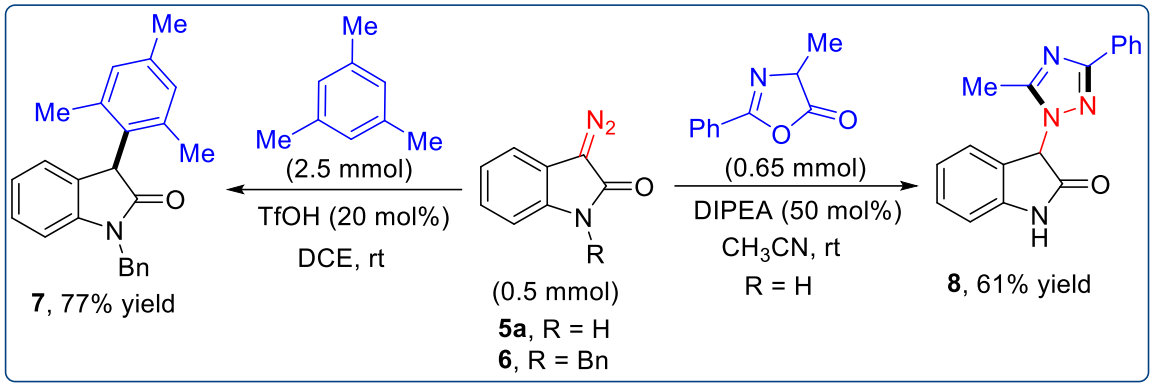


Scheme 6A.12. Gram-scale synthesis

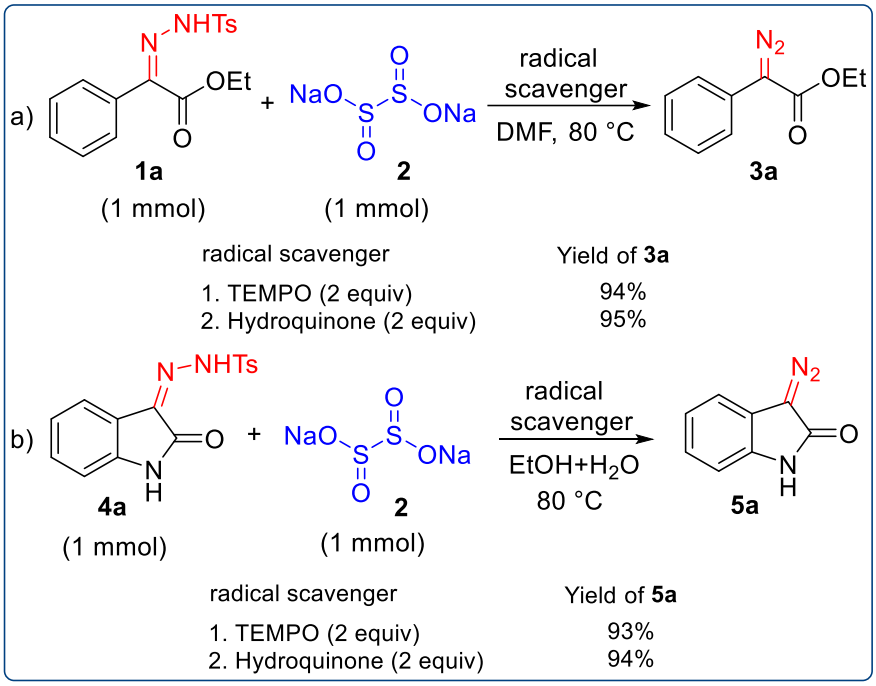
Finally, we have examined the synthetic potential of our protocols on gram scale by taking ethyl-2-phenyl-2-(2-tosylhydrazono)acetate **1a** (3.5 g, 10 mmol) and sodium dithionite **2** (1.74 g, 10 mmol) in DMF (15 mL) at 80 °C gave the desired product ethyl 2-diazo-2-phenylacetate **3a** in 88% yield in 5 min (scheme 6A.12a). Similarly, we have conducted another gram scale reaction on isatin-3-*p*-tosylhyadrazone **4a** (3.15 g, 10 mmol) using sodium dithionite **2** (1.74 g, 10 mmol) in EtOH+H_2O (15 mL) at 80 °C and acquired the 3-diazoindolin-2-one **5a** in 84% yield (Scheme 6A.12b).

Further, we explored the utility of this protocol by conducting some synthetic transformations. 3-Diazo-2-oxindoles were successfully transformed to 1-benzyl-3-mesitylindolin-2-one **7** using mesitylene *via* C-H functionalization[20] in 77% yield and 3-(5-methyl-3-phenyl-1*H*-1,2,4-triazol-

1-yl)indolin-2-one **8** by employing azlactone *via* cycloaddition reaction[21] in 61% yield, respectively (Scheme 6A.13).



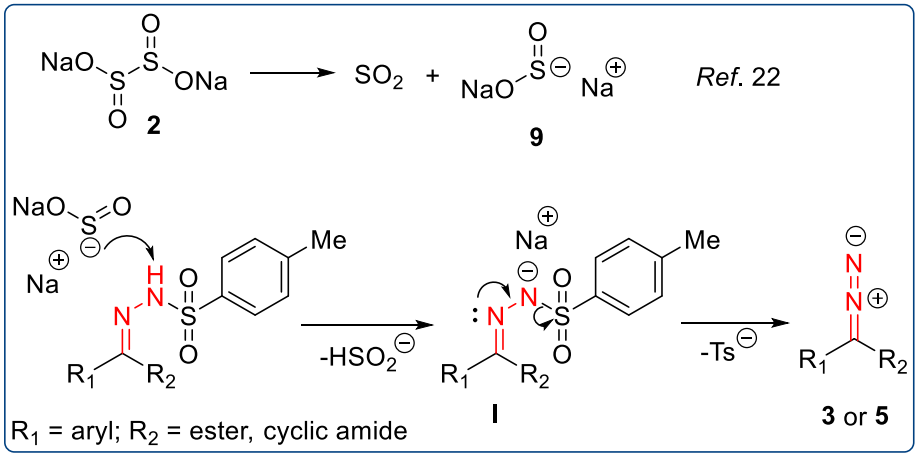
Scheme 6A.13. Synthetic transformations of 3-diazo-2-oxindoles



Scheme 6A.14. Control experiments

We have conducted some control experiments with radical scavengers such as TEMPO and hydroquinone to know the reaction pathway, because it is well known that sodium dithionite is a good single electron transfer reagent (Scheme 6A.14). Initially, ethyl-2-phenyl-2-(2-tosylhydrazono)acetate **1a** (1 mmol) taken as model substrate, to this sodium dithionite **2** (1 mmol), TEMPO/hydroquinone (2 equiv) and DMF (2 mL) were added and the mixture was stirred at 80 °C. The two reactions were completed within 5 min without significant drop in the yield. These results indicated that the convertion of ethyl-2-phenyl-2-(2-tosylhydrazono)acetate

1a to ethyl 2-diazo-2-phenylacetate **3a** is not undergoing through radical mechanism (Scheme 6A.14a). Similarly, two more reactions were conducted on isatin-3-*p*-tosylhyadrazone **4a** under standard conditions with radical scavengers TEMPO and hydroquinone and observed the formation of 3-diazoindolin-2-one **5a** without change in the yield of product (Scheme 6A.14b). These two experiments are indicating that the formation of 3-diazo-2-oxindoles is also not going through radical mechanism.



Scheme 6A.15. Plausible reaction mechanism

Based on the previous literature[22-23] and controlled experiments, a possible mechanism is proposed in Scheme 6A.15. Initially, sodium dithionite dissociates into sulfur dioxide and sodium salt of sulfoxylate dianion **9** under reaction conditions. The formed sulfoxylate dianion abstracts the proton of tosylhydrazones to form the intermediate **I**. Later, the lone pair on the nitrogen atom of intermediate **I** drives the loss of tosyl group to produce the target diazo compound **3** or **5**, this mechanism is similar to the first step of Bamford-Stevens reaction.

6A.3. Conclusion

We have developed an alkali-free protocol for the synthesis of *α*-diazo esters and 3-diazo-2-oxindoles from respective tosylhydrazones using sodium dithionite. Sodium dithionite is a readily available, an inexpensive and an industrial reagent. This methodology allows the rapid synthesis of wide range of *α*-diazo esters and 3-diazo-2-oxindoles in 80-95% yields with functional group compatibility. In addition, the utility of this protocol is explored by carrying out some synthetic transformations. Also, this protocol is applicable to gram-scale synthesis.

6A.4. Experimental section

6A.4.1. General information

All chemicals and solvents were purchased from Alfa Aesar, Spectrochem, SRL, Finar and used as received. Thin layer chromatography was performed on 200 µm aluminum-foil backed silica gel plates and the column chromatography was performed using 100-200 mesh silica gel (Merk). Bruker Avance 400 MHz spectrometer was used to record ^{1}H NMR spectra and used $CDCl_3$ and DMSO-d_6 as solvents and TMS as an internal standard. The multiplicities were described using the following acronyms: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Coupling constants, *J* were reported in Hertz unit (Hz). Bruker Avance 100 MHz spectrometer was used to record $^{13}C\{^{1}H\}$ NMR spectra, and they were fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to the center line of a triplet at 77.16 ppm of chloroform-*d* (a multiplet at 39.52 ppm of DMSO-d_6). A Stuart SMP30 apparatus was used to determine the melting points and are uncorrected. FT-IR spectra were recorded on a Perkin Elmer spectrometer. HRMS were analyzed with Agilent Q-TOF 6230.

6A.4.2. General procedure for synthesis of 2-aryl-2-(2-tosylhydrazono)esters (1a-1s)[24]

An oven dried 25 mL reaction flask was charged with appropriate *α*-keto ester (5 mmol), *p*-toluenesulfonyl hydrazide (5 mmol) and MeOH (10 mL). The mixture was stirred at room temperature for overnight. After completion of reaction, MeOH was evaporated under vacuum and the crude product was purified by column chromatography using hexanes and ethyl acetate as an eluent and silica gel as stationary phase.

6A.4.3. General procedure for synthesis of isatin-3-*p*-tosylhyadrazones (4a-4s)[9b]

An oven dried 50 mL reaction flask was charged with appropriate isatin (10 mmol), *p*-toluenesulfonyl hydrazide (10 mmol, 1 equiv) and MeOH (20 mL). The mixture was stirred at room temperature for the appropriate time (10 min-3 h). The reaction was monitored by TLC using hexanes and ethyl acetate as an eluent. After reaction has completed, the resulted yellow solid was filtered off and washed with cold methanol. The air dried isatin-3-*p*-tosylhydrazones were used in the next step directly.

6A.4.4. General procedure (A) for synthesis of 2-diazo-2-phenylacetates (3a-3s)

An oven dried 10 mL reaction flask was charged with appropriate 2-phenyl-2-(2-tosylhydrazono)ester **1** (1 mmol), sodium dithionite **2** (1 mmol) and DMF (2 mL), stirred

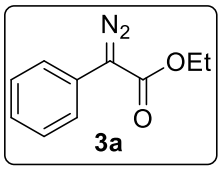
at 80 °C for 5 min. The progress of the reaction was monitored by TLC using hexanes and ethyl acetate as an eluent. After completion of reaction, organic compound was extracted with ethyl acetate (3 x 10 mL). The organic layers were separated, dried (Na_2SO_4) and evaporated to give a residue that was purified on silica gel by column chromatography using hexanes and ethyl acetate as an eluent.

6A.4.5. General procedure (B) for synthesis of 3-diazoindolin-2-ones (5a-5s)

An oven dried 25 mL reaction flask was charged with appropriate isatin-3-*p*-tosylhyadrazone **3** (1 mmol), sodium dithionite **2** (1 mmol) and EtOH+H_2O (9:1 v/v, 3 mL), stirred at 80 °C for the appropriate time (1-2 h) and the reaction was monitored by TLC using hexanes and ethyl acetate as an eluent. After completion of reaction, EtOH was evaporated under vacuum and the product was extracted with ethyl acetate (3 x 10 mL). The organic layers were separated, dried (Na_2SO_4) and evaporated to give a residue that was purified on silica gel by column chromatography using hexanes and ethyl acetate as an eluent.

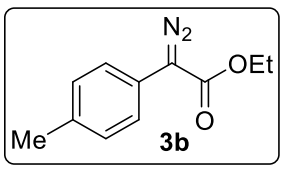
6B.5. Characterization data of products 3a-3s, 5a-5s, 7 & 8

ethyl 2-diazo-2-phenylacetate (3a).[10] Red liquid; Yield (181 mg, 95%); The title



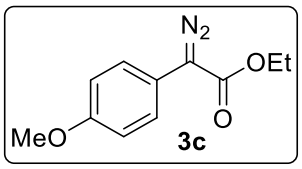
compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3092, 2982, 2085, 1703, 1558, 755; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39 (d, J = 8.4 Hz, 2H), 7.28 (t, J = 8.0 Hz, 2H), 7.08 (t, J = 7.6 Hz, 1H), 4.24 (q, J = 7.2 Hz, 2H), 1.25 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 165.2, 128.9, 125.8, 125.7, 123.9, 60.9, 14.5 (The resonance resulting from the diazo carbon was not observed).

ethyl 2-diazo-2-(*p*-tolyl)acetate (3b).[25] Orange liquid; Yield (186 mg, 91%); The title



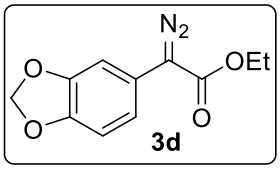
compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3090, 2980, 2084, 1703, 1515, 1019; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 4.31 (q, J = 7.2 Hz, 2H), 2.33 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 165.5, 135.6, 129.7, 124.1, 122.3, 60.9, 20.9, 14.5 (The resonance resulting from the diazo carbon was not observed).

ethyl 2-diazo-2-(4-methoxyphenyl)acetate (3c).[10] Orange liquid; Yield (194 mg, 88%);

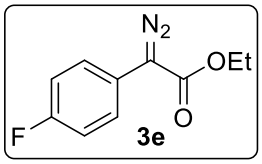


The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3049, 2927, 2082, 1741, 1476, 1030; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.93 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 4.36 (q, J = 7.2 Hz, 2H), 3.82 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 165.0, 164.2, 132.6, 125.6, 114.3, 62.2, 55.7, 14.1 (The resonance resulting from the diazo carbon was not observed).

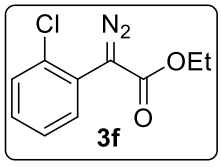
ethyl 2-(benzo[*d*][1,3]dioxol-5-yl)-2-diazoacetate (3d).[26] Red liquid; Yield (201 mg, 86%); The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3094, 2981, 2084, 1729, 1505, 984; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.98 (dd, J = 1.6, 0.4 Hz, 1H), 6.79 – 6.73 (m, 2H), 5.88 (s, 2H), 4.24 (q, J = 7.2 Hz, 2H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 165.5, 148.4, 146.0, 118.8, 117.8, 108.8, 105.8, 101.3, 61.0, 14.5 (The resonance resulting from the diazo carbon was not observed).



ethyl 2-diazo-2-(4-fluorophenyl)acetate (3e).[16] Orange liquid; Yield (187 mg, 90%); The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3099, 2986, 2101, 1718, 1459, 856; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.40 – 7.34 (m, 2H), 7.03 – 6.99 (m, 2H), 4.25 (q, J = 7.2 Hz, 2H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 165.3, 161.0 (d, $^1J_{C\text{-}F}$ = 245.0 Hz), 125.9 (d, $^3J_{C\text{-}F}$ = 8.0 Hz), 121.4 (d, $^4J_{C\text{-}F}$ = 3.0 Hz), 116.0 (d, $^2J_{C\text{-}F}$ = 22.0 Hz), 61.1, 14.5 (The resonance resulting from the diazo carbon was not observed).

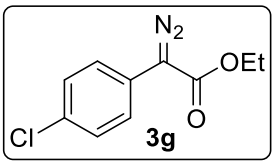


ethyl 2-(2-chlorophenyl)-2-diazoacetate (3f).[27] Yellow liquid; Yield (190 mg, 85%); The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3074, 2926, 2087, 1704, 1685, 828; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.55 (dd, J = 8.0, 1.6 Hz, 1H), 7.45 (dd, J = 7.6, 1.6 Hz, 1H), 7.32 – 7.28 (m, 1H), 7.16 – 7.11 (m, 1H), 4.24 (q, J = 7.2 Hz, 2H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 165.6,



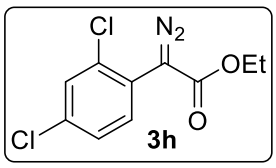
133.4, 132.9, 130.0, 127.7, 125.9, 124.5, 61.3, 14.5 (The resonance resulting from the diazo carbon was not observed).

ethyl 2-(4-chlorophenyl)-2-diazoacetate (3g).[16] Yellow liquid; Yield (193 mg, 86%);



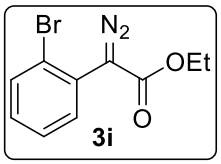
The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3075, 2928, 2088, 1704, 1686, 820; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 4.26 (q, J = 7.2 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 164.9, 131.4, 129.1, 125.1, 124.3, 61.2, 14.5 (The resonance resulting from the diazo carbon was not observed).

ethyl 2-diazo-2-(2,4-dichlorophenyl)acetate (3h). Yellow solid; Yield (212 mg, 82%);



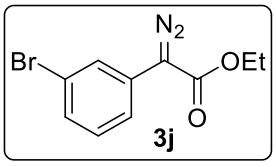
mp 88-89 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3074, 2926, 2087, 1704, 1685, 828; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.50 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 2.0 Hz, 1H), 7.30 (dd, J = 8.4, 2.0 Hz, 1H), 4.31 (q, J = 7.2 Hz, 2H), 1.32 (t, J = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 164.2, 133.7, 133.1, 131.8, 128.8, 126.6, 121.7, 60.4, 13.4 (The resonance resulting from the diazo carbon was not observed).

ethyl 2-(2-bromophenyl)-2-diazoacetate (3i).[26] Yellow liquid; Yield (226 mg, 84%);



The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3074, 2981, 2096, 1704, 1480, 990; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.48 (dd, J = 7.6, 1.6 Hz, 1H), 7.37 – 7.33 (m, 1H), 7.26 – 7.18 (m, 2H), 4.24 (q, J = 7.2 Hz, 2H), 1.25 (t, J = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 165.6, 133.7, 132.3, 130.1, 129.5, 127.1, 124.1, 61.3, 14.5 (The resonance resulting from the diazo carbon was not observed).

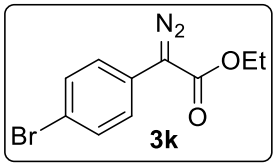
ethyl 2-(3-bromophenyl)-2-diazoacetate (3j).[28] Orange liquid; Yield (229 mg, 85%);



The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3074, 2986, 2090, 1704, 1634, 1077; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.62 (t, J = 1.6

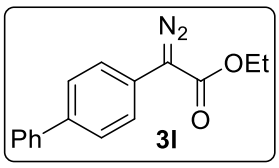
Hz, 1H), 7.31 (ddd, *J* = 7.6, 1.6, 1.2 Hz, 1H), 7.23 – 7.15 (m, 2H), 4.25 (q, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 164.6, 130.3, 128.6, 128.1, 126.5, 123.1, 122.1, 61.2, 14.5 (The resonance resulting from the diazo carbon was not observed).

ethyl 2-(4-bromophenyl)-2-diazoacetate (3k).[10] Orange liquid; Yield (237 mg, 88%);



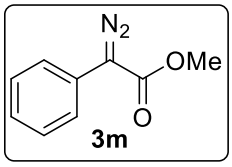
The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3076, 2988, 2092, 1701, 1635, 1077; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.42 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 8.8 Hz, 2H), 4.26 (q, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 164.9, 132.0, 125.4, 124.9, 119.3, 61.2, 14.5 (The resonance resulting from the diazo carbon was not observed).

ethyl 2-([1,1'-biphenyl]-4-yl)-2-diazoacetate (3l).[26] Orange liquid; Yield (245 mg,



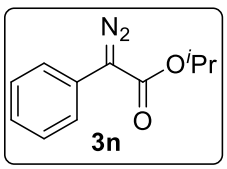
92%); The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3090, 2924, 2091, 1704, 1240, 761; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.55 – 7.46 (m, 6H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.25 (ddd, *J* = 7.6, 4.0, 1.2 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 165.2, 140.4, 138.6, 128.9, 127.6, 127.4, 126.9, 124.6, 124.3, 61.1, 14.5 (The resonance resulting from the diazo carbon was not observed).

methyl 2-diazo-2-phenylacetate (3m).[26] Red liquid; Yield (160 mg, 91%); The title



compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3064, 2953, 2088, 1707, 1250, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.47 (d, *J* = 8.4 Hz, 2H), 7.37 (t, *J* = 8.0 Hz, 2H), 7.17 (t, *J* = 7.6 Hz, 1H), 3.86 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 164.6, 127.9, 124.8, 124.5, 122.9, 50.9 (The resonance resulting from the diazo carbon was not observed).

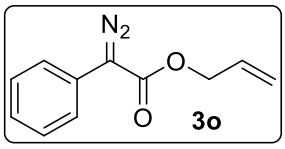
isopropyl 2-diazo-2-phenylacetate (3n).[26] Orange liquid; Yield (188 mg, 92%); The title



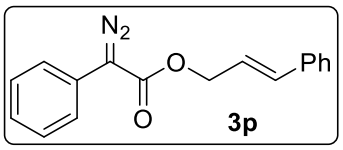
compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3091, 2981, 2086, 1701, 1009, 689; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.48 (d, *J* = 8.4 Hz, 2H), 7.36 (t, *J* =

8.0 Hz, 2H), 7.16 (t, *J* = 7.6 Hz, 1H), 5.20 (sept, *J* = 6.4 Hz, 1H), 1.32 (d, *J* = 6.4 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 164.8, 128.9, 125.8, 125.7, 123.9, 68.7, 22.1 (The resonance resulting from the diazo carbon was not observed).

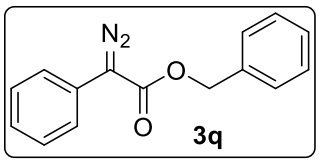
allyl 2-diazo-2-phenylacetate (3o).[26] Yellow liquid; Yield (182 mg, 90%); The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3090, 2982, 2088, 1652, 1414, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.41 (d, *J* = 8.4 Hz, 2H), 7.31 (t, *J* = 8.0 Hz, 2H), 7.11 (t, *J* = 7.6 Hz, 1H), 5.91 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.29 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.20 (dd, *J* = 10.4, 1.6 Hz, 1H), 4.72 – 4.68 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 164.9, 132.1, 128.9, 125.9, 125.5, 124.0, 118.4, 65.4 (The resonance resulting from the diazo carbon was not observed).



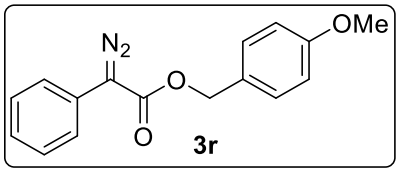
cinnamyl 2-diazo-2-phenylacetate (3p).[29] Orange liquid; Yield (245 mg, 88%); The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3094, 2983, 2084, 1652, 1415, 882; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.54 (d, *J* = 8.4 Hz, 2H), 7.47 – 7.40 (m, 4H), 7.36 (d, *J* = 7.6 Hz, 2H), 7.31 (d, *J* = 7.2 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 16.0 Hz, 1H), 6.38 (dt, *J* = 16.0, 6.4 Hz, 1H), 4.97 (dd, *J* = 6.4, 1.2 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 165.0, 136.2, 134.5, 128.9, 128.7, 128.2, 126.7, 125.9, 125.5, 124.1, 123.1, 65.5 (The resonance resulting from the diazo carbon was not observed).



benzyl 2-diazo-2-phenylacetate (3q).[26] Orange liquid; Yield (214 mg, 85%); The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3094, 2955, 2089, 1717, 1459, 778; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.40 (d, *J* = 8.4 Hz, 2H), 7.33 – 7.24 (m, 7H), 7.09 (t, *J* = 7.2 Hz, 1H), 5.23 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 165.0, 135.9, 128.9, 128.7, 128.4, 128.2, 125.9, 125.5, 124.1, 66.5 (The resonance resulting from the diazo carbon was not observed).



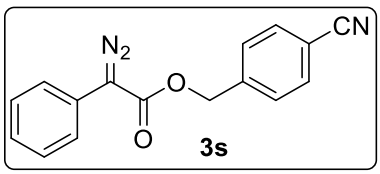
4-methoxybenzyl 2-diazo-2-phenylacetate (3r).[30] Orange liquid; Yield (243 mg, 86%);



3r

The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3090, 2955, 2086, 1717, 1515, 1010; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.40 (d, J = 8.8 Hz, 2H), 7.31 – 7.25 (m, 4H), 7.09 (t, J = 7.6 Hz, 1H), 6.82 (d, J = 8.8 Hz, 2H), 5.17 (s, 2H), 3.73 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 165.1, 159.7, 130.1, 128.9, 128.0, 125.8, 125.5, 124.0, 114.0, 66.4, 55.3 (The resonance resulting from the diazo carbon was not observed).

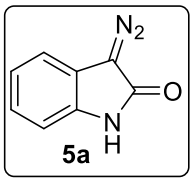
4-cyanobenzyl 2-diazo-2-phenylacetate (3s). Orange solid; Yield (235 mg, 85%); mp



3s

121-122 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3092, 2981, 2233, 2090, 1703, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.60 (d, J = 8.4 Hz, 2H), 7.44 – 7.37 (m, 4H), 7.32 (t, J = 8.0 Hz, 2H), 7.13 (t, J = 7.6 Hz, 1H), 5.28 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 164.6, 141.2, 132.5, 129.1, 128.3, 126.2, 124.9, 124.1, 118.5, 112.2, 65.3 (The resonance resulting from the diazo carbon was not observed).

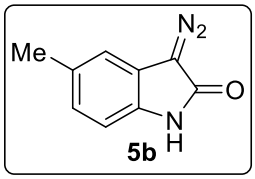
3-diazoindolin-2-one (5a).[31] Red solid; Yield (150 mg, 94%); mp 171-172 °C; The title



5a

compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3433, 3061, 2103, 1683, 1641, 1557; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.66 (s, 1H), 7.41 (d, J = 7.6 Hz, 1H), 7.11 (t, J = 7.6 Hz, 1H), 7.01 (t, J = 7.6 Hz, 1H), 6.92 (d, J = 7.6 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 173.0, 137.8, 130.4, 126.5, 124.5, 122.2, 115.2, 65.3.

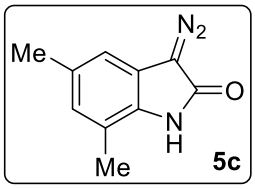
3-diazo-5-methylindolin-2-one (5b).[32] Red solid; Yield (158 mg, 91%); mp 191-192 °C; The



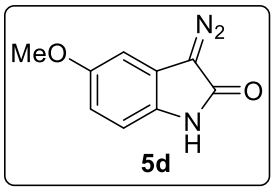
5b

title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3420, 3061, 2980, 2090, 1685, 1640, 1557, 1077; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.29 (s, 1H), 6.98 (s, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 2.27 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 168.5, 130.8, 130.7, 126.1, 119.3, 117.3, 110.2, 60.4, 21.2.

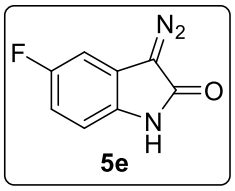
3-diazo-5,7-dimethylindolin-2-one (5c). Red solid; Yield (168 mg, 90%); mp 205-206 °C (decomposed); The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3435, 3054, 2982, 2099, 1681, 1640, 1078; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.57 (s, 1H), 7.03 (s, 1H), 6.73 (s, 1H), 2.24 (s, 3H), 2.19 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 168.8, 130.7, 129.5, 127.8, 119.6, 117.6, 117.1, 60.5, 21.2, 16.7; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{10}H_{10}N_3O$ 188.0824; found 188.0820.



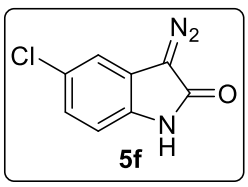
3-diazo-5-methoxyindolin-2-one (5d).[32] Red solid; Yield (162 mg, 86%); mp 181-182 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3430, 3091, 2980, 2096, 1682, 1642, 1557; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.44 (s, 1H), 7.13 (d, J = 2.4 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 6.68 (dd, J = 8.4, 2.4 Hz, 1H), 3.73 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 168.3, 155.1, 126.8, 118.5, 111.8, 110.9, 105.8, 61.1, 56.0.



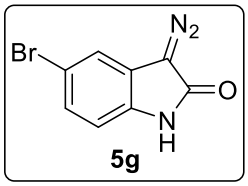
3-diazo-5-fluoroindolin-2-one (5e).[32] Red solid; Yield (150 mg, 85%); mp 190-191 °C (decomposed); The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3430, 3012, 2107, 1683, 1640, 1557, 1076; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.67 (s, 1H), 7.39 (dd, J = 8.8, 2.4 Hz, 1H), 6.94 – 6.85 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 168.1, 158.1 (d, $^{1}J_{C\text{-}F}$ = 234.0 Hz), 129.3, 118.9 (d, $^{3}J_{C\text{-}F}$ = 11.2 Hz), 112.0 (d, $^{2}J_{C\text{-}F}$ = 24.0 Hz), 110.9 (d, $^{3}J_{C\text{-}F}$ = 8.8 Hz), 107.1 (d, $^{2}J_{C\text{-}F}$ = 28.0 Hz), 61.6.



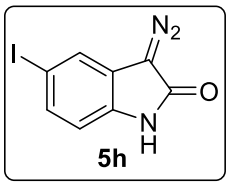
5-chloro-3-diazoindolin-2-one (5f).[32] Off-white solid; Yield (162 mg, 84%); mp 198-199 °C (decomposed); The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3391, 3082, 2104, 1673, 1373, 806; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.78 (s, 1H), 7.56 (d, J = 2.0 Hz, 1H), 7.12 (dd, J = 8.4, 2.0 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 167.9, 130.3, 125.0, 122.9, 119.4, 118.3, 114.6, 61.7.



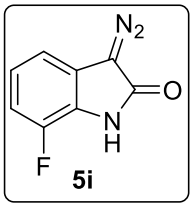
5-bromo-3-diazoindolin-2-one (5g).[32] Red solid; Yield (193 mg, 81%); mp 212-213 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3428, 3042, 2104, 1681, 1642, 1557, 1077; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.79 (s, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.24 (dd, J = 8.4, 2.0 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 167.7, 132.2, 127.9, 122.2, 119.9, 113.3, 111.9, 61.0.



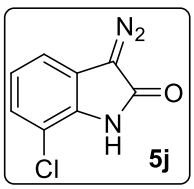
3-diazo-5-iodoindolin-2-one (5h).[33] Off-white solid; Yield (245 mg, 86%); mp 200-201 °C (decomposed); The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3437, 3058, 2126, 1686, 1663, 1558, 1077; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.77 (s, 1H), 7.81 (d, J = 1.6 Hz, 1H), 7.41 (dd, J = 8.4, 1.6 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 167.6, 133.7, 132.6, 127.7, 120.3, 112.5, 84.2, 60.5.



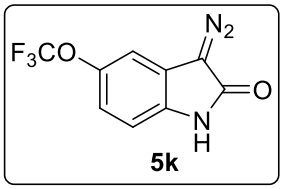
3-diazo-7-fluoroindolin-2-one (5i).[33] Red solid; Yield (143 mg, 81%); mp 194-195 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3430, 3012, 2107, 1686, 1640, 1557, 1076; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.17 (s, 1H), 7.29 – 7.25 (m, 1H), 7.03 – 6.98 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 167.8, 147.0 (d, $^{1}J_{C\text{-}F}$ = 240.0 Hz), 122.5 (d, $^{3}J_{C\text{-}F}$ = 6.5 Hz), 120.6 (d, $^{3}J_{C\text{-}F}$ = 6.0 Hz), 120.1 (d, $^{2}J_{C\text{-}F}$ = 15.0 Hz), 115.9 (d, $^{4}J_{C\text{-}F}$ = 3.2 Hz), 111.9 (d, $^{2}J_{C\text{-}F}$ = 17.2 Hz), 61.5.



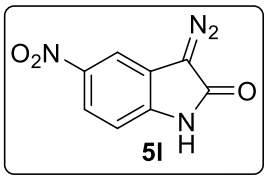
7-chloro-3-diazoindolin-2-one (5j).[34] Red solid; Yield (154 mg, 80%); mp 178-179 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3391, 3082, 2104, 1673, 1373, 806; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.10 (s, 1H), 7.41 (d, J = 7.6 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 7.02 (t, J = 8.0 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 167.9, 130.3, 125.0, 122.9, 119.4, 118.3, 114.6, 61.7.



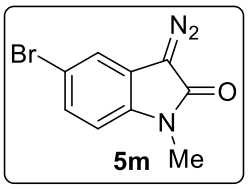
3-diazo-5-(trifluoromethoxy)indolin-2-one (5k).[32] Off-white solid; Yield (197 mg, 81%); mp 157-158 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3434, 3062, 2104, 1683, 1412, 733; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.84 (s, 1H), 7.58 (d, J = 1.6 Hz, 1H), 7.07 (dd, J = 8.4, 1.6 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 168.0, 143.2 (q, $^{3}J_{C\text{-}F}$ = 1.6 Hz), 131.9, 120.7 (q, $^{1}J_{C\text{-}F}$ = 254.0 Hz), 119.1, 118.6, 113.2, 110.9, 61.7.



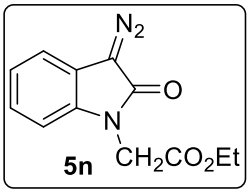
3-diazo-5-nitroindolin-2-one (5l).[32] Off-white solid; Yield (167 mg, 82%); mp 228-229 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3389, 3054, 2145, 1681, 1558, 882; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.35 (s, 1H), 8.46 (d, J = 2.4 Hz, 1H), 8.02 (dd, J = 8.8, 2.4 Hz, 1H), 7.06 (d, J = 8.8 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 168.0, 142.2, 138.6, 121.9, 118.8, 115.3, 110.0, 62.1.



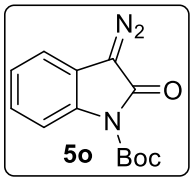
5-bromo-3-diazo-1-methylindolin-2-one (5m).[35] Red solid; Yield (168 mg, 81%); mp 153-154 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3063, 2981, 2108, 1652, 1557, 1078; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.63 (d, J = 2.0 Hz, 1H), 7.22 (dd, J = 8.4, 2.0 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 3.24 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 166.2, 133.4, 126.2, 125.2, 119.3, 118.6, 110.5, 61.1, 27.2.



ethyl 2-(3-diazo-2-oxoindolin-1-yl)acetate (5n).[35] Orange solid; Yield (208 mg, 85%); mp 111-112 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3061, 2981, 2112, 1736, 1691, 1046; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.51 (d, J = 7.6 Hz, 1H), 7.21 – 7.16 (m, 1H), 7.13 – 7.07 (m, 2H), 4.68 (s, 2H), 4.15 (q, J = 7.2 Hz, 2H), 1.21 (t, J = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 168.4, 166.8, 133.8, 125.7, 122.5, 119.8, 116.5, 109.7, 61.6, 60.8, 42.0, 14.5.

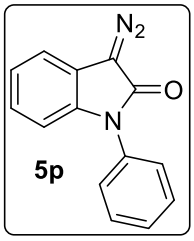


***tert*-butyl 3-diazo-2-oxoindoline-1-carboxylate (5o).** Red liquid; Yield (210 mg, 81%); The



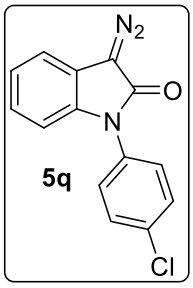
title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3069, 2987, 2114, 1741, 1698, 1022; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.91 – 7.87 (m, 1H), 7.19 (m, 3H), 1.66 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 164.9, 148.9, 130.8, 126.1, 124.5, 117.6, 115.9, 115.6, 84.7, 62.5, 28.1.

3-diazo-1-phenylindolin-2-one (5p).[31] Red solid; Yield (190 mg, 81%); mp 131-132 °C; The



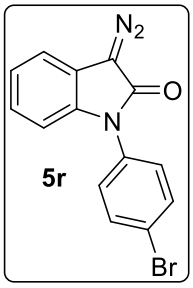
title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3094, 2103, 1647, 1413, 1078, 752; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.62 – 7.55 (m, 3H), 7.51 – 7.44 (m, 3H), 7.18 – 7.11 (m, 2H), 6.88 – 6.82 (m, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 166.2, 134.8, 134.1, 130.1, 128.6, 127.4, 125.9, 122.9, 119.9, 116.7, 109.8, 61.3.

1-(4-chlorophenyl)-3-diazoindolin-2-one (5q). Red solid; Yield (212 mg, 79%); mp 152-153



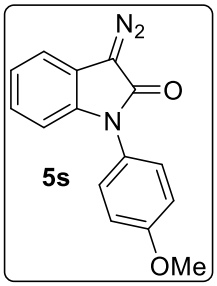
°C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3092, 2118, 1652, 1550, 1078, 809; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.64 (d, J = 8.8 Hz, 2H), 7.58 (dt, J = 6.8, 2.8 Hz, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.18 – 7.13 (m, 2H), 6.92 – 6.87 (m, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 166.1, 133.8, 133.6, 132.8, 130.1, 129.1, 125.9, 123.1, 119.9, 116.8, 109.8, 61.5; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{14}H_9ClN_3O$ 270.0434; found 270.0430.

1-(4-bromophenyl)-3-diazoindolin-2-one (5r). Off-white solid; Yield (251 mg, 80%); mp 174-



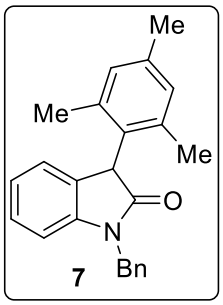
175 °C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3092, 2118, 1653, 1414, 1077, 806; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.77 (d, J = 8.8 Hz, 2H), 7.61 – 7.55 (m, 1H), 7.45 (d, J = 8.8 Hz, 2H), 7.19 – 7.13 (m, 2H), 6.93 – 6.88 (m, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 166.1, 134.1, 133.7, 133.0, 129.4, 125.9, 123.1, 121.2, 120.0, 116.8, 109.8, 61.5; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{14}H_9BrN_3O$ 313.9929; found 313.9922.

3-diazo-1-(4-methoxyphenyl)indolin-2-one (5s). Red solid; Yield (225 mg, 85%); mp 144-145



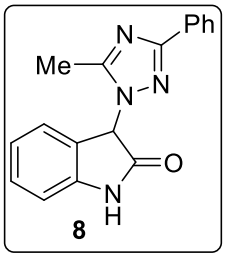
°C; The title compound is prepared according to the general procedure (B) described as above; FT-IR (KBr, cm^{-1}) 3054, 2983, 2105, 1644, 1557, 1078; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.59 – 7.54 (m, 1H), 7.37 (d, J = 8.8 Hz, 2H), 7.16 – 7.09 (m, 4H), 6.80 – 6.75 (m, 1H), 3.83 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 166.4, 159.3, 134.7, 128.9, 127.3, 125.9, 122.7, 119.9, 116.6, 115.3, 109.7, 61.1, 55.9; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{12}N_3O_2$ 266.0930; found 266.0930.

1-benzyl-3-mesitylindolin-2-one (7).[20] Red liquid; Yield (131 mg, 77%); ^1H NMR (400 MHz,



$CDCl_3$) δ (ppm): 7.42 – 7.37 (m, 2H), 7.35 – 7.29 (m, 2H), 7.28 – 7.23 (m, 1H), 7.19 – 7.15 (m, 1H), 6.97 – 6.91 (m, 3H), 6.82 (d, J = 7.8 Hz, 1H), 6.75 (s, 1H), 5.06 – 4.86 (m, 3H), 2.52 (s, 3H), 2.25 (s, 3H), 1.61 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 176.5, 143.2, 137.9, 137.2, 137.1, 136.1, 130.5, 130.3, 129.1, 128.8, 128.7, 127.9, 127.8, 127.8, 123.7, 122.7, 48.2, 44.3, 21.4, 20.9, 19.3.

3-(5-methyl-3-phenyl-1H-1,2,4-triazol-1-yl)indolin-2-one (8).[21] White solid; Yield (88 mg,



61% yield); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.85 (s, 1H), 7.89 – 7.84 (m, 2H), 7.42 – 7.31 (m, 4H), 7.22 (d, J = 7.4 Hz, 1H), 7.04 – 6.96 (m, 2H), 6.39 (s, 1H), 2.58 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 173.1, 160.7, 155.6, 142.9, 131.1, 130.3, 129.6, 129.1, 126.2, 125.6, 125.3, 122.7, 110.8, 59.9, 12.1.

6A.6. References

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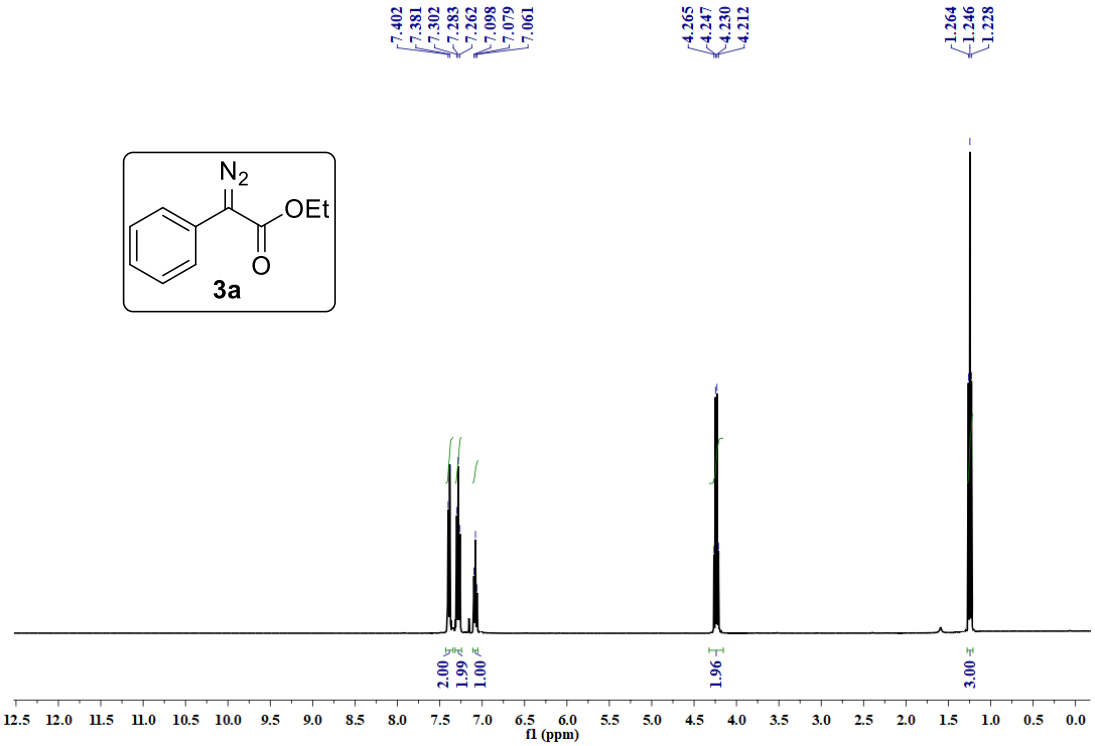
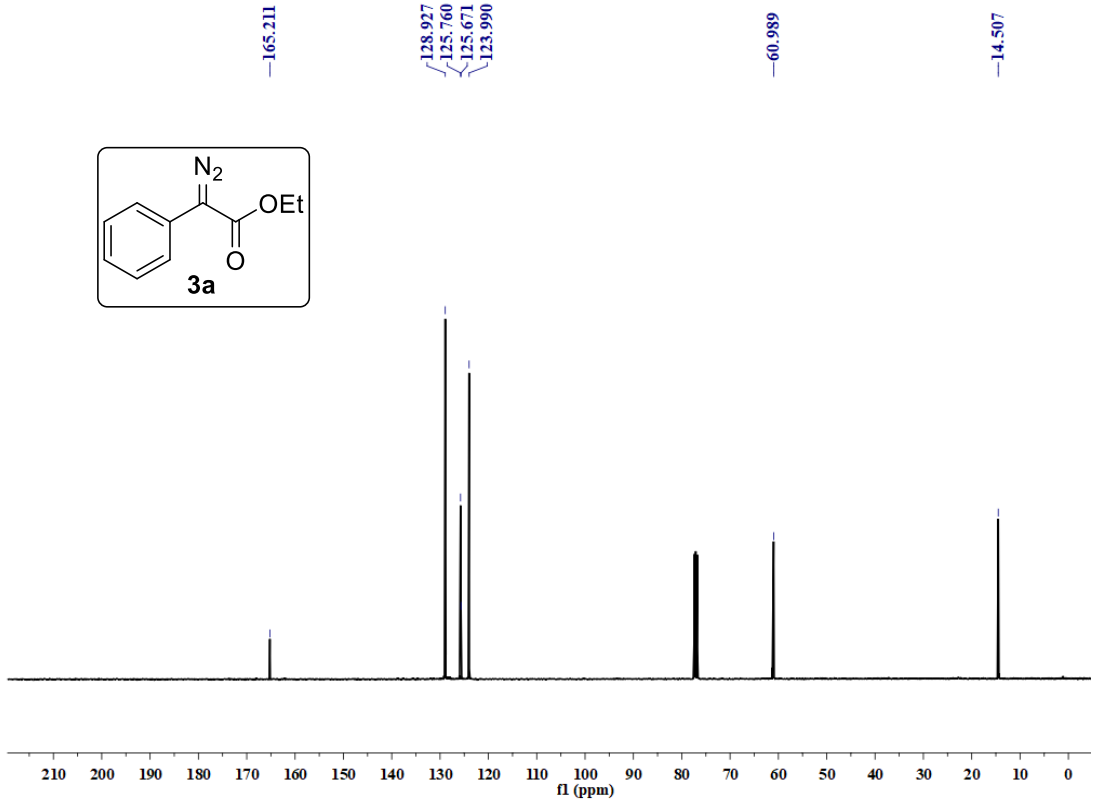
6A.7. Selected HRMS and NMR (^{1}H & ^{13}C) spectra

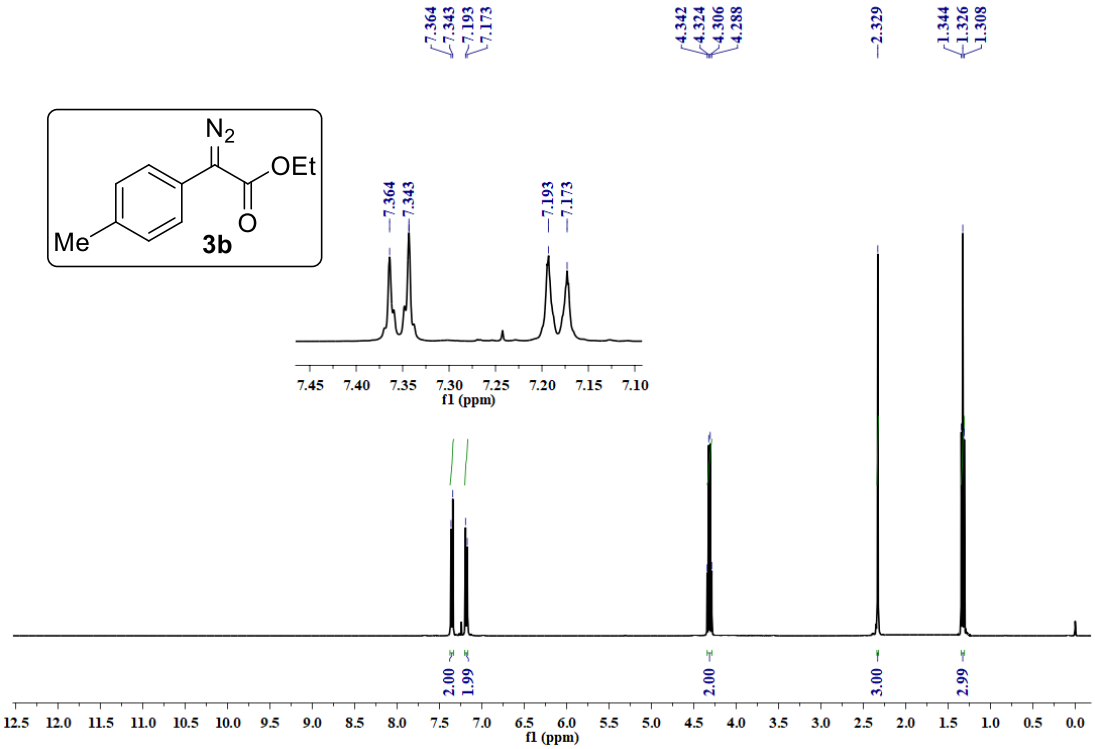
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of ethyl 2-diazo-2-phenylacetate (3a)



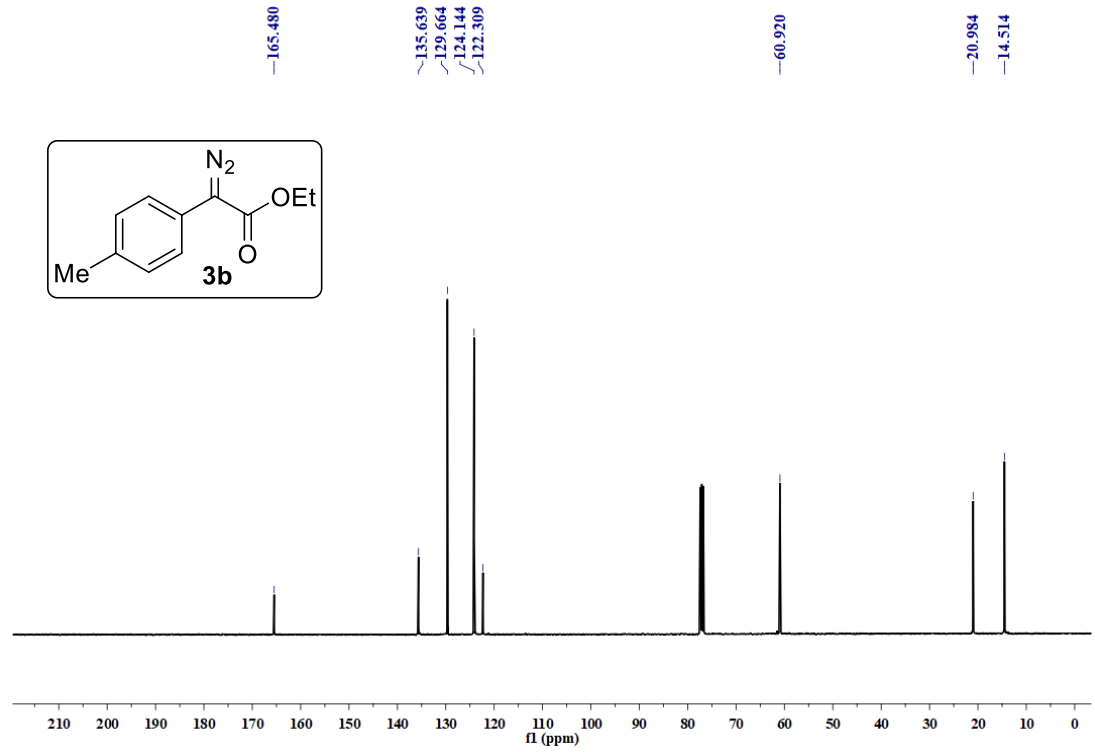
$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of ethyl 2-diazo-2-phenylacetate (3a)



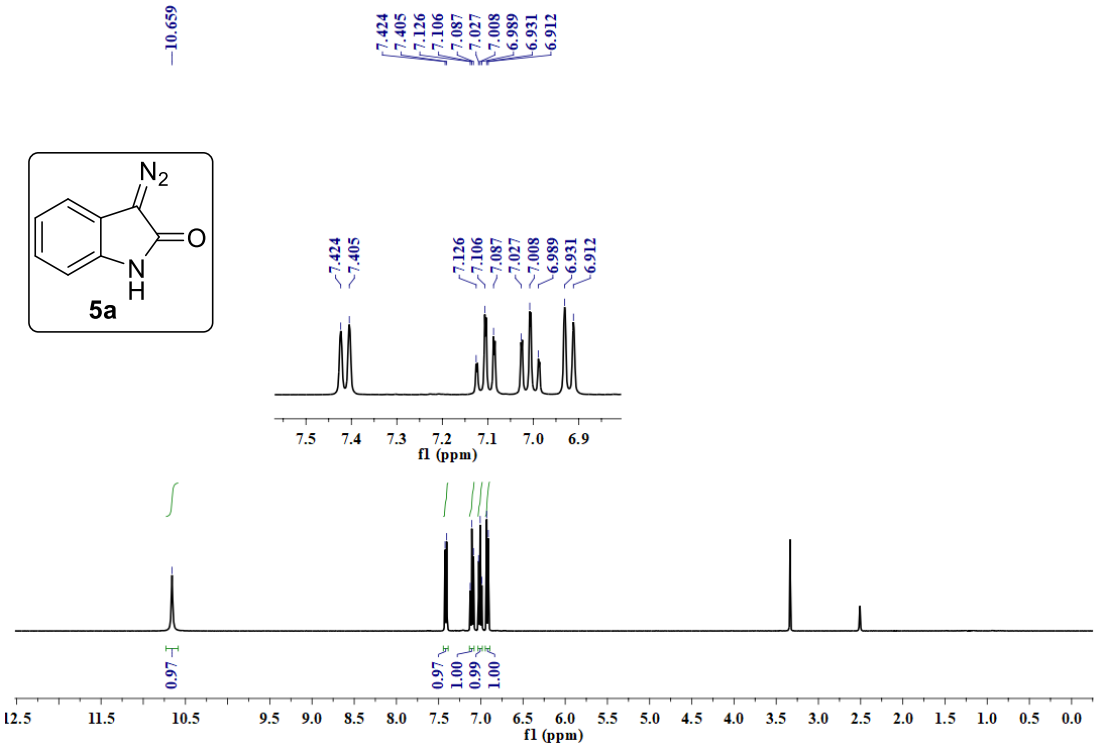
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of ethyl 2-diazo-2-(*p*-tolyl)acetate (3b)



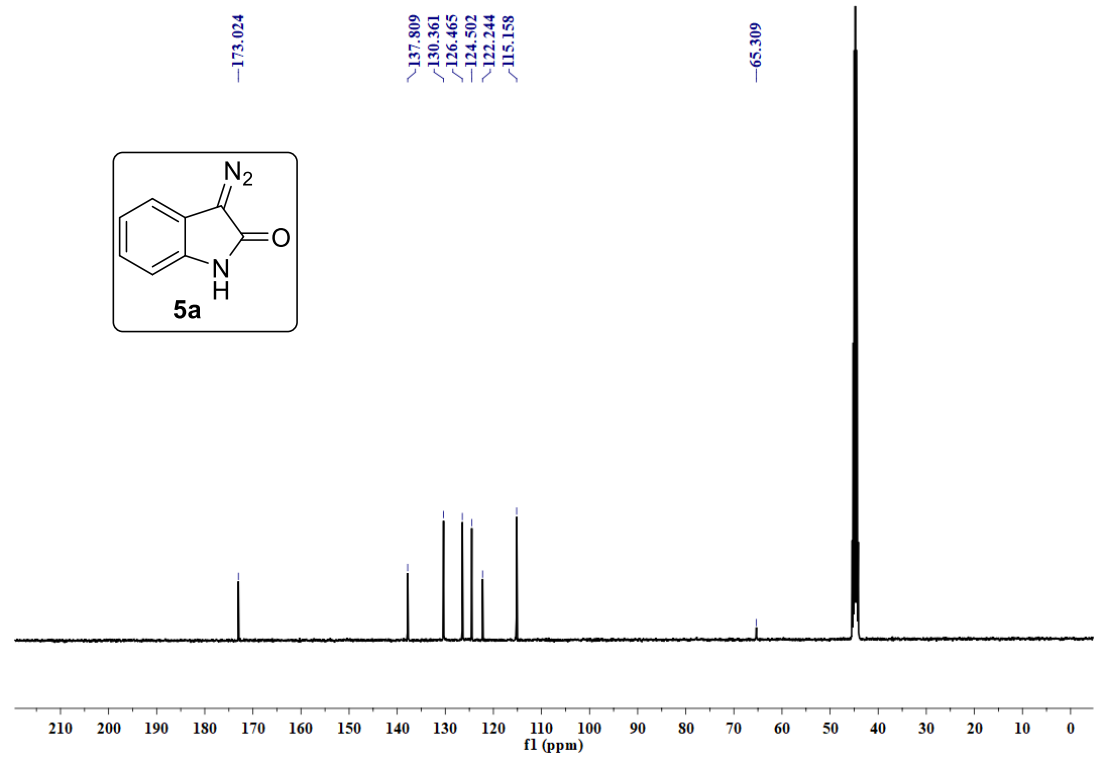
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of ethyl 2-diazo-2-(*p*-tolyl)acetate (3b)



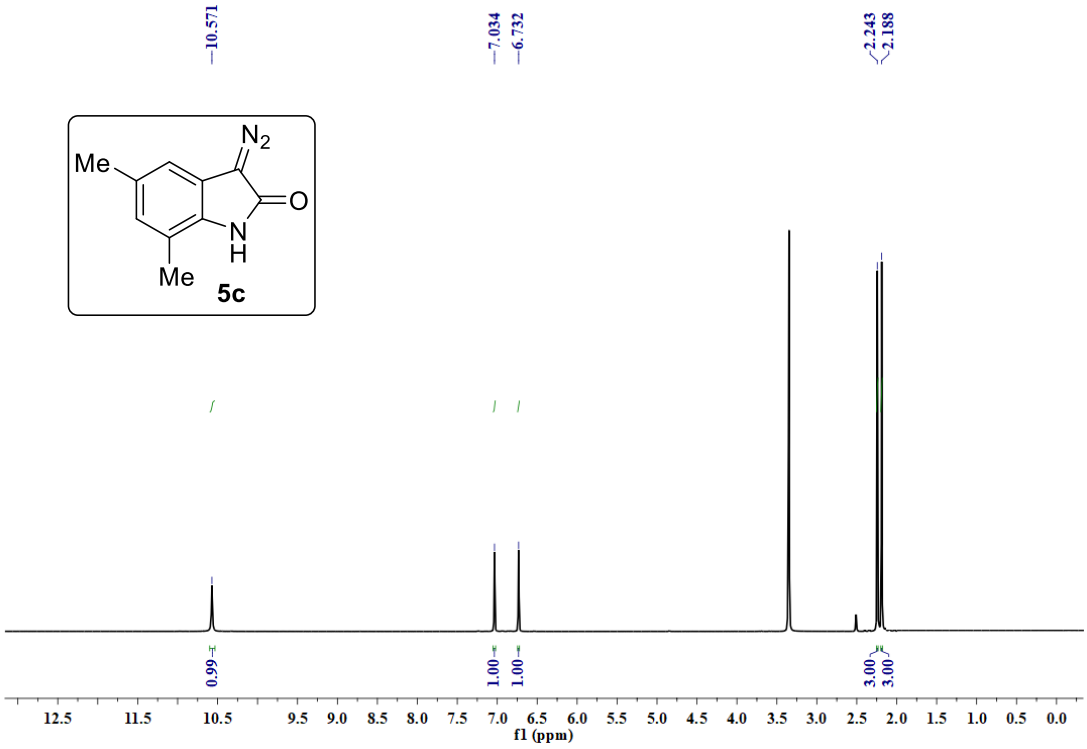
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of 3-diazoindolin-2-one (5a)



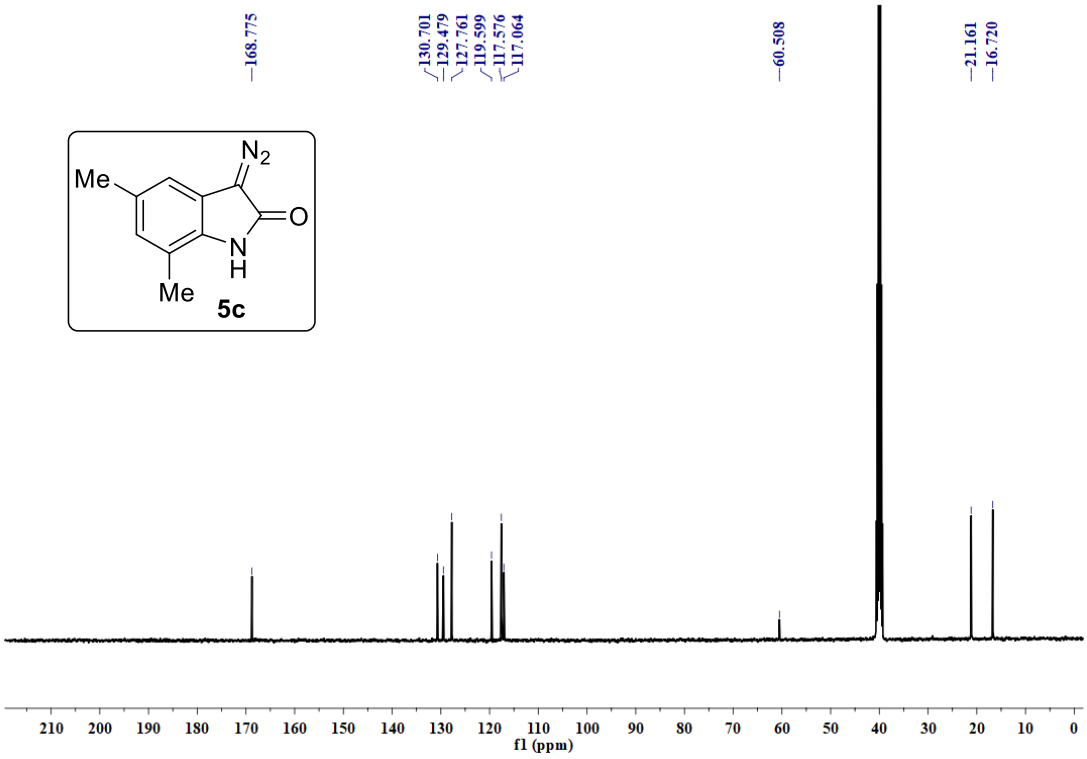
^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) spectrum of 3-diazoindolin-2-one (5a)



^{1}H NMR (400 MHz, DMSO-d_6) spectrum of 3-diazo-5,7-dimethylindolin-2-one (5c)

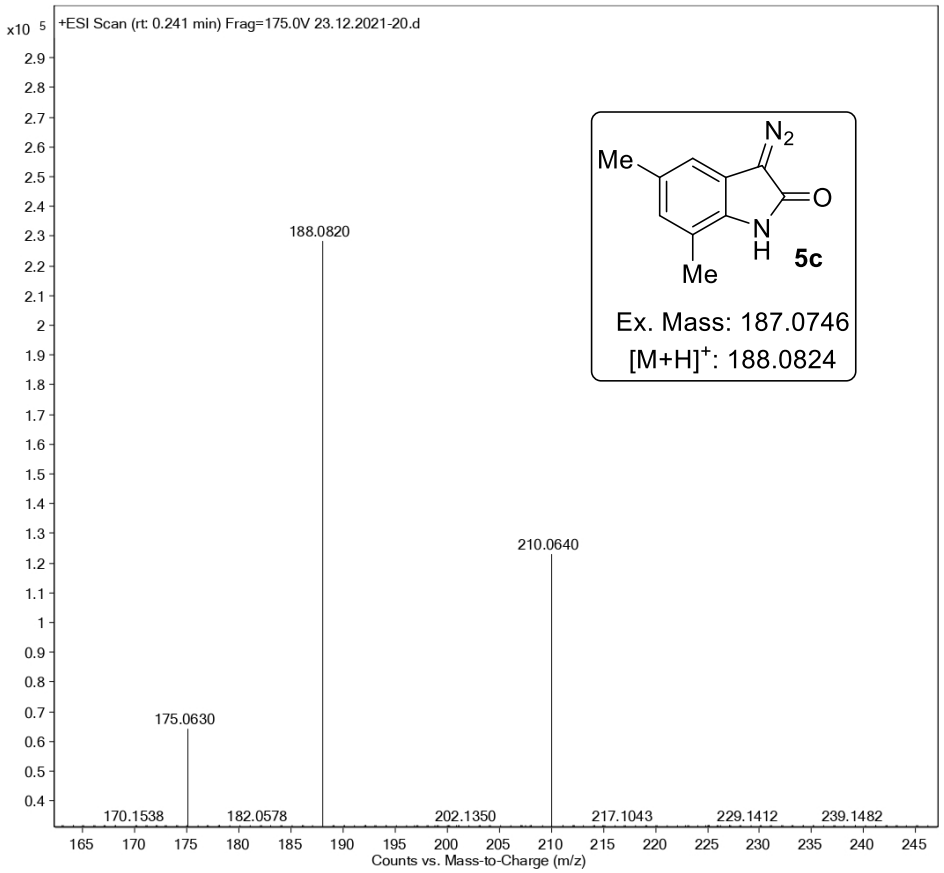


^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) spectrum of 3-diazo-5,7-dimethylindolin-2-one (5c)



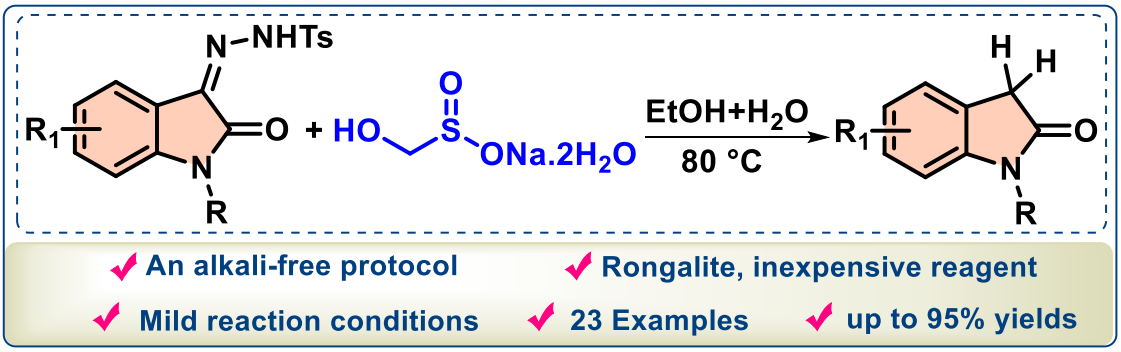
HRMS of 3-diazo-5,7-dimethylindolin-2-one (5c)

Sample Name	5 7DIMEIN2	**Position**	P1-C2	**Instrument Name**	Instrument 1
User Name		**Inj Vol**	2	**InjPosition**	
Sample Type	Sample	**IRM Calibration Status**	Success	**Data Filename**	23.12.2021-20.d
ACQ Method	NITW-W.m	**Comment**		**Acquired Time**	23-Dec-21 6:42:44 PM



CHAPTER-VIB

Rongalite-Induced Reduction of Isatin-3-*p*-Tosylhydrazones: A Rapid Access to 2-Oxindoles



6B.1 Introduction

The indolin-2-one is a highly privileged heterocyclic scaffold and found as the core structure of many natural products and commercially available drugs, which exhibit wide range of pharmacological properties. For example, i) rhynchophylline,[1] which is isolated from the Chinese herb *Uncaria* species, exhibits antihypertensive and neuroprotective activities, ii) ammosamide B,[2] belongs to the *Streptomyces* species which is derived from marine and acts as cell cycle modulators, iii) ziprasidone,[3] a commercial drug works as an antipsychotic for treating schizophrenia, iv) ropinirole,[4] sold under the brand name Requip, which is a non-ergoline dopamine agonist helps to control the early Parkinson's disease, v) sunitinib,[5] is an oral drug used to treat various cancers such as renal cell carcinoma and gastrointestinal stromal tumors, and vi) nintedanib,[6] is a recently approved drug for idiopathic pulmonary fibrosis and also used in other chronic fibrosing interstitial lung diseases (Figure 6B.1).

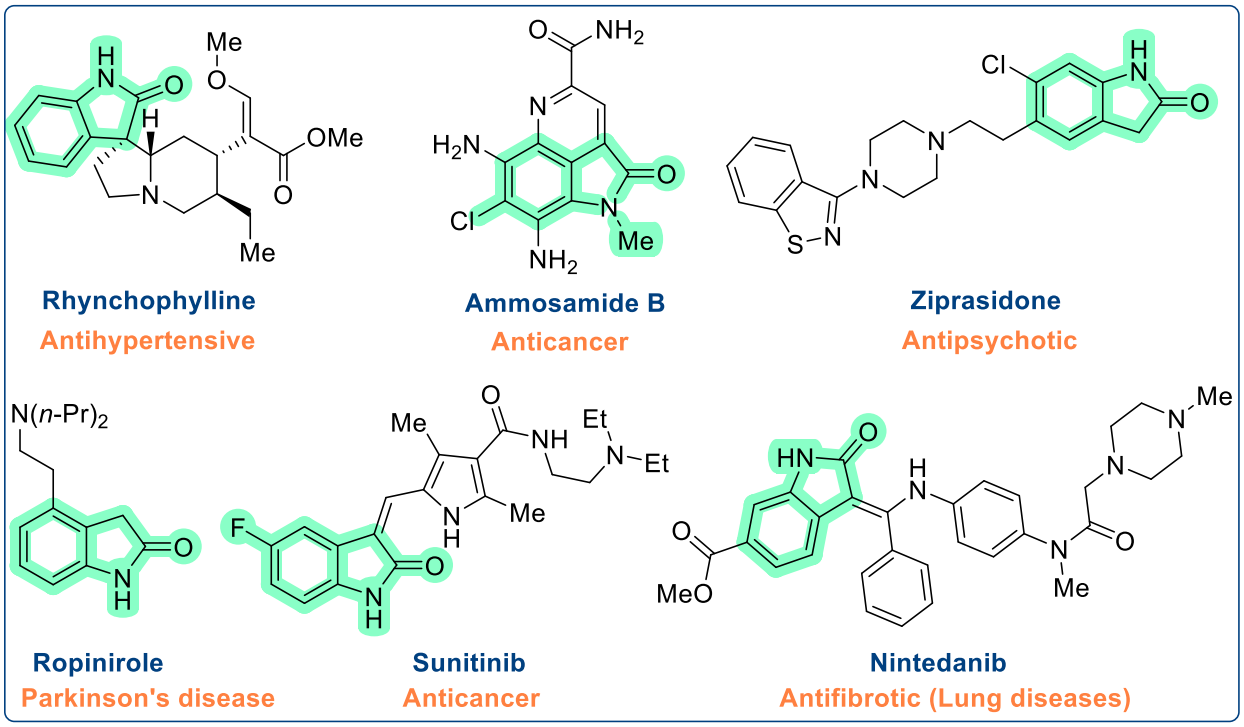


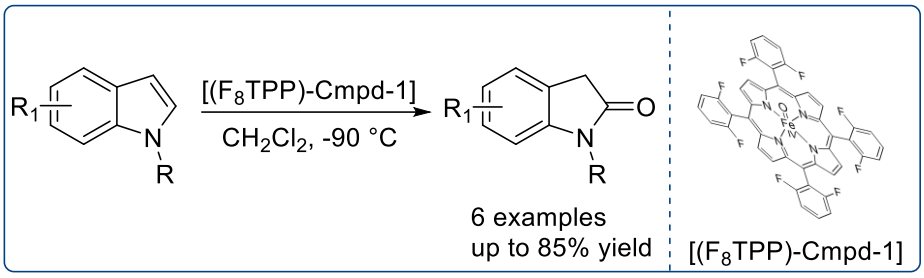
Figure 6B.1. Biologically active natural products and pharmaceuticals with 2-oxindole scaffold

Besides the biological activities, 2-oxindoles are the versatile synthetic precursors to the complex molecules such as functionalized xanthenes,[7] spiro *N*-heterocyclic oxindoles,[8] 3,3-disubstituted oxindoles,[9] bis-indole indigoids,[10] di-indolinones,[11] 3-alkyl-2-oxindoles,[12-13]

spiro[cyclohexanone-oxindoles],[14] isoindigo derivatives,[15] 3-alkenyl-2-oxindoles[16] and also employed in the total synthesis of (-)-horsfiline.[17]

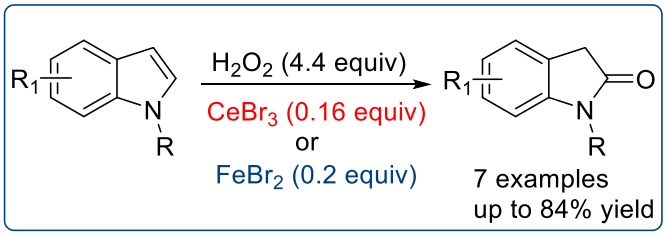
6B.1.1. Previous reports for the synthesis of indolin-2-ones

Wijeratne and co-workers developed a bioinspired monooxygenation protocol for the oxidation of indoles to 2-oxindoles using high-valent heme-oxo enzyme [(F_8TPP)-Cmpd-1] as an oxidizing agent, which is generated *in situ* from [(F_8TPP)Fe^{III}]SbF_6 using *m*-CPBA in dichloromethane (CH_2Cl_2) solvent at -90 °C. This methodology offers the synthesis of 2-oxindoles in 75-85% yields (Scheme 6B.1).[18]



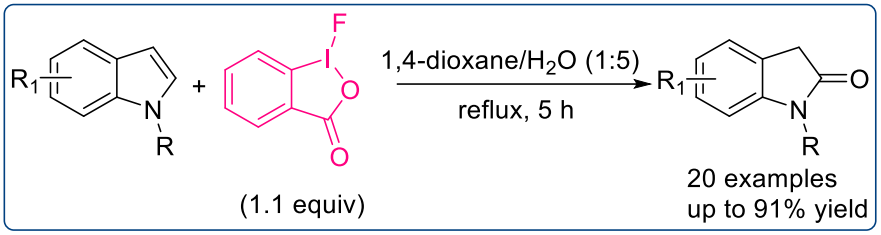
Scheme 6B.1

Zhao et al. introduced a method for the synthesis of 2-oxindoles *via* oxidative rearrangement of indoles using Fenton's chemistry ($FeBr_2$–H_2O_2 or $CeBr_3$–H_2O_2). In this protocol, bromide undergoes oxidation to form reactive bromine species *in situ* (bromine or hypobromous acid), which acts as a catalyst in this transformation. This methodology produces the 2-oxindoles up to 84% yield (Scheme 6B.2).[19]



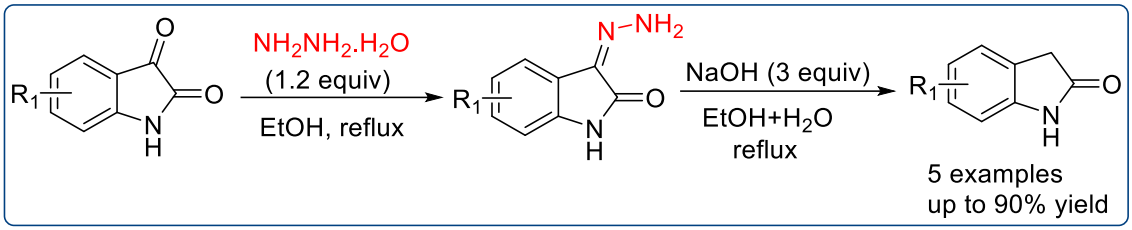
Scheme 6B.2

Yu and co-workers reported a strategy for the synthesis of 2-oxindoles from the corresponding indoles using hypervalent iodine in a mixture of 1,4-dioxane and H_2O under reflux condition. This protocol is applicable to synthesize a marketed drug ropinirole, which is used to treat Parkinson's disease and also prepared the various 2-oxindoles in 43-91% yields (Scheme 6B.3).[20]



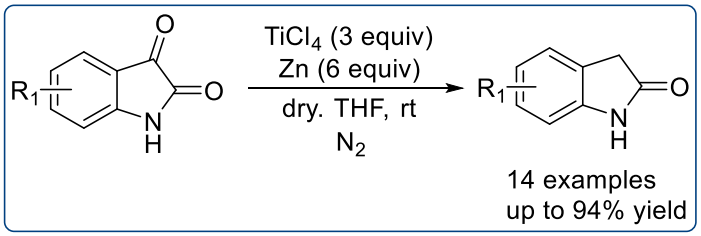
Scheme 6B.3

Lai and co-workers described the synthesis of 2-oxindoles from the corresponding isatins by employing Wolf-Kishner reduction conditions. This protocol is basically a one-pot two-step process, the first step involves the formation of hydrazone with hydrazine hydrate in ethanol under reflux condition and second step is about the formation of 2-oxindole with the expulsion of N_2, by using NaOH in a mixture of EtOH+H_2O under reflux condition (Scheme 6B.4).[21]



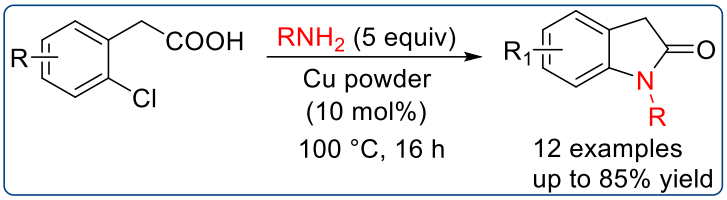
Scheme 6B.4

Lin et al. developed a chemoselective reduction protocol for the preparation of 2-oxindoles from the respective isatins using low-valent titanium reagent, which is generated *in situ* from the titanium tetrachloride and the zinc metal in dry THF under nitrogen atmosphere at room temperature. This protocol enables the synthesis of 2-oxindoles in 85-94% yields (Scheme 6B.5).[22]



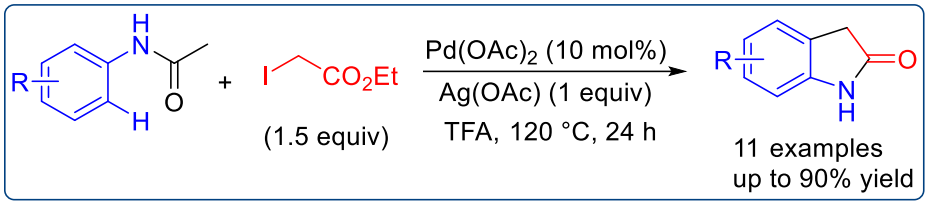
Scheme 6B.5

Li and co-workers reported a copper catalyzed method for the synthesis of 2-oxindoles from the corresponding *o*-chloroarylacetic acids using amines under solvent- and ligand-free conditions at 100 °C for 16 h. This protocol involves the Ullmann amination of unactivated C–Cl bond followed by annulative *N*-acylation results the 2-oxindoles with 55-85% yields (Scheme 6B.6).[23]



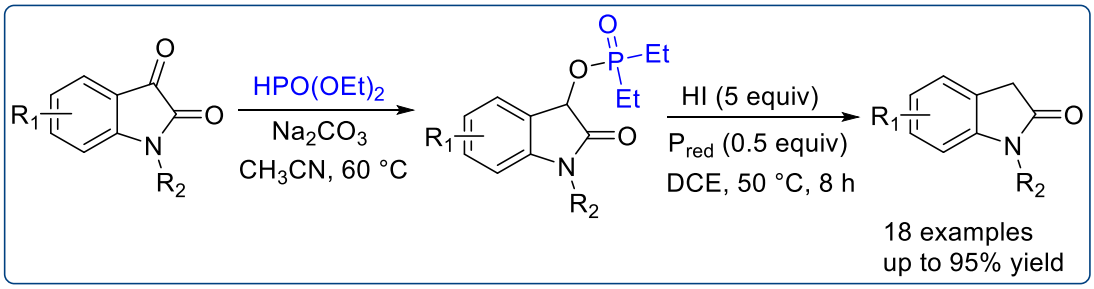
Scheme 6B.6

Gandeepan et al. introduced a palladium catalyzed strategy for the synthesis of 2-oxindoles *via* C–H activation and cyclization of anilides with 2-iodoacetates in the presence of additive i.e., AgOAc in trifluoroacetic acid at 120 °C for 24 h. This protocol allows the synthesis of 2-oxindoles with 53-90% yields (Scheme 6B.7).[24]



Scheme 6B.7

Wu and co-workers reported a two-step protocol for the synthesis of 2-oxindoles from the corresponding isatins *via* phospha-Brook rearrangement of isatins with diethyl phosphite followed by reductive dephosphorylation of 3-(diethylphosphoryloxy)oxindoles using hydroiodic acid and red phosphorus in dichloroethane (DCE) solvent at 50 °C for 8 h. This protocol enables the synthesis of 2-oxindoles in 60-95% yields (Scheme 6B.8).[25]



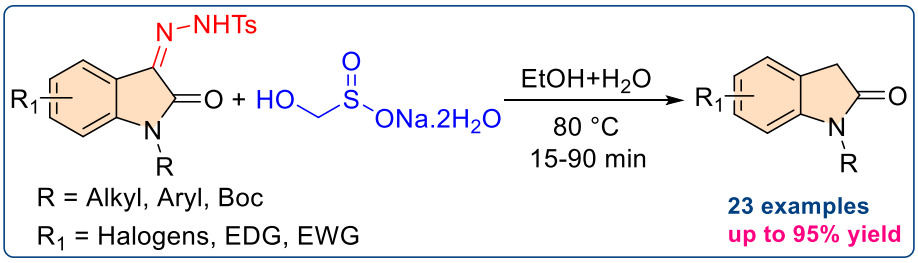
Scheme 6B.8

In the literature, we found several reports for the synthesis of 2-oxindoles and the most common methods involve the oxidative rearrangement of indoles and the reduction of isatins. But the aforementioned methods have its own limitations such as narrow substrate scope and the necessity of more equiv of bases, reagents and low-valent transition-metals. In addition, many transition-metal catalyzed strategies were also available,[26-31] but which are limited due to the

requirement of high reaction temperatures, prefunctionalized precursors and need one more step for the deprotection at the end of the reaction. To address the problems associated with previous methods, we aim to develop a transition-metal and an alkali-free protocol for the synthesis of 2-oxindoles from easily available starting materials.

6B.2. Present study

Considering the significance of 2-oxindoles in the synthetic chemistry and the challenges associated with their preparation, we have developed an efficient protocol for the synthesis of 2-oxindoles from the corresponding isatin-3-*p*-tosylhydrazones using rongalite. Here, rongalite functions as both a mild base and a nucleophile. This transition metal and an alkali-free protocol offers the synthesis of wide range of 2-oxindoles up to 95% yields. The key features of this synthetic approach include, one-pot oxidation and reduction, broad substrate scope with functional group tolerance, mild reaction conditions. This protocol is also applicable to gram-scale synthesis (Scheme 6B.9).



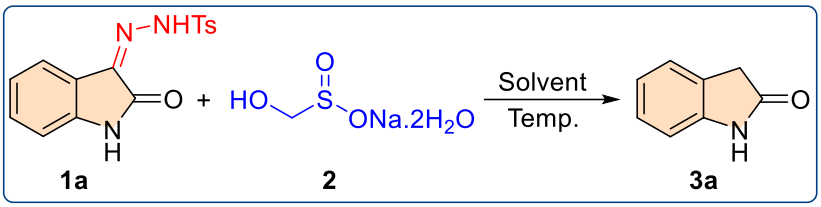
Scheme 6B.9

6B.2.1. Results and discussion

We commenced our study by taking isatin-3-*p*-tosylhydrazone **1a** (1 mmol) as a model substrate, was treated with rongalite **2** (3 mmol) in CH_3CN+H_2O (9:1 v/v) at ambient temperature and observed the formation of indolin-2-one **3a** in 10% yield (Table 6B.1, entry 1), which was later confirmed by ^{1}H and ^{13}C NMR data. To our delight, 69% yield of **3a** was achieved, when the reaction was performed at 70 °C (Table 6B.1, entry 2). With this satisfactory result, the reaction was tested with other polar aprotic solvents such as DMF, DMSO, aq. THF and aq. acetone to improve the yield of **3a,** but observed inferior results (Table 6B.1, entries 3-6). We have noticed that non-polar solvents such as aq. toluene and aq. *p*-xylene were not suitable for the progress of reaction (Table 6B.1, entries 7-8). Later, reaction was screened in polar protic solvents such as

H_2O, aq. MeOH, aq. ^{i}PrOH and aq. EtOH (Table 6B.1, entries 9-12). Among all these, aq. EtOH was found to be superior and furnished the target product i.e., indolin-2-one **3a** in 95% yield (Table 6B.1, entry 12). Further, observed that the variants in equiv of rongalite and temperature were not useful and low yield of 3-diazo-2-oxindole **5a** was obtained, when 2 equiv of rongalite was used (Table 6B.1, entries 13-14). Therefore, the optimized reaction conditions are isatin-3-*p*-tosylhydrazone **1a** (1 mmol) and rongalite **2** (3 mmol) in EtOH+H_2O (9:1 v/v) at 80 °C (Table 6B.1, entry 12).

Table 6B.1. Optimization of reaction conditions[a]

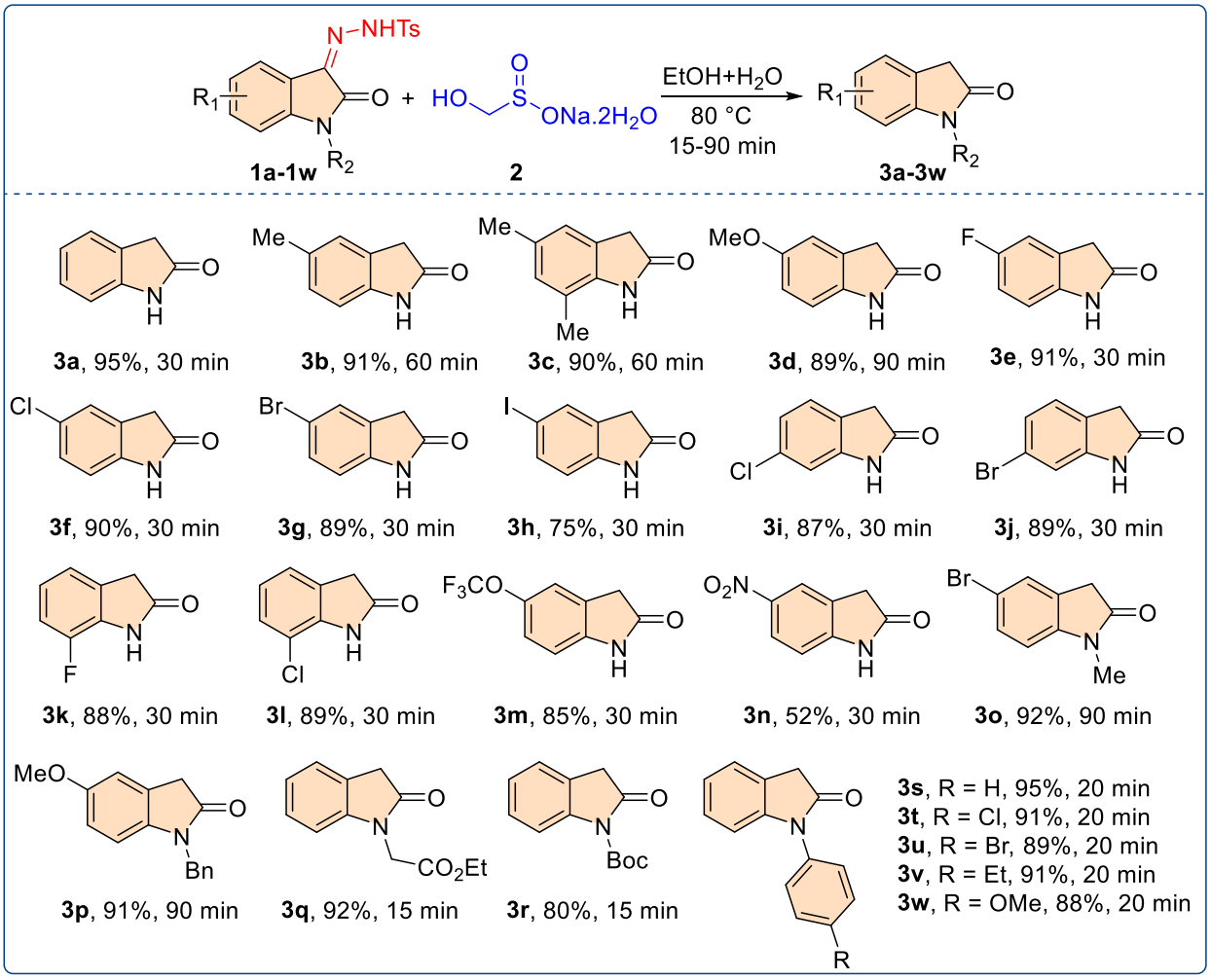


Entry	Solvent (9:1 v/v)	Reagent	Temp. (°C)	Time (h)	Yield (%)[b]
1	CH_3CN+H_2O	Rongalite	rt	16	10
2	CH_3CN+H_2O	Rongalite	70	1	69
3	DMF	Rongalite	80	1	60
4	DMSO	Rongalite	80	1	65
5	$THF+H_2O$	Rongalite	65	1	10
6	$Acetone+H_2O$	Rongalite	60	5	15
7	$Toluene+H_2O$	Rongalite	80	5	n.r.
8	*p*-$Xylene+H_2O$	Rongalite	80	5	n.r.
9	H_2O	Rongalite	80	5	n.r.
10	$MeOH+H_2O$	Rongalite	70	0.3	91
11	$^{i}PrOH+H_2O$	Rongalite	80	1	46
12	**$EtOH+H_2O$**	**Rongalite**	**80**	**0.3**	**95**
13	$EtOH+H_2O$	Rongalite	80	1	52[c]
14	$EtOH+H_2O$	Rongalite	70	0.5	92

[a]Reaction conditions: Isatin-3-*p*-tosylhydrazone **1a** (1 mmol) and rongalite **2** (3 mmol, 3 equiv) in different reaction media at variable temperatures. [b]Yields of isolated products. [c]2 equiv of rongalite was used. rt = room temperature. n.r. = no reaction.

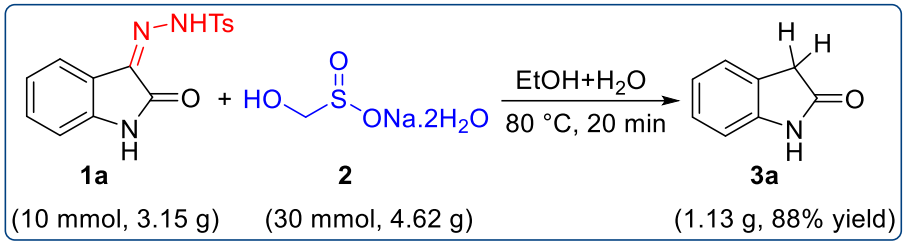
With the optimized reaction conditions in hand (Table 6B.1, entry 12), next we have focused on the scope of the reaction by using various substituted isatin-3-*p*-tosylhydrazones and the results were summarized in Table 6B.2. Electron-donating groups such as methyl and methoxy having

Table 6B.2. Substrate scope of rongalite mediated synthesis of indolin-2-ones[a,b]

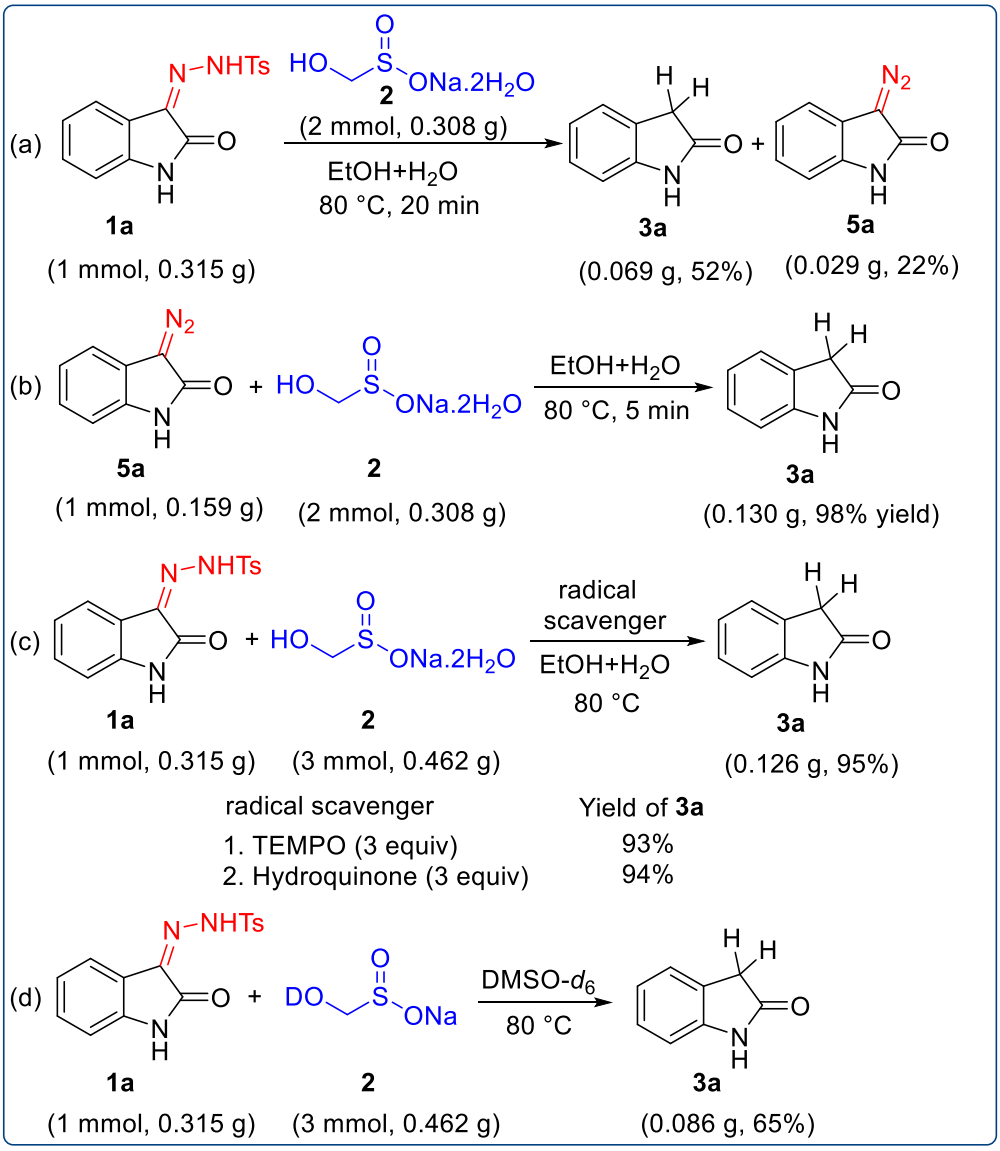


[a]Reaction conditions: Isatin-3-*p*-tosylhydrazone **1** (1 mmol) and rongalite **2** (3 mmol, 3 equiv) in 3 mL of EtOH+H_2O (9:1 v/v) at 80 °C. [b]Yield of isolated products.

isatin-3-*p*-tosylhydrazones reacted smoothly with rongalite to furnish the respective 2-oxindoles **3b-3d** in 89-91% yields (Table 6B.2). Also, halogens (–F, –Cl, –Br, and –I) containing isatin-3-*p*-tosylhydrazones immediately underwent reaction and afforded the desired products **3e-3l** in 75-91% yields (Table 6B.2). Moreover, strong electron withdrawing groups such as $–OCF_3$ and $–NO_2$ substituted isatin-3-*p*-tosylhydrazones were delivered the corresponding 2-oxindoles **3m** and **3n** in 85% and 52% yields, respectively (Table 6B.2). In addition, both *N*-alkylated and *N*-arylated isatin-3-*p*-tosylhydrazones effortlessly involved in the reaction and offered the products **3o**, **3p** and **3s-3w** in 88-95% yields (Table 6B.2). Pleasingly, ester and Boc protecting groups were compatible with rongalite and produced **3q** and **3r** in 92% and 80% yields, respectively (Table 6B.2).



Scheme 6B.10. Gram-scale synthesis



Scheme 6B.11. Control experiments

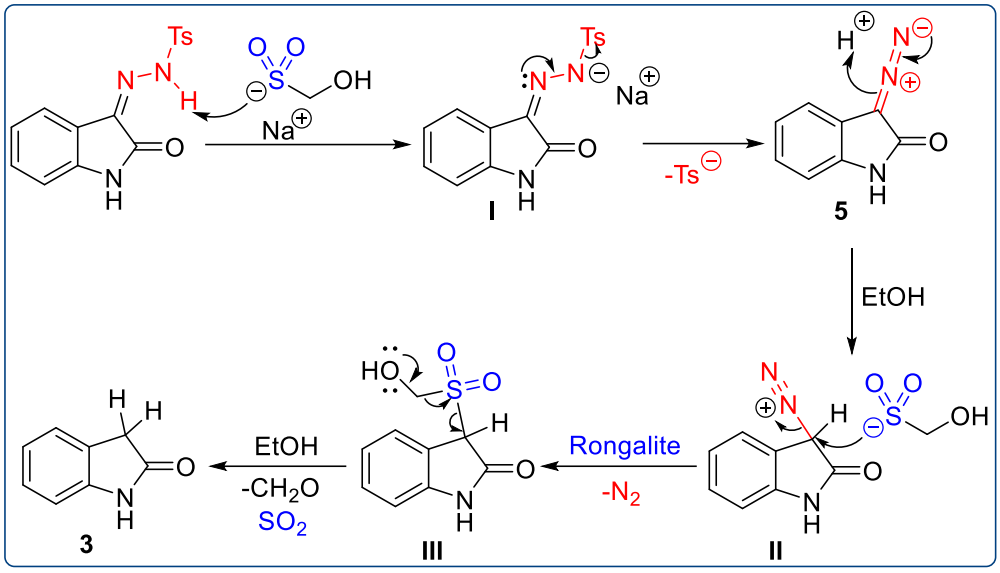
Finally, we have examined the synthetic potential of our developed protocol by conducting a gram scale reaction using isatin-3-*p*-tosylhyadrazone **1a** (3.15 g, 10 mmol) and rongalite **2** (4.62

g, 30 mmol) in EtOH+H_2O (30 mL) at 80 °C, gave the desired product indolin-2-one **3a** in 88% yield in 20 min (scheme 6B.10).

In order to unveil the reaction mechanism and to know the role of rongalite, we have conducted some control experiments (Scheme 6B.11). Initially, we have conducted a reaction between isatin-3-*p*-tosylhyadrazone **1a** (1 mmol) and rongalite **2** (2 mmol) in EtOH+H_2O at 80 °C, and observed the formation of mixture of two products i.e., indolin-2-one **3a** and 3-diazoindolin-2-one **5a** in 52% and 22% yields, respectively (Scheme 6B.11a). Later, we have carried out another reaction by employing 3-diazoindolin-2-one **5a** (1 mmol) as a starting material with rongalite **2** (2 mmol) in EtOH+H_2O at 80 °C and observed the formation of desired product **3a** in 98% yield within 5 min (Scheme 6B.11b). These two control experiments indicate that the 3-diazoindolin-2-one **5a** is an intermediate in the convertion of isatin-3-*p*-tosylhyadrazone **1a** to 2-oxindole **3a**.

Further, we have performed two more control experiments with radical scavengers such as TEMPO and hydroquinone to know the reaction pathway and observed that there is no significant change in the yield of product **3a** (Scheme 6B.11c). These two control experiments ruled out the radical mechanism. Furthermore, to know whether the rongalite is acting as a proton source, we have carried out a reaction with anhydrous deuterated rongalite and found that there is no incorporation of deuterium in the product **3a**, which indicates that the rongalite is not acting as a proton source in this reaction (Scheme 6B.11d).

Based on the previous literature[32-33] and controlled experiments, a plausible reaction mechanism is proposed in Scheme 6B.12. Initially, rongalite abstracts the proton of isatin-3-*p*-tosylhydrazones to form the intermediate **I**. Later, the lone pair on the nitrogen atom of intermediate **I** drives the loss of tosyl group to produce the intermediate diazo compound **5**. Further, the intermediate **5** undergoes protonation under protic solvent to generate intermediate **II,** which further undergoes nucleophilic substitution with rongalite with the expulsion of N_2 to form the intermediate **III**. Finally, intermediate **III** yields desired 2-oxindole **3** by the loss of formaldehyde and sulfur dioxide.



Scheme 6B.12. Plausible reaction mechanism

6B.3. Conclusions

We have developed an efficient protocol for the synthesis of 2-oxindoles form the corresponding isatin-3-*p*-tosylhydrazones using rongalite. In this protocol, rongalite functions both as a mild base and a nucleophile. This alkali-free method enables the rapid synthesis of wide range of 2-oxindoles up to 95% yields. Broad substrate scope with functional group tolerance and mild reaction conditions are some of the key features of this methodology. Also, this method is applicable to gram-scale synthesis.

6B.4. Experimental section

6B.4.1. General information

All chemicals and solvents were purchased from Alfa Aesar, Spectrochem, SRL, Finar and used as received. Thin layer chromatography was performed on 200 µm aluminum-foil backed silica gel plates and the column chromatography was performed using 100-200 mesh silica gel (Merk). Bruker Avance 400 MHz spectrometer was used to record ^{1}H NMR spectra and used $CDCl_3$ and DMSO-d_6 as solvents and TMS as an internal standard. The multiplicities were described using the following acronyms: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Coupling constants, *J* were reported in Hertz unit (Hz). Bruker Avance 100 MHz spectrometer was used to record $^{13}C\{^{1}H\}$ NMR spectra, and they were fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to the center line of a triplet at

77.16 ppm of chloroform-*d* (a multiplet at 39.52 ppm of DMSO-d_6). A Stuart SMP30 apparatus was used to determine the melting points and are uncorrected. FT-IR spectra were recorded on a Perkin Elmer spectrometer. HRMS were analyzed with Agilent Q-TOF 6230.

6B.4.2. General procedure for synthesis of isatin-3-*p*-tosylhyadrazones (1a-1w)[34]

An oven dried 50 mL reaction flask was charged with appropriate isatin (10 mmol), *p*-toluenesulfonyl hydrazide (10 mmol, 1 equiv) and MeOH (20 mL), stirred at room temperature for the appropriate time (10 min-3 h). The reaction was monitored by TLC using hexanes and ethyl acetate as an eluent. After completion, the resulted yellow solid was filtered off and washed with cold methanol. The air dried isatin-3-*p*-tosylhydrazones were used in the next step without further purification.

6B.4.3. General procedure (A) for synthesis of indolin-2-one derivatives (3a-3w)

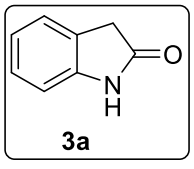
An oven dried 25 mL reaction flask was charged with appropriate isatin-3-*p*-tosylhyadrazone **1** (1 mmol, 1 equiv), rongalite **2** (3 mmol, 3 equiv) and EtOH+H_2O (9:1 v/v, 3 mL), stirred at 80 °C for the appropriate time (15-90 min). The progress of the reaction was monitored by TLC using hexanes and ethyl acetate as an eluent. After reaction has completed, EtOH was evaporated under vacuum and the organic compound was extracted with ethyl acetate (3 x 10 mL). The organic layers were separated, dried (Na_2SO_4) and evaporated to give a residue that was purified on silica gel by column chromatography using hexanes and ethyl acetate as an eluent.

6B.4.4. Preparation of deuterated rongalite

An oven dried 10 mL reaction flask was charged with anhydrous rongalite (0.3 g) and methanol-d_4 (3 mL), the resulting mixture was stirred for 2 h at ambient temperature. After that, the methanol-d_4 was evaporated and the formed deuterated rongalite dried under vacuum.

6B.5. Characterization data of products 3a-3w

indolin-2-one (3a).[22] Off-white solid; Yield (126 mg, 95%); mp 127-128 °C; The title compound

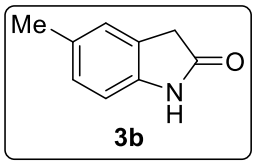


3a

is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3214, 3078, 2918, 1696, 1617, 1470; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.35 (s, 1H), 7.21 – 7.13 (m, 2H), 6.92 (t, J = 7.6 Hz, 1H), 6.82 (d,

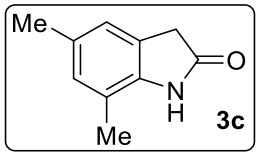
J = 7.6 Hz, 1H), 3.46 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 176.8, 144.1, 127.9, 126.2, 124.8, 121.6, 109.6, 36.2.

5-methylindolin-2-one (3b).[24] White solid; Yield (134 mg, 91%); mp 173-174 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3209, 3081, 2917, 1692, 1621, 1459; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.24 (s, 1H), 7.02 (s, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 3.41 (s, 2H), 2.24 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 176.8, 142.4, 130.4, 128.1, 126.3, 125.6, 109.3, 36.2, 21.1.



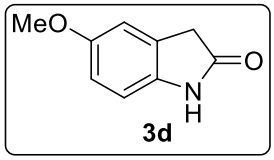
3b

5,7-dimethylindolin-2-one (3c).[35] Off-white solid; Yield (144 mg, 90%); mp 164-165 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3212, 3081, 2917, 1692, 1615, 1458, 751; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.29 (s, 1H), 6.83 (s, 1H), 6.78 (s, 1H), 3.41 (s, 2H), 2.20 (s, 3H), 2.15 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 177.2, 140.3, 130.3, 129.5, 125.9, 122.8, 118.5, 36.5, 21.0, 16.9.



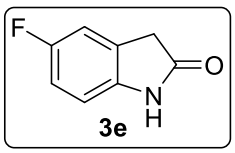
3c

5-methoxyindolin-2-one (3d).[24] Off-white solid; Yield (146 mg, 89%); mp 152-153 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3219, 3081, 2837, 1692, 1615, 1151; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.17 (s, 1H), 6.86 (s, 1H), 6.76 – 6.70 (m, 2H), 3.69 (s, 3H), 3.43 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 176.6, 155.0, 137.5, 127.5, 112.7, 111.9, 109.8, 55.9, 36.7.



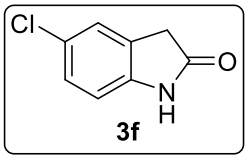
3d

5-fluoroindolin-2-one (3e).[22] White solid, Yield (138 mg, 91% yield); mp 133-134 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3214, 3078, 2918, 1696, 1617, 711; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.39 (s, 1H), 7.17 – 7.09 (m, 1H), 7.06 – 6.99 (m, 1H), 6.84 – 6.78 (m, 1H), 3.53 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 176.7, 158.2 (d, $^{1}J_{C\text{-}F}$ = 234.0 Hz), 140.4 (d, $^{4}J_{C\text{-}F}$ = 1.2 Hz), 128.1 (d, $^{3}J_{C\text{-}F}$ = 8.8 Hz), 114.0 (d, $^{2}J_{C\text{-}F}$ = 24.0 Hz), 112.7 (d, $^{2}J_{C\text{-}F}$ = 24.4 Hz), 110.0 (d, $^{3}J_{C\text{-}F}$ = 8.4 Hz), 36.7 (d, $^{4}J_{C\text{-}F}$ = 1.2 Hz).



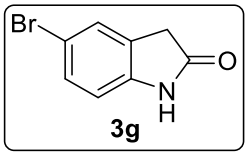
3e

5-chloroindolin-2-one (3f).[22] White crystalline solid; Yield (75 mg, 90% yield); mp 192-193 °C;



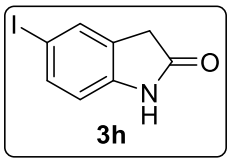
The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3210, 3084, 2917, 1692, 1615, 1459; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.46 (s, 1H), 7.25 (s, 1H), 7.22 – 7.18 (m, 1H), 6.80 (d, J = 8.0 Hz, 1H), 3.50 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 176.5, 143.1, 128.5, 127.7, 125.6, 124.9, 110.8, 36.3.

5-bromoindolin-2-one (3g).[22] White solid; Yield (94 mg, 89% yield); mp 218-219 °C; The title



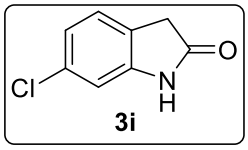
compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3211, 3074, 2912, 2705, 1694, 792; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.47 (s, 1H), 7.41 – 7.30 (m, 2H), 6.76 (d, J = 8.4 Hz, 1H), 3.50 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 176.4, 143.5, 130.5, 128.9, 127.7, 113.3, 111.3, 36.2.

5-iodoindolin-2-one (3h).[36] White solid; Yield (97 mg, 75%); mp 190-192 °C; The title



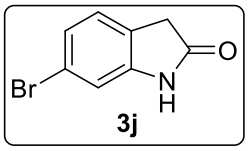
compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3209, 3092, 2914, 2702, 1691, 1618, 1152; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.51 (s, 1H), 7.58 – 7.53 (m, 2H), 7.42 (d, J = 8.0 Hz, 1H), 3.53 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 176.2, 143.9, 136.4, 133.2, 129.8, 111.9, 84.3, 35.9.

6-chloroindolin-2-one (3i).[22] White solid; Yield (146 mg, 87%); mp 190-191 °C; The title



compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3210, 3084, 2917, 1692, 1615, 1459; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.49 (s, 1H), 7.30 – 6.70 (m, 3H), 3.46 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 176.8, 145.6, 132.2, 126.2, 125.2, 121.2, 109.6, 35.8.

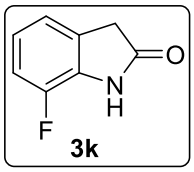
6-bromoindolin-2-one (3j).[22] White solid; Yield (188 mg, 89%); mp 210-211 °C; The title



compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3211, 3074, 2912, 2705, 1694, 792; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.48 (s, 1H), 7.15 (d, J = 8.0 Hz, 1H),

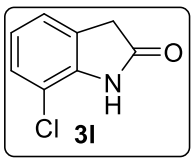
7.10 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.94 (d, *J* = 2.0 Hz, 1H), 3.44 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 176.7, 145.8, 126.6, 125.7, 124.1, 120.3, 112.3, 35.9.

7-fluoroindolin-2-one (3k).[19] Off-white solid; Yield (132 mg, 88%); mp 195-196 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3214, 3078, 2918, 1696, 1617, 711; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.83 (s, 1H), 7.12 – 7.02 (m, 2H), 6.97 – 6.90 (m, 1H), 3.56 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 176.5, 147.0 (d, $^{1}J_{C\text{-}F}$ = 240.0 Hz), 131.0 (d, $^{2}J_{C\text{-}F}$ = 12.0 Hz), 129.4 (d, $^{3}J_{C\text{-}F}$ = 4.2 Hz), 122.4 (d, $^{3}J_{C\text{-}F}$ = 6.0 Hz), 120.9 (d, $^{4}J_{C\text{-}F}$ = 3.2 Hz), 114.9 (d, $^{2}J_{C\text{-}F}$ = 17.0 Hz), 36.4 (d, $^{4}J_{C\text{-}F}$ = 2.4 Hz).



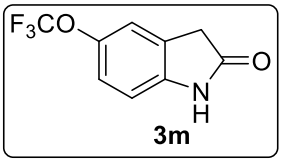
3k

7-chloroindolin-2-one (3l).[25] Off-white solid; Yield (146 mg, 87%); mp 216-217 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3210, 3084, 2917, 1692, 1615, 1459; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.76 (s, 1H), 7.23 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, 1H), 6.95 (dd, *J* = 8.4, 7.6 Hz, 1H), 3.60 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 176.6, 141.7, 128.2, 127.9, 123.5, 122.9, 113.8, 36.9.



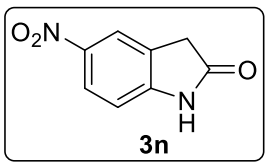
3l

5-(trifluoromethoxy)indolin-2-one (3m).[36] White solid; Yield (184 mg, 85%); mp 138-139 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3214, 3091, 2909, 1697, 1616, 1214; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.54 (s, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.25 (s, 1H), 7.20 – 7.15 (m, 1H), 3.55 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 177.9, 144.5, 129.7, 126.3, 121.2, 120.5 (q, $^{1}J_{C\text{-}F}$ = 255.0 Hz), 118.5, 110.3, 36.5.



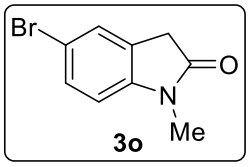
3m

5-nitroindolin-2-one (3n).[20] White solid; Yield (92 mg, 52%); mp 241-242 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3210, 3084, 2917, 1692, 1615, 1550, 1359; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.04 (s, 1H), 8.16 (dd, *J* = 8.6, 2.4 Hz, 1H), 8.10 (s, 1H), 6.99 (d, *J* = 8.6 Hz, 1H), 3.64 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 177.2, 150.8, 142.2, 127.6, 125.4, 120.5, 109.5, 36.1.

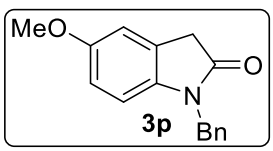


3n

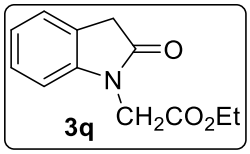
5-bromo-1-methylindolin-2-one (3o).[20] White crystalline solid; Yield (206 mg, 92%); mp 136-137 °C; The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3091, 2902, 1651, 1615, 1459, 1152; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39 – 7.23 (m, 2H), 6.61 (d, J = 8.4 Hz, 1H), 3.44 (s, 2H), 3.12 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 173.3, 143.3, 129.7, 126.5, 125.4, 113.9, 108.4, 34.5, 25.2.



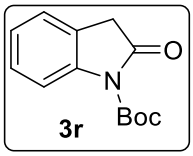
1-benzyl-5-methoxyindolin-2-one (3p).[37] Colorless semi solid; Yield (230 mg, 91%); The title compound is prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3092, 2911, 1655, 1614, 1457, 1216; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.23 – 7.15 (m, 5H), 6.81 – 6.77 (m, 1H), 6.59 (dd, J = 8.4, 2.8 Hz, 1H), 6.51 (d, J = 8.4 Hz, 1H), 4.80 (s, 2H), 3.65 (s, 3H), 3.51 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 173.7, 154.8, 136.8, 134.9, 127.7, 126.5, 126.3, 124.8, 111.1, 110.9, 108.3, 54.7, 42.8, 35.1.



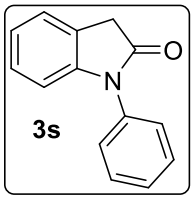
ethyl 2-(2-oxoindolin-1-yl)acetate (3q).[38] White crystalline solid; Yield (202 mg, 92%); mp 129-130 °C; The title compound was prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3091, 2972, 1732, 1651, 1615, 1459, 1214; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.20 – 7.16 (m, 2H), 6.98 (t, J = 8.4 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 4.40 (s, 2H), 4.15 (q, J = 7.2 Hz, 2H), 3.53 (s, 2H), 1.20 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 175.0, 167.6, 143.9, 127.9, 124.6, 124.2, 122.7, 108.2, 61.8, 41.3, 35.5, 14.1.



***tert*-butyl 2-oxoindoline-1-carboxylate (3r).**[39] Off-white solid; Yield (186 mg, 80%); mp 61-62 °C; The title compound was prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3091, 2902, 1751, 1651, 1615, 1459, 1152; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.71 (d, J = 8.0 Hz, 1H), 7.22 (t, J = 8.4 Hz, 1H), 7.16 (d, J = 7.6 Hz, 1H), 7.06 (td, J = 7.6, 0.8 Hz, 1H), 3.57 (s, 2H), 1.57 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 173.1, 149.2, 141.0, 128.1, 124.2, 123.2, 115.1, 84.3, 36.6, 28.1.

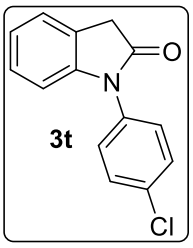


1-phenylindolin-2-one (3s).[20] White crystalline solid; Yield (198 mg, 95%); mp 120-121 °C;



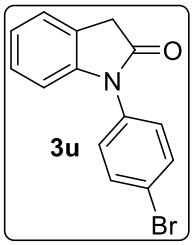
The title compound was prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3092, 2911, 1656, 1611, 1412, 1162; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.50 – 7.41 (m, 2H), 7.37 – 7.30 (m, 3H), 7.23 (d, J = 7.2 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 7.00 (t, J = 7.6 Hz, 1H), 6.71 (d, J = 7.6 Hz, 1H), 3.64 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 174.5, 145.3, 134.6, 129.7, 128.1, 127.8, 126.7, 124.6, 124.4, 122.8, 109.4, 36.1.

1-(4-chlorophenyl)indolin-2-one (3t).[40] White crystalline solid; Yield (220 mg, 91%); mp 122-



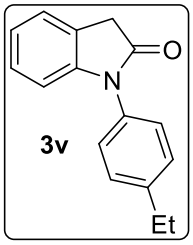
123 °C; The title compound was prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3212, 3084, 2917, 1656, 1614, 1459, 1215; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.76 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 7.2 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 3.76 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ (ppm): 174.3, 144.8, 134.3, 132.9, 129.3, 128.0, 125.3, 125.2, 123.1, 120.9, 109.2, 35.9.

1-(4-bromophenyl)indolin-2-one (3u).[40] Pale red solid; Yield (256 mg, 89%); mp 115-116 °C;



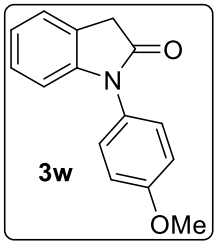
The title compound was prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3091, 2902, 1651, 1615, 1459, 1152; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.58 (d, J = 8.8 Hz, 2H), 7.26 – 7.21 (m, 3H), 7.14 (t, J = 7.6 Hz, 1H), 7.02 (t, J = 7.6 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 3.63 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 174.3, 144.7, 133.6, 132.9, 128.2, 127.9, 124.8, 124.3, 123.1, 121.7, 109.3, 36.0.

1-(4-ethylphenyl)indolin-2-one (3v). Off-white solid; Yield (260 mg, 91%); mp 118-119 °C;



The title compound was prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3091, 2908, 1654, 1612, 1412, 1162; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.30 – 7.20 (m, 5H), 7.11 (t, J = 7.6 Hz, 1H), 6.98 (t, J = 7.2 Hz, 1H), 6.70 (d, J = 7.6 Hz, 1H), 3.62 (s, 2H), 2.64 (q, J = 7.6 Hz, 2H), 1.21 (t, J = 7.6 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 174.6, 145.5, 144.3, 132.0, 129.1, 127.8, 126.5, 124.6, 124.4, 122.7, 109.5, 36.1, 28.6, 15.5.

1-(4-methoxyphenyl)indolin-2-one (3w).[40] White crystalline solid; Yield (210 mg, 88%); mp 139-140 °C; The title compound was prepared according to the general procedure (A) described as above; FT-IR (KBr, cm^{-1}) 3092, 2911, 1651, 1614, 1457, 1214; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.26 – 7.21 (m, 3H), 7.12 (t, J = 8.0 Hz, 1H), 7.01 – 6.94 (m, 3H), 6.65 (d, J = 8.0 Hz, 1H), 3.78 (s, 3H), 3.62 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm): 174.8, 159.2, 145.7, 128.0, 127.8, 127.1, 124.6, 124.3, 122.7, 115.0, 109.3, 55.6, 36.0.



6B.6. References

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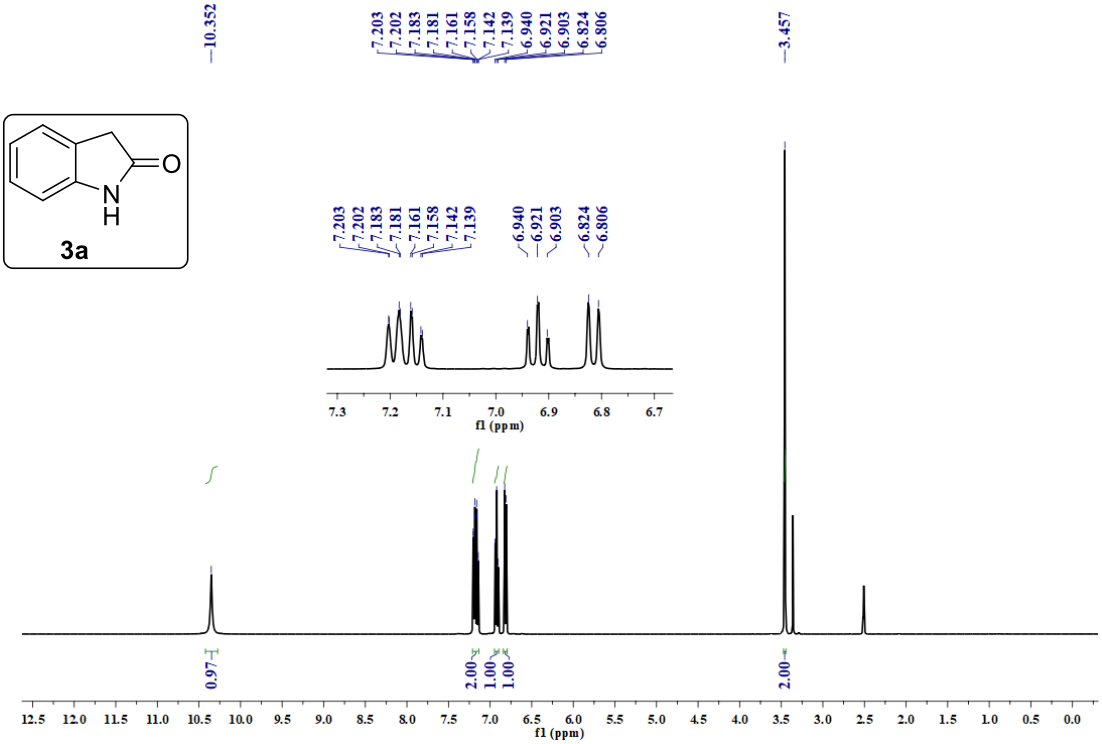
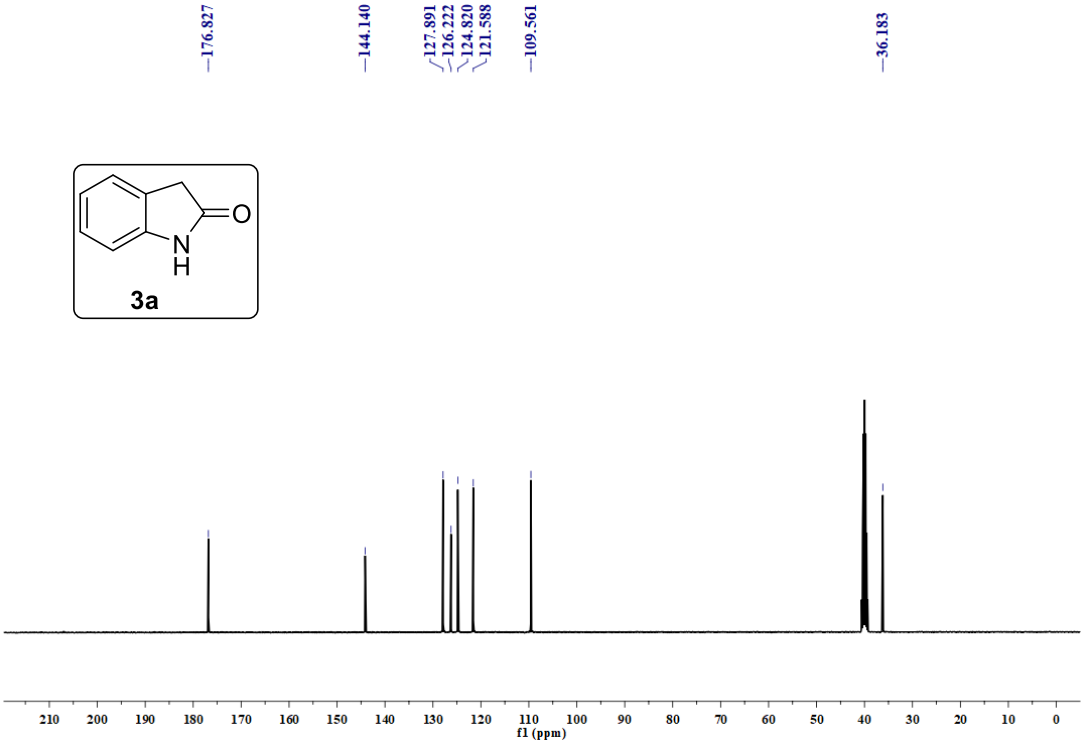
6B.7. Selected ^{1}H & ^{13}C NMR spectra

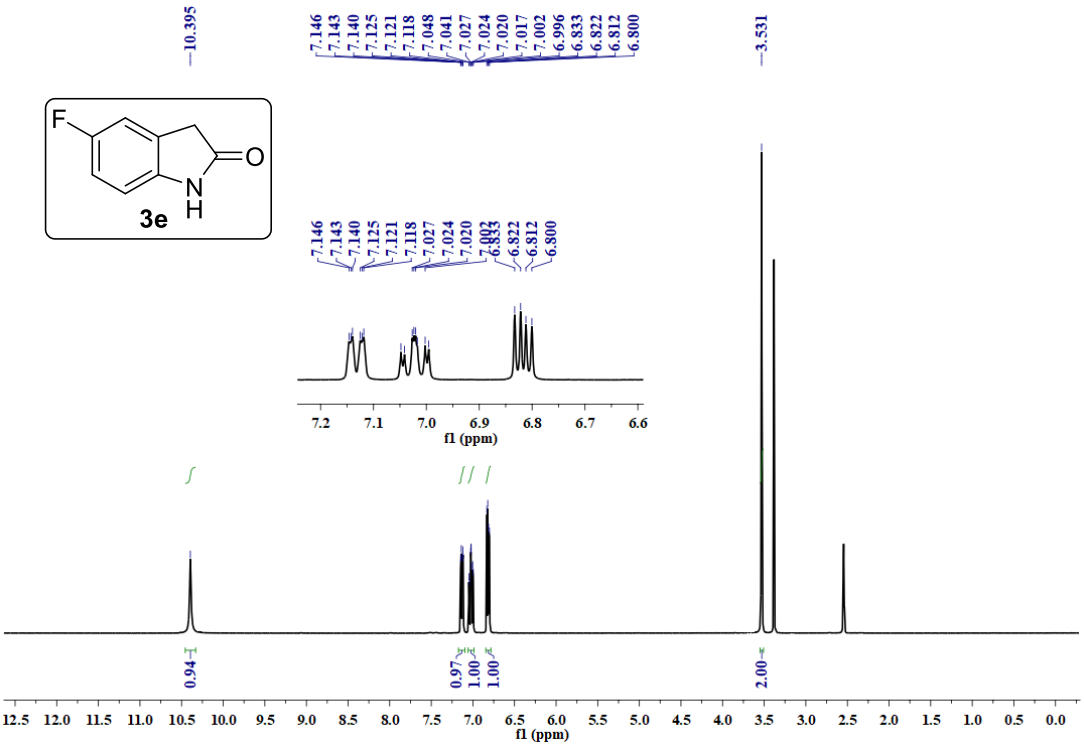
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of indolin-2-one (3a)



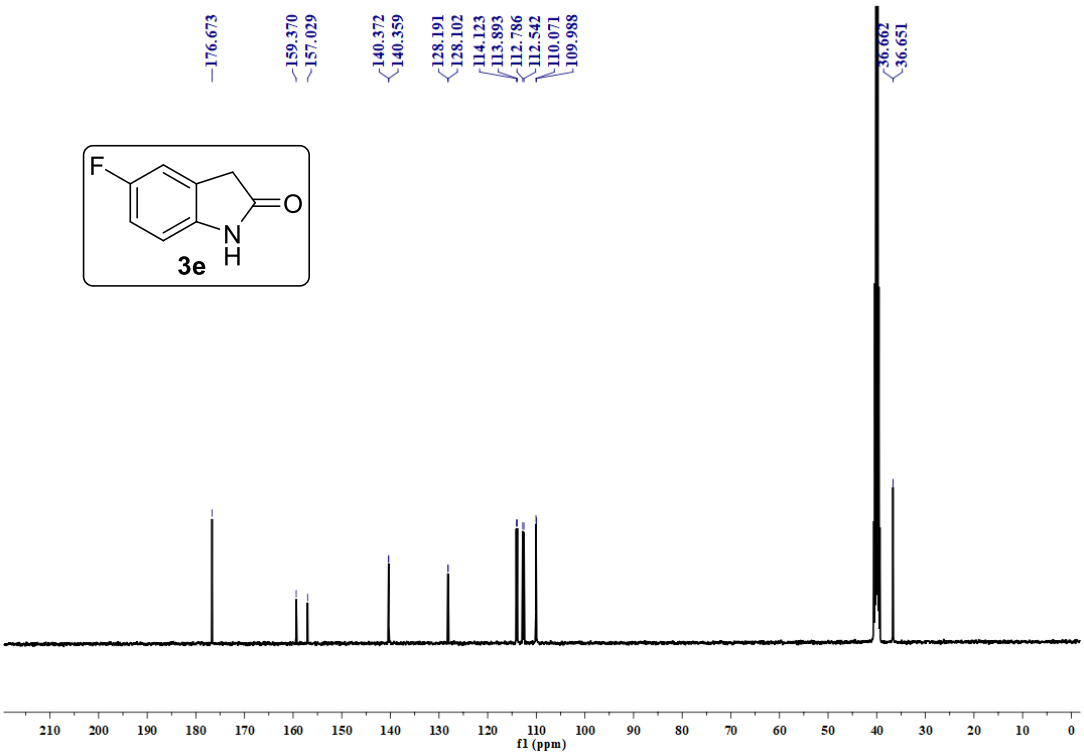
$^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) spectrum of indolin-2-one (3a)



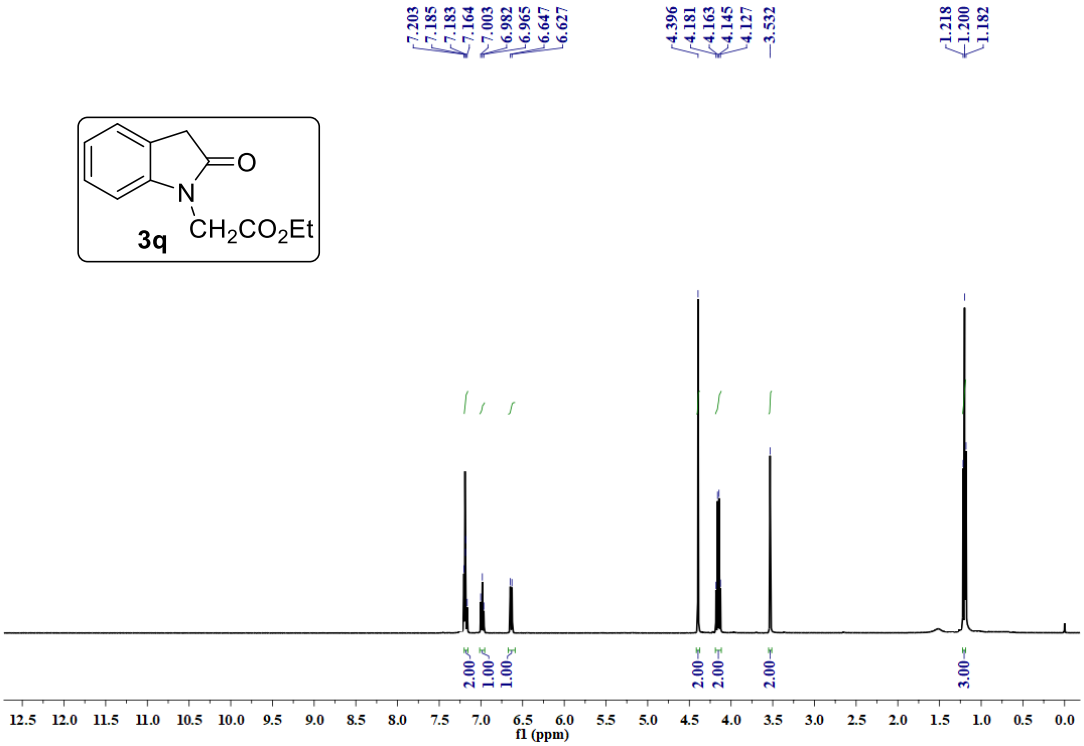
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of 5-fluoroindolin-2-one (3e)



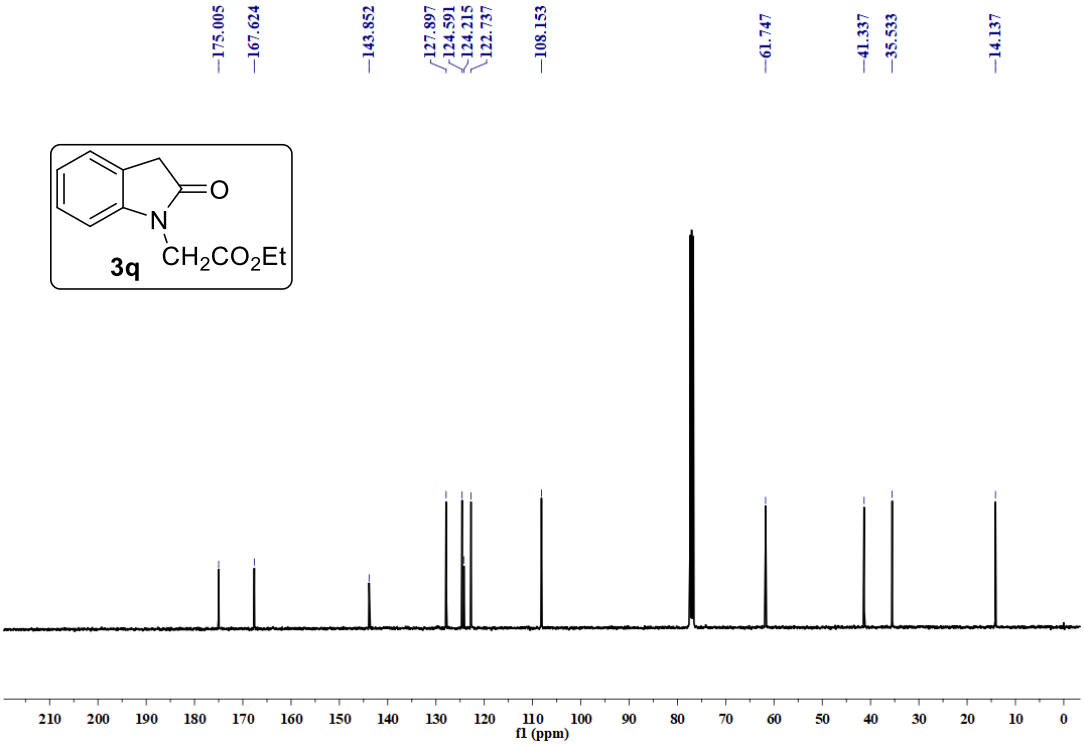
^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) spectrum of 5-fluoroindolin-2-one (3e)



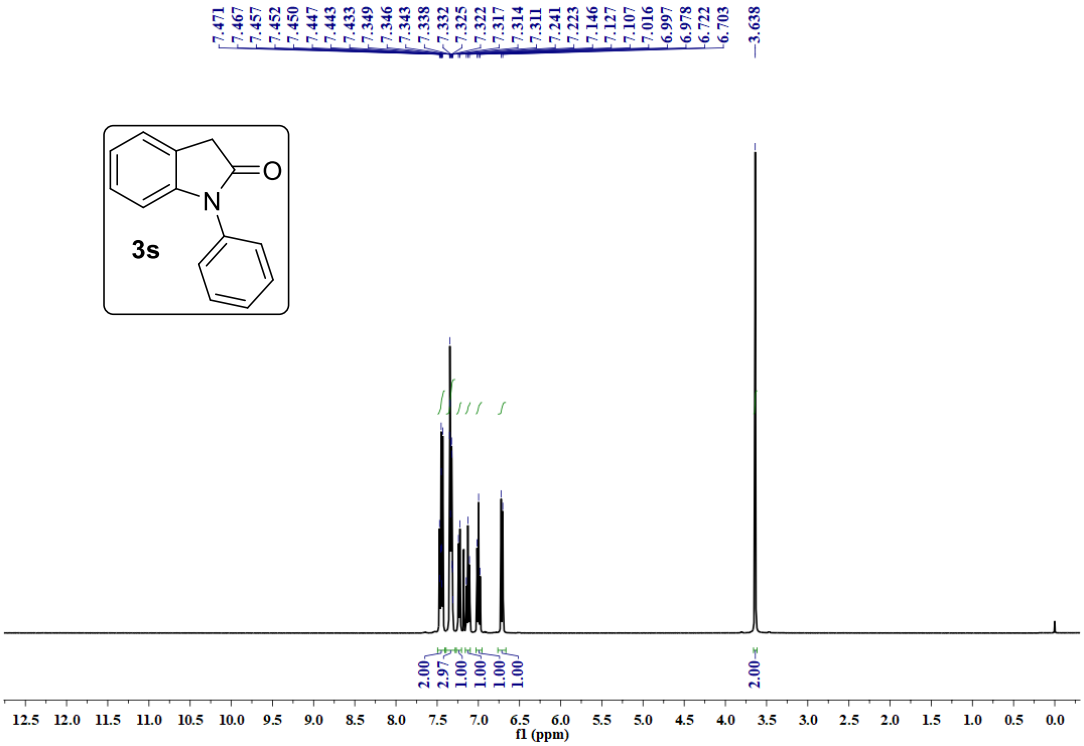
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of ethyl 2-(2-oxoindolin-1-yl)acetate (3q)



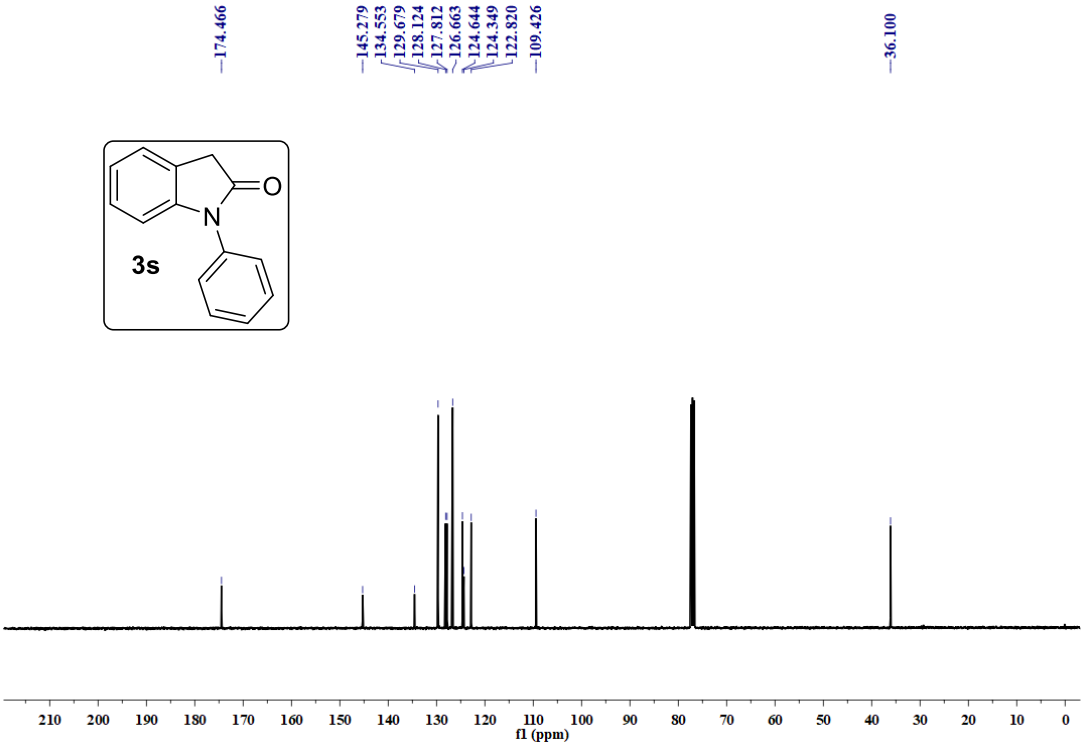
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of ethyl 2-(2-oxoindolin-1-yl)acetate (3q)



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 1-phenylindolin-2-one (3s)



^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of 1-phenylindolin-2-one (3s)

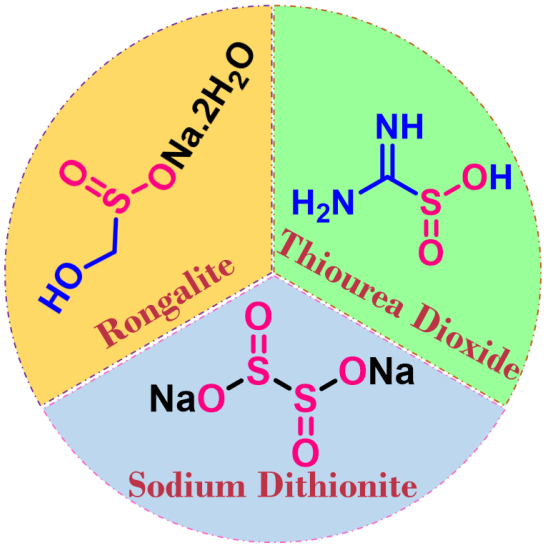


SUMMARY

Chapter-I

Introduction

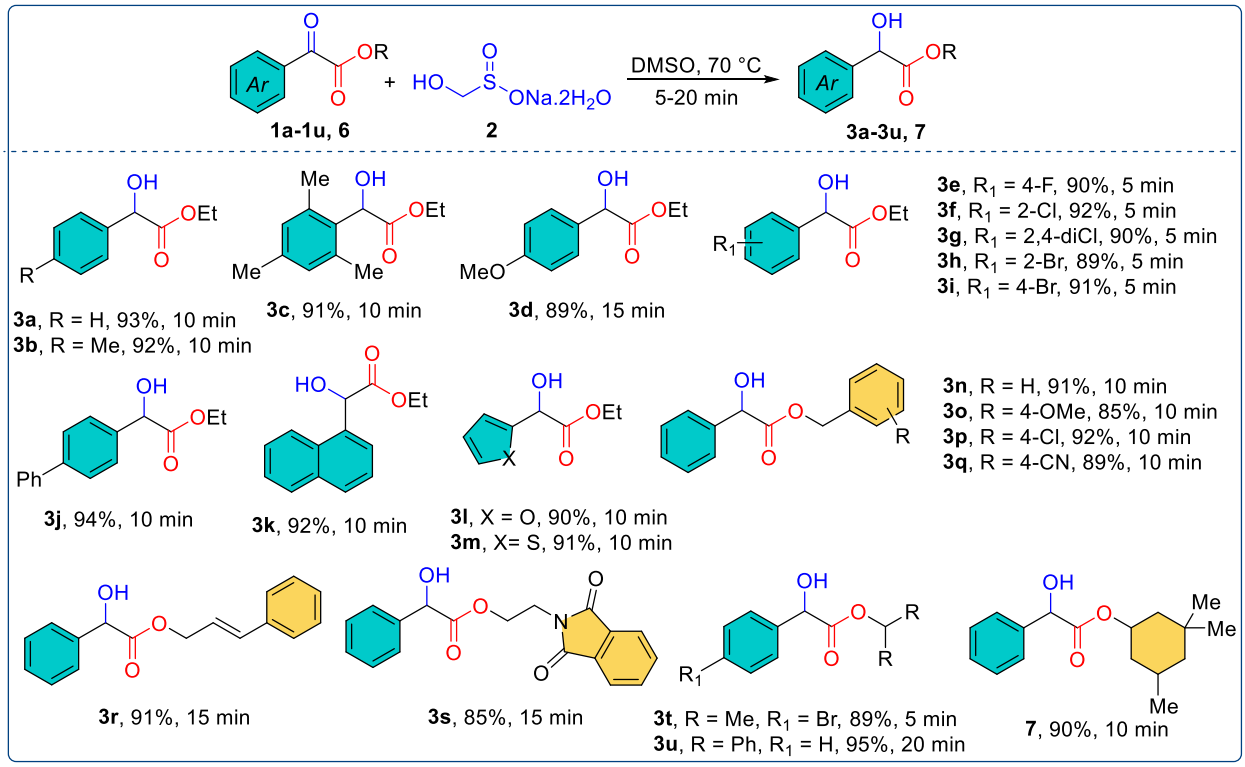
The literature survey of the present study is described in this chapter. The development of sulfur-containing reducing agents such as dithionites, α-hydroxyalkanesulfinates and thiourea oxides was started in the 18th century. Among all, sodium hydroxymethanesulfinate dihydrate (rongalite), sodium dithionite and thiourea dioxide are the versatile reductants in the chemistry and also captivated the synthetic community. This chapter includes various organic applications of rongalite, thiourea dioxide and sodium dithionite, which are inexpensive and industrial reagents. Rongalite is used as a surrogate of sulfone, C1 unit source and as single electron reductant.[1] Also, thiourea dioxide and sodium dithionite are used as single electron reductants and as sulfone sources for the synthesis of various functionalized molecules.[2] All the compounds described in the thesis were synthesized using conventional methods and characterized by FT-IR, NMR and HRMS.



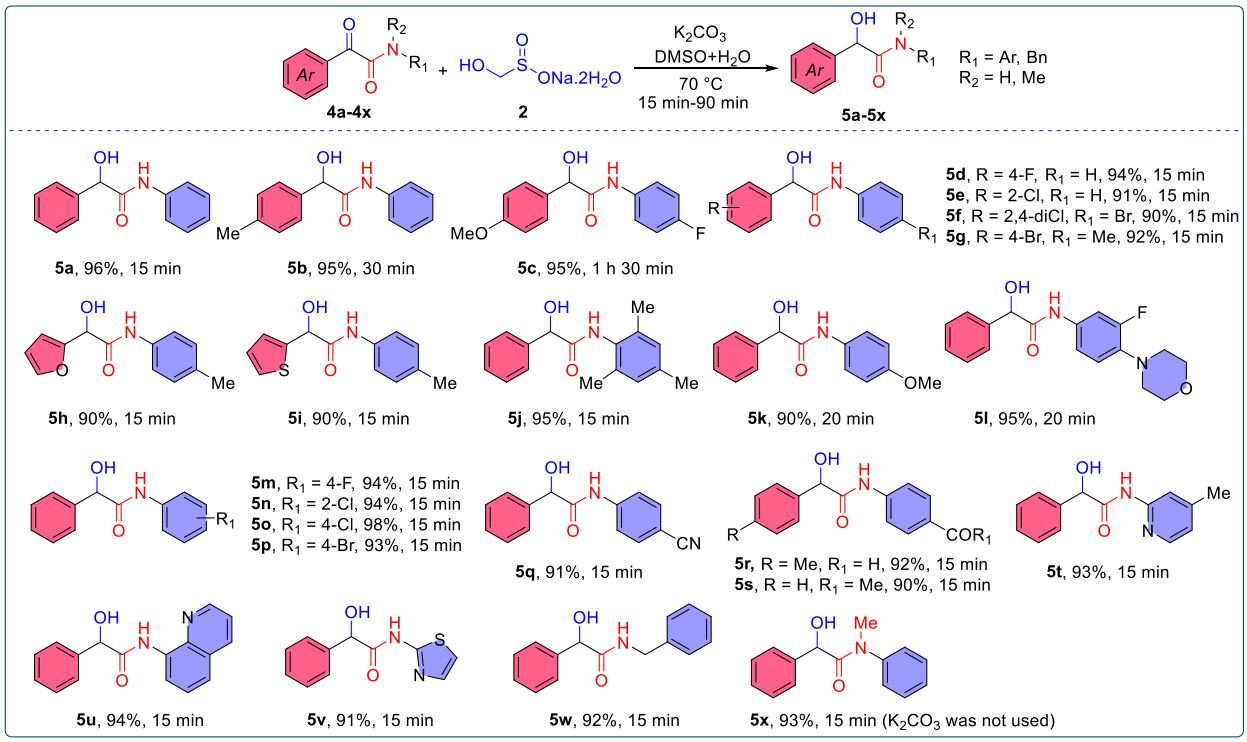
Chapter-II

Transition Metal and Hydride-Free Chemoselective Reduction of *α*-Keto Esters and *α*-Keto Amides Using Rongalite

The chemoselective reduction of ketone moiety to an alcohol in the presence of other reducible functionalities is an important process and it helps in the synthesis of complex molecules.[3] The chemoselective reduction of *α*-keto esters and *α*-keto amides gives *α*-hydroxy esters and *α*-



Scheme 2.1. Substrate scope of the chemoselective reduction of α-keto esters by rongalite



Scheme 2.2. Substrate scope of the chemoselective reduction of α-keto amides by rongalite

hydroxy amides, which are important pharmacophores and exhibit broad spectrum of biological activities.[4] In addition to biological activities, *α*-hydroxy esters and *α*-hydroxy amides are valuable synthetic precurssors.[5]

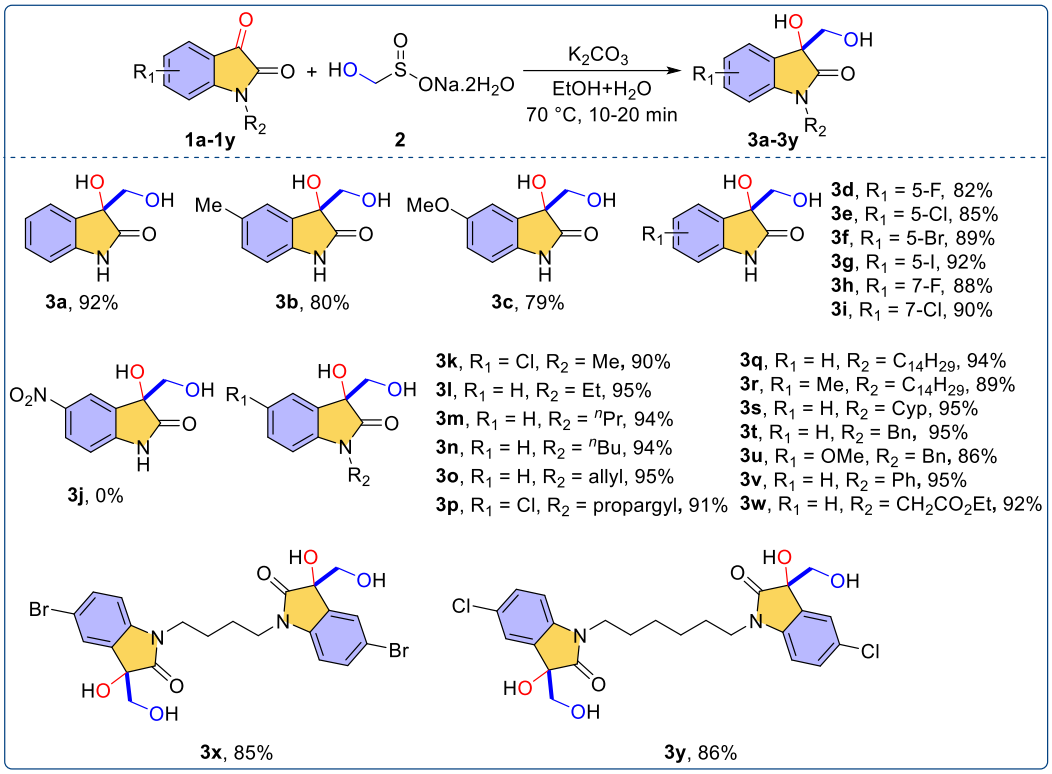
The optimized reaction conditions for the synthesis of **3a**-**3u** & **7** are as follows, an oven dried 10 mL reaction flask was charged with *α*-keto ester **1a**-**1u** & **6** (1 mmol), rongalite **2** (2 mmol) and DMSO (2 mL). The mixture was stirred at 70 °C for the appropriate time (5-20 min) to produce the desired *α*-hydroxy esters **3a**-**3u** & **7** (Scheme 2.1). Also, this protocol was extended to *α*-keto amides with slight modifications to accomplish *α*-hydroxy amides. The optimized reaction conditions are as follows, an oven dried 10 mL reaction flask was charged with *α*-keto amide **4a**-**4x** (1 mmol), rongalite **2** (2 mmol), K_2CO_3 (1.5 mmol) and DMSO+H_2O (2 mL, 8:2 v/v). The mixture was stirred at 70 °C for the appropriate time (15-90 min) to produce the desired *α*-hydroxy amides **5a**-**5x** (Scheme 2.2)

Chapter-III

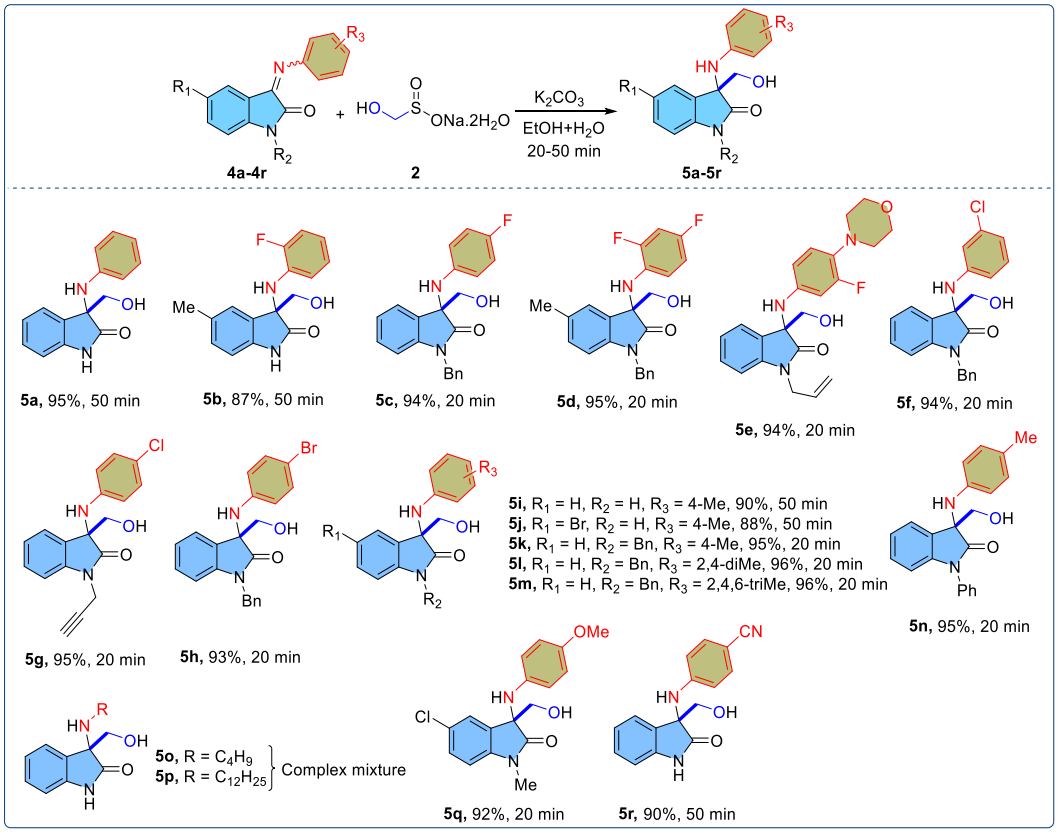
Rongalite-Promoted Transition Metal and Hydride-Free Reductive Aldol Reaction: A Direct Access to 3,3´- Disubstituted Oxindoles

Oxindole is a privileged structural motif in many natural products and bioactive compounds.[6] Among these, 3,3´-disubstituted oxindoles have attracted the chemists due to this wide spectrum of biological activities.[7] In the realm of oxindoles, the skeleton with a hydroxy and amine-bearing quaternary centre at C3 position (3-hydroxy-2-oxindole and 3-amino-2-oxindole) has significantly intersected the biological space through its three-dimensional spatial arrangement and notably, these are the core structures of many pharmaceuticals.[8] Recently, 3-amino-3-hydroxymethyloxindoles reported as anti-cancer agents *via in vitro* screening, and exhibits anti-proliferating effect against HCT-116, SJSA-1 and Jurkat cancer cell lines.[9]

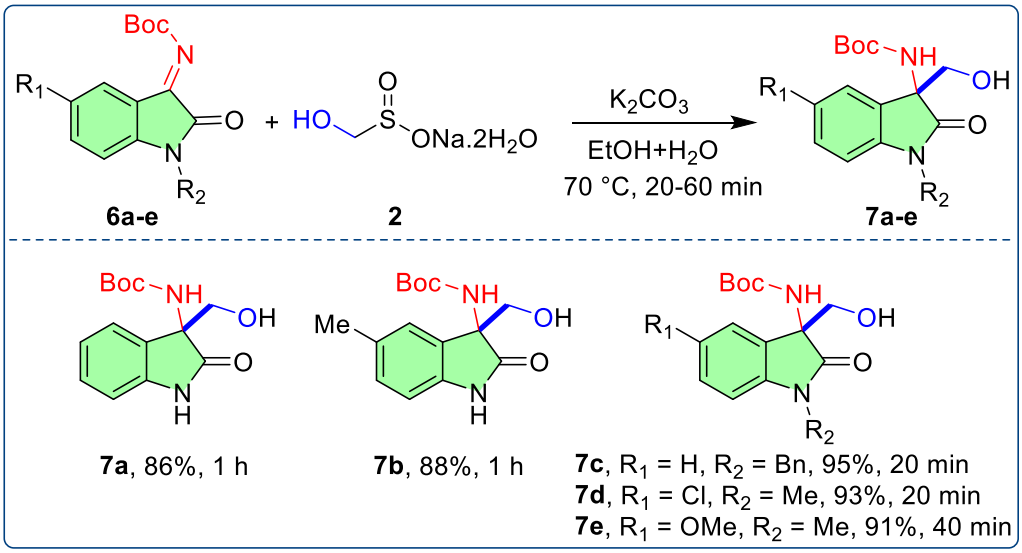
The optimized reaction conditions for the synthesis of **3a**-**3y** are as follows, an oven dried 10 mL reaction flask was charged with appropriate isatin-derivative **1a**-**1y** (1 mmol), rongalite **2** (2 mmol), K_2CO_3 (2 mmol) and EtOH+H_2O (2 mL, 8:2 v/v). The mixture was stirred at 70 °C for the appropriate time (10-20 min) to produce the desired 3-hydroxy-3-(hydroxymethyl)indolin-2-one derivatives **3a**-**3y** (Scheme 3.1). Also, this methodology was extended to isatin Schiff bases **4a**-**4r** and isatin-derived ketimines **6a**-**6e** to produce the corresponding 3-amino-3-(hydroxymethyl)indolin-2-ones **5a**-**5r** (Scheme 3.2) and **7a**-**7e** (Scheme 3.3).



Scheme 3.1. Scope of isatins for the synthesis of 3-hydroxy-3-(hydroxymethyl)indolin-2-ones



Scheme 3.2. Synthesis of 3-amino-3-(hydroxymethyl)indolin-2-ones



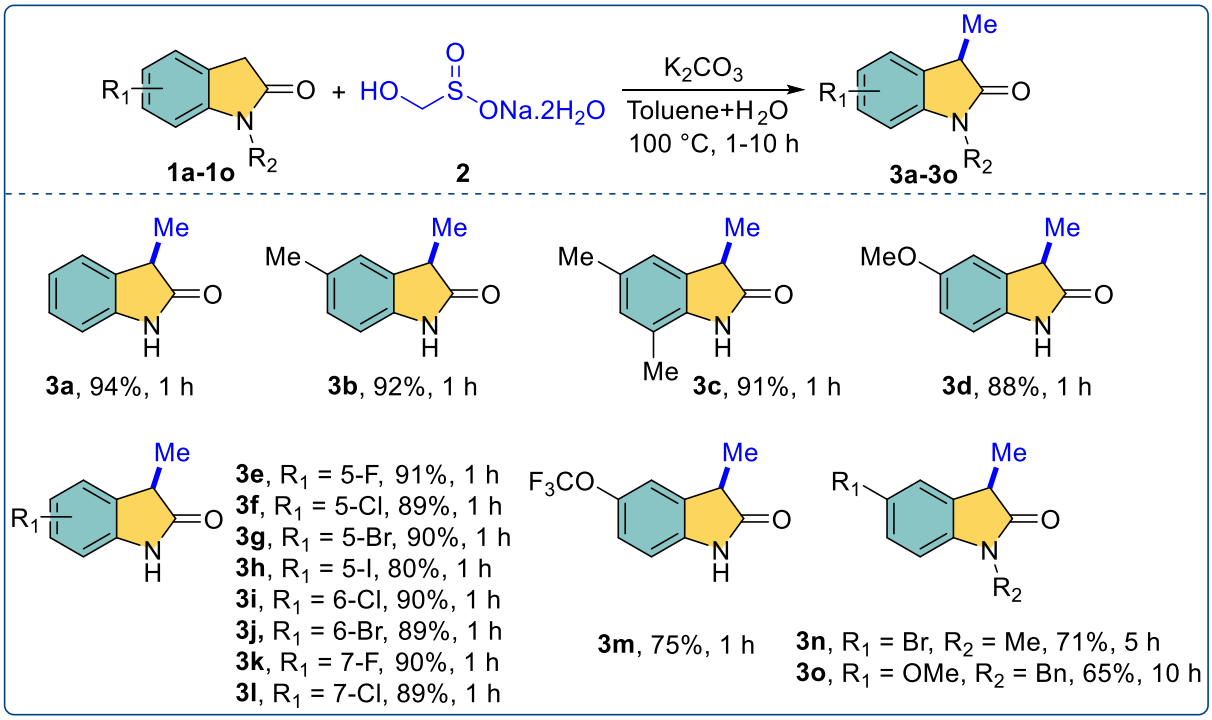
Scheme 3.3. Substrate scope of isatin-derived ketimines

Chapter-IV

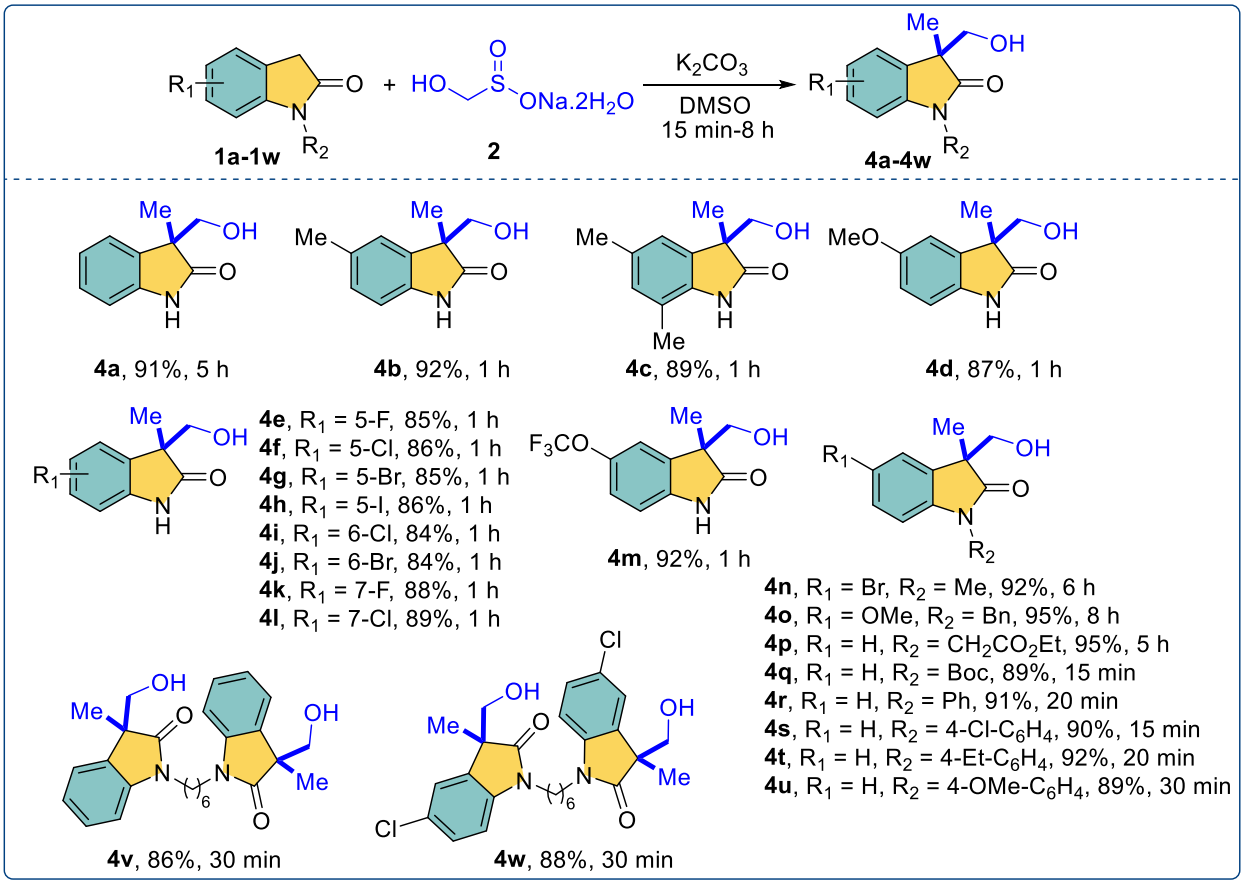
Functionalization of 2-Oxindoles via Sequential Aldol and Reductive Aldol Reactions Using Rongalite as Double C1 Source

Oxindoles are ubiquitous motifs in bioactive natural products and pharmaceutical lead compounds,[10] and have attracted the synthetic community to develop novel 2-oxindole scaffolds with pharmacological properties.[11] Among 2-oxindoles, 3-methyl-2-oxindoles and 3-(hydroxymethyl)-3-methyl-2-oxindoles are used as synthetic precursors for the total synthesis of (–)-physostigmine, which is a potent acetylcholinesterase inhibitor,[12] and also used in the treatment of glaucoma, atropine, myasthenia gravis and also works as an antidote against organophosphorous poisoning. Also, it is employed for the relief of intoxication induced by overdoses of benzodiazepines, antihistamines, antidepressants and antipsychotics.[13]

The optimized reaction conditions for the synthesis of **3a-3o** are as follows, an oven dried 10 mL reaction flask equipped with a magnetic stirring bar was charged with appropriate indolin-2-one-derivative **1a-1o** (1 mmol), rongalite **2** (2 mmol), K_2CO_3 (2 mmol) and toluene+H_2O (2 mL, 8:2 v/v). The mixture was stirred at 100 °C for the appropriate time (1-10 h) to produce the desired products 3-methylindolin-2-ones **3a-3o** (Scheme 4.1). Also, we prepared 3-(hydroxymethyl)-3-methylindolin-2-ones **4a-4w**, by taking indolin-2-one-derivatives **1a-1w** (1 mmol), rongalite **2** (3 mmol) and K_2CO_3 (2.5 mmol) in 2 mL of DMSO at 80 °C (Scheme 4.2).



Scheme 4.1. Synthesis of 3-methyl-2-oxindoles from indolin-2-ones



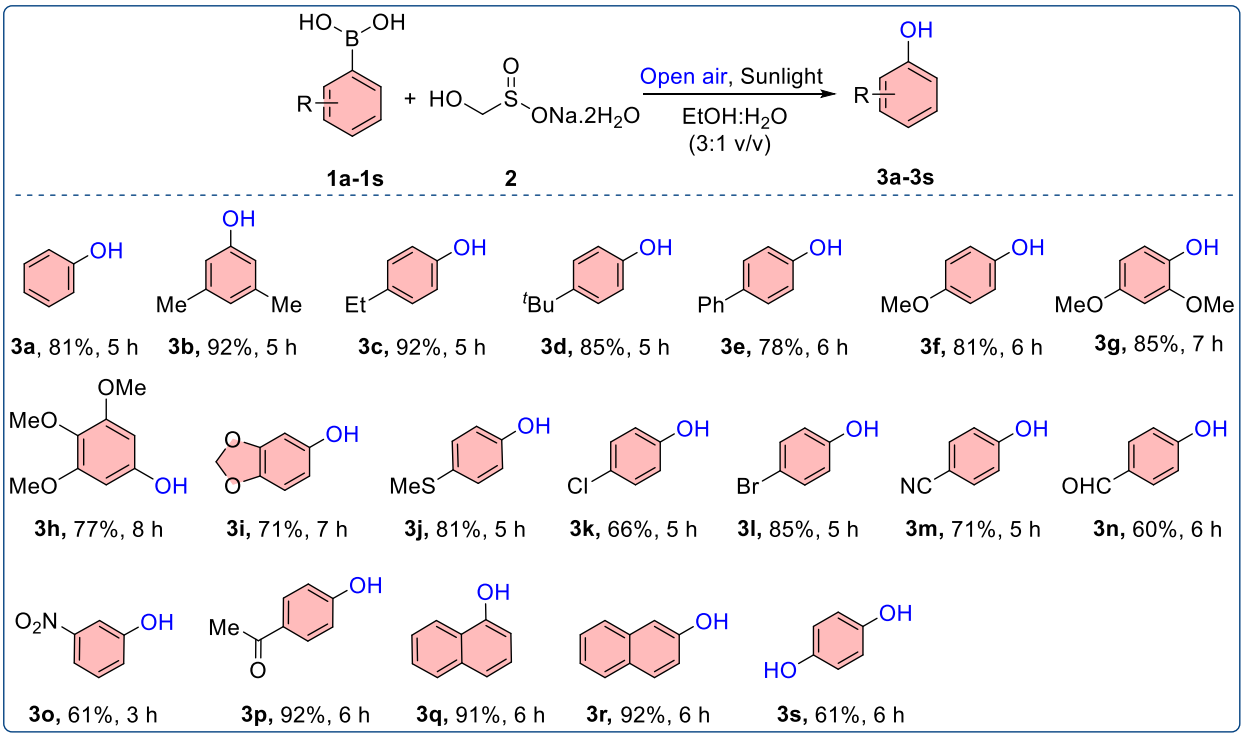
Scheme 4.2. Synthesis of 3-(hydroxymethyl)-3-methyl-2-oxindoles

Chapter-V

Section-A

Sunlight-Promoted Aerobic *ipso*-Hydroxylation of Arylboronic Acids Using Rongalite

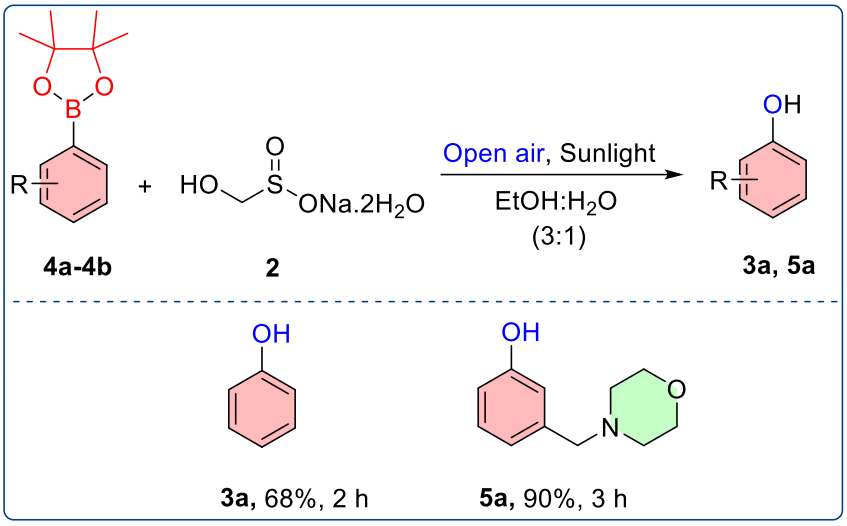
Phenol was first isolated by Friedlieb Ferdinand Runge from coal tar (in impure form) and named it as 'coal oil acid' or 'carbolic acid' in 1834. Dietary plants and medicinal herbs are the major source of phenols, which categorizes into phenolic acids, tannins, lignans, quinones, stilbenes, flavonoids, curcuminoids, coumarins etc.[14] These phenolic compounds exhibit broad spectrum of biological activities.[15] In addition to medicinal applications, phenols are also employed in the polymer chemistry to made electrical appliances.[16] Also, phenols are the versatile substrates for the preparation of *O*-containing heterocycles such as chromenes,[17] chromones,[18] flavones,[19] benzofurans,[20] coumarins[21] and xanthones.[22]



Scheme 5A.1. Substrate scope of arylboronic acids for the synthesis of phenols

The optimized reaction conditions for the synthesis of **3a-3s** are as follows, an oven dried round bottom flask was charged with phenylboronic acids **1a-1s** (0.5 mmol), rongalite **2** (1.0 mmol) and 1 mL of EtOH+H_2O (3:1 v/v) and the resulting mixture was stirred at room temperature

under sunlight irradiation in open air to produce the desired products **3a-3s** (Scheme 5A.1). Also, this protocol was extended to phenylboronic acid pinacol esters **4a-4b** and produced the corresponding phenols **3a** and **5a** (Scheme 5A.2).



Scheme 5A.2. Substrate scope of arylboronic acid pinacol esters

Chapter-V

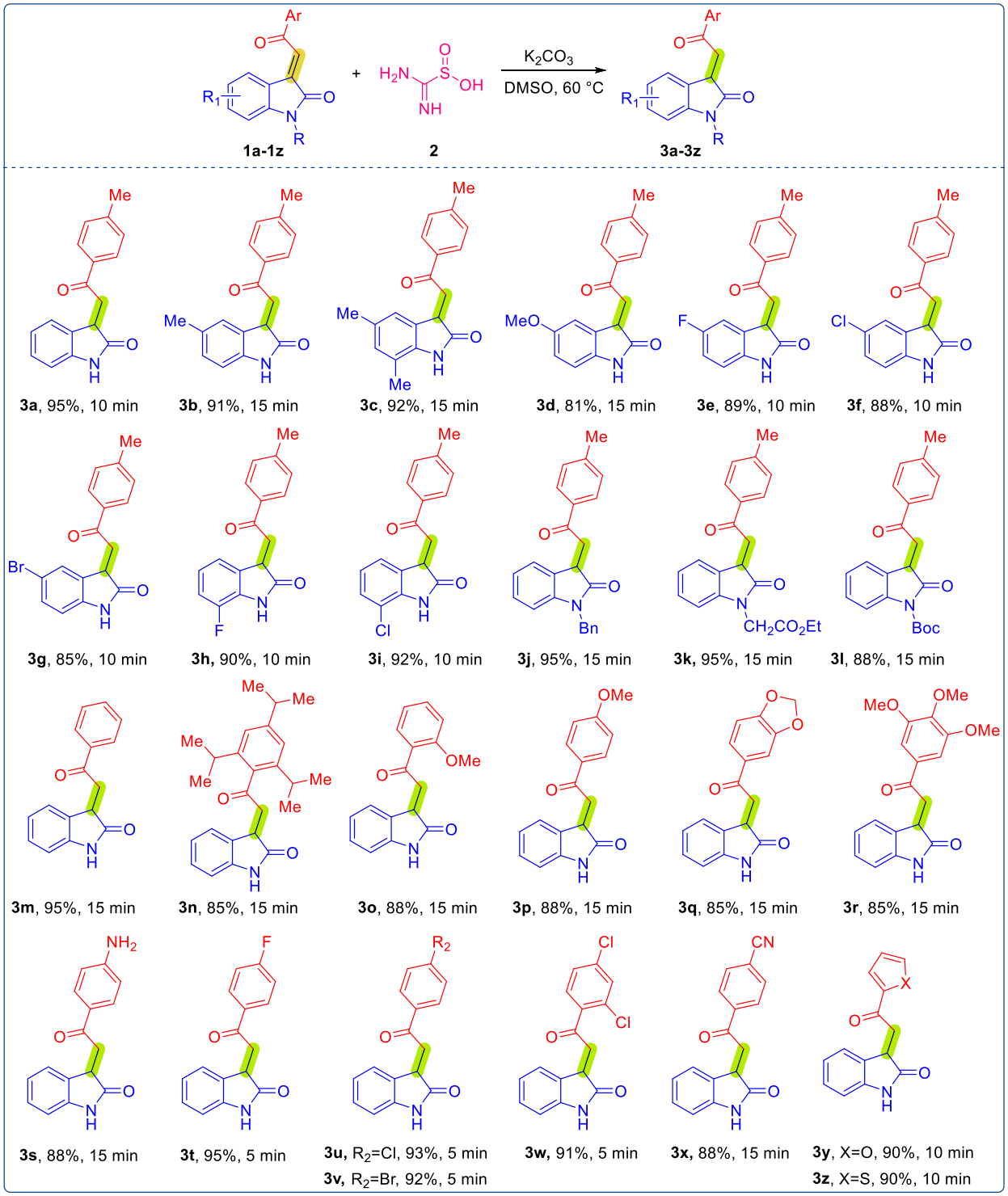
Section-B

Chemoselective Reduction of 3-Phenacylidene-2-oxindoles Using Thiourea Dioxide

Chemoselective reduction is one of the most prominent methods in organic synthesis and it helps in the synthesis of many natural products and industrial chemicals.[23] Among chemoselective reductions, the selective reduction of activated olefins attracted the researchers and allowed the preparation of useful complex molecules.[24] Many biosynthetic pathways rely on the selective reduction of activated alkenes and allows the synthesis of fatty acids by enolate reductases in the living microorganisms.[25] 3-Phenacyl-2-oxindoles showed higher DPPH radical scavenging activity and also due to the presence of 3-phenacyl substitution, these compounds exert greater lipid peroxidation-inhibitory activity.

The optimized reaction conditions for the synthesis of **3a-3z** are as follows, an oven dried 10 mL round bottom flask was charged with 3-phenacyl-2-indolinones **1a-1z** (1 mmol), thiourea dioxide

2 (2 mmol), K_2CO_3 (1 mmol) and DMSO (2 mL). The reaction mixture was stirred at 60 °C for 5-15 min for producing the desired products **3a-3z** (Scheme 5B).



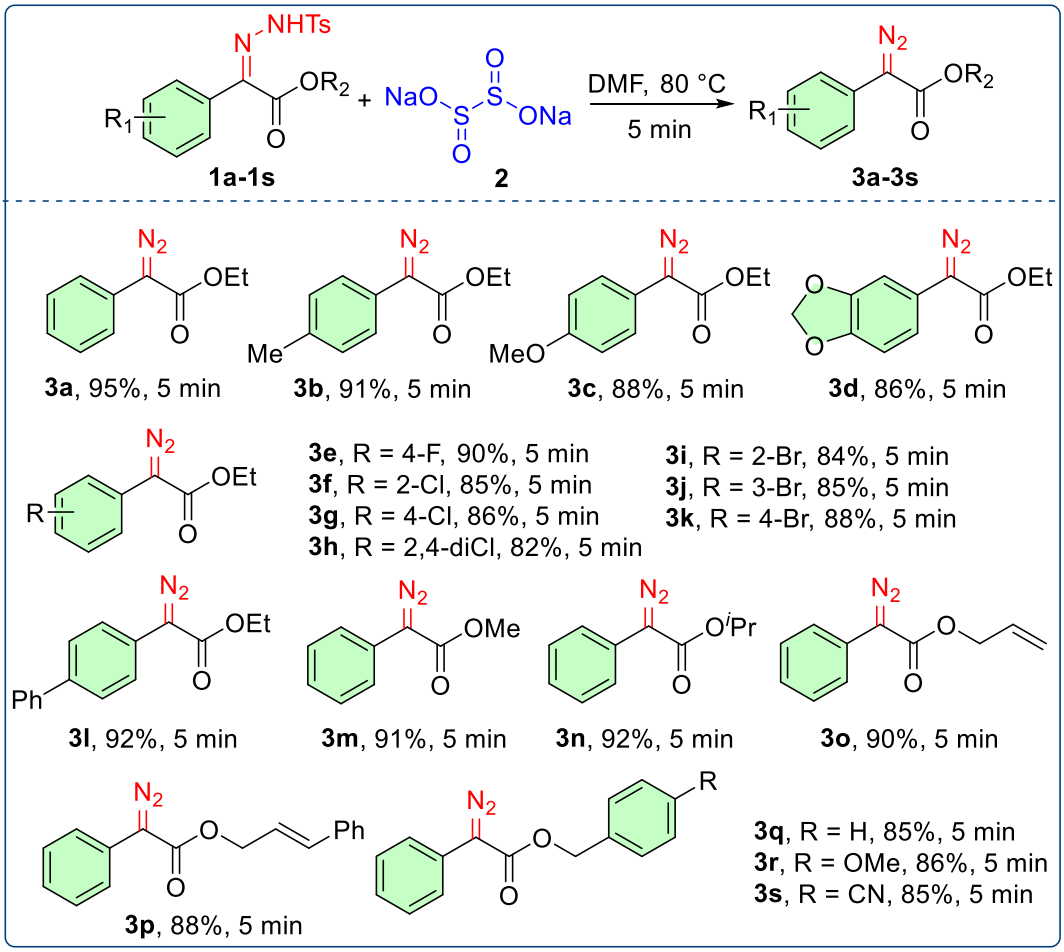
Scheme 5B. Substrate scope of chemoselective reduction of isatin-chalcones

Chapter-VI

Section-A

Sodium Dithionite Mediated Synthesis of *α*-Diazo Esters and 3-Diazooxindoles: An Alkali-Free Approach

Many natural products having diazo groups such as kinamycins A-D,[26] lomaiviticins A-B,[27] and amino acids such as azaserine, *N*-alanylazaserine, thrazarine, 6-diazo-5-oxonorleucine, duazomycin A-B and alazopeptin[28] containing diazo groups exhibit potent anticancer and antibiotic activities. Mainly, diazo compounds are employed in carbene chemistry, which include

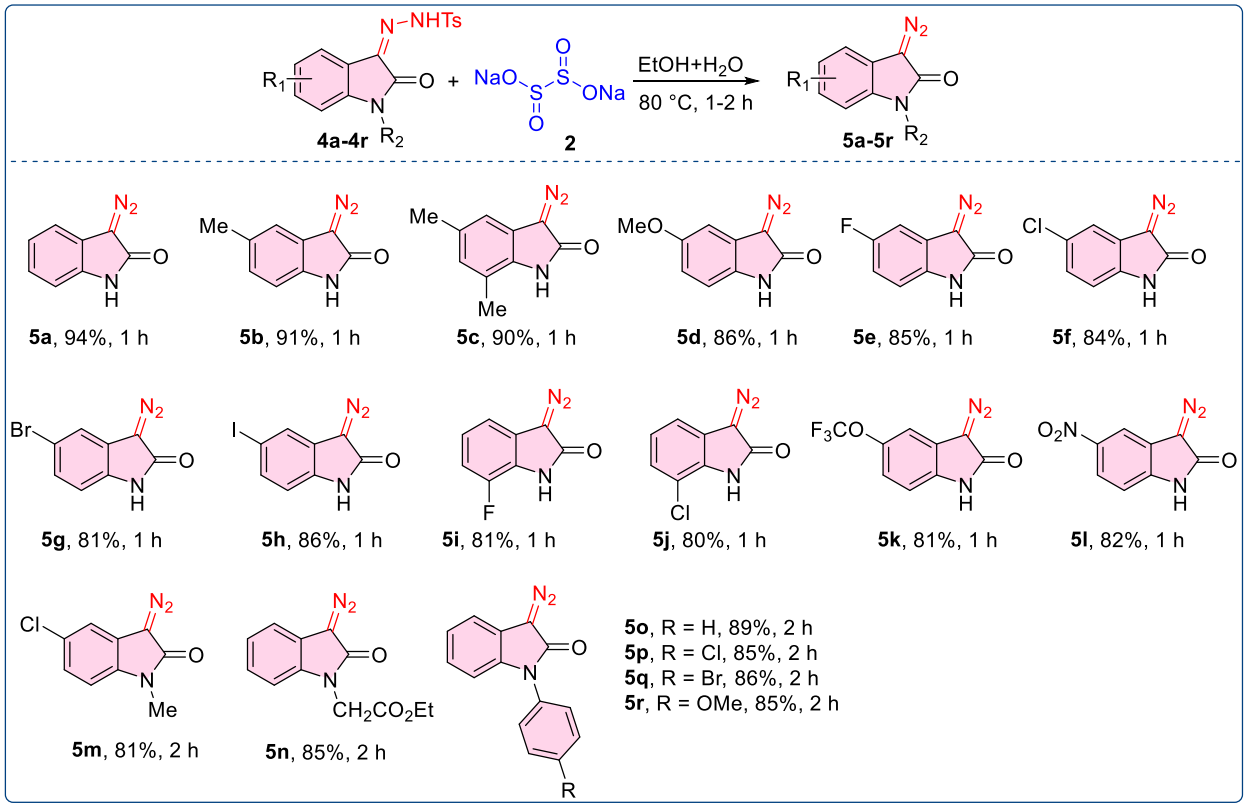


Scheme 6A.1. Synthesis of *α*-diazo esters from tosylhydrazones

cyclopropanation,[29] X-H insertions[30] (X = C, N, O, S and Si), cycloadditions[31] and moreover which are employed as cross-coupling partners.[32] Among diazo compounds, *α*-diazo esters and

3-diazooxindoles received a significant interest of chemists due to widespread usage in organic synthesis, leads to development of multifunctionalized compounds.

The optimized reaction conditions for the synthesis of **3a-3s** are as follows, an oven dried round bottom flask was charged with tosylhydrazones of *α*-keto ester **1a-1s** (1 mmol), sodium dithionite **2** (1 mmol) and DMF (2 mL). The reaction mixture was stirred at 80 °C for 5 min for producing the desired products **3a-3s** (Scheme 6A.1). Also, this methodology was modified and applied to the isatin-3-*p*-tosylhyadrazones **4a-4r** (1 mmol) for the synthesis of corresponding 3-diazooxindoles **5a-5r** by employing sodium dithionite (1 mmol) in EtOH+H_2O (2 mL, 8:2 v/v) at 80 °C (Scheme 6A.2).



Scheme 6A.2. Synthesis of 3-diazooxindoles from isatin-*p*-tosylhydrazones

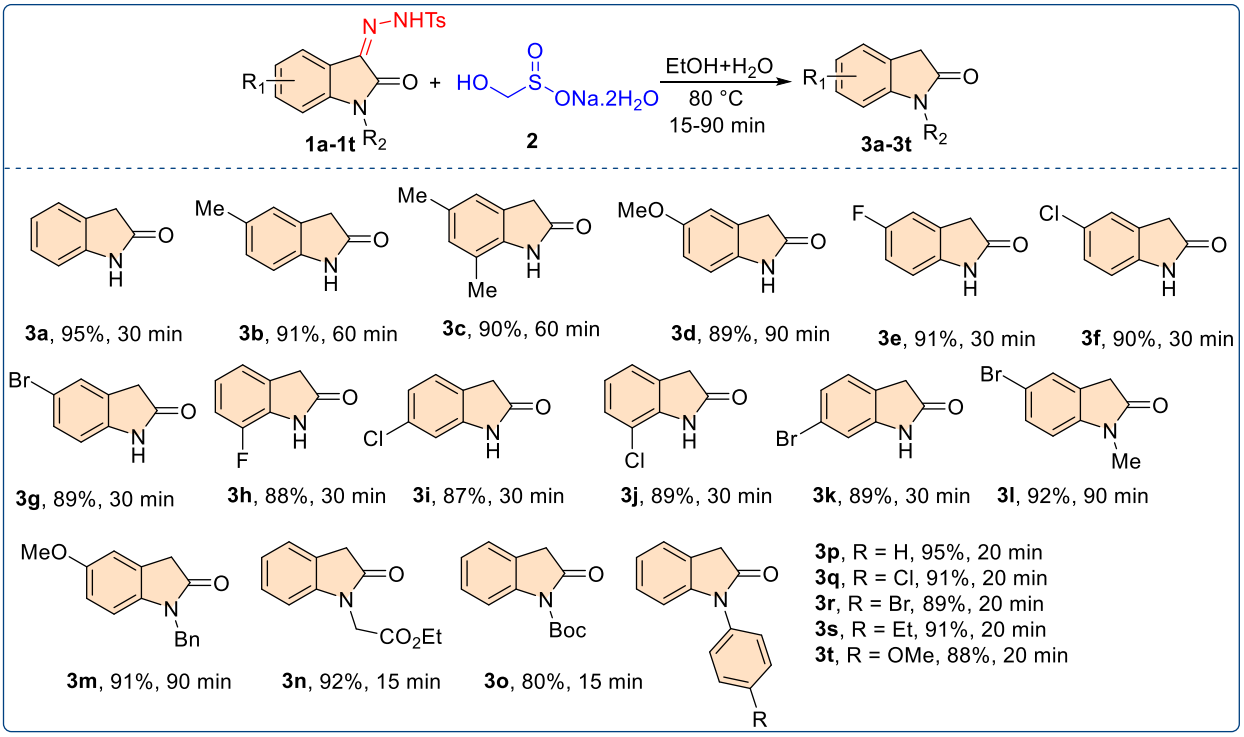
Chapter-VI

Section-B

Rongalite-Induced Reduction of Isatin-3-*p*-Tosylhydrazones: A Rapid Access to 2-Oxindoles

Indolin-2-ones are the versatile synthetic intermediates for the synthesis of various functionalized molecules such as 3-alkenylated oxindoles,[33] 3-alkylated oxindoles,[34] isoindigo molecules,[35] trisindoles,[36] spiro *N*-heterocyclic oxindoles[37] and highly functionalized xanthenes.[38] 2-Oxindoles are prepared from isatins and hydrazine hydrate by employing huge equivalents of bases such as NEt_3[39] and NaOH,[40] but cumbersome workup is involved in the purification of products and also offered less percentage of yields. To avoid the limitations existed with previous reports, we planned to develop a mild and an alkali-free protocol for the synthesis of 2-oxindoles using rongalite.

The optimized reaction conditions for the synthesis of **3a**-**3t** are as follows, an oven dried round bottom flask was charged with isatin-*p*-tosylhydrazones **1a**-**1t** (1 mmol), rongalite **2** (3 mmol) and EtOH+H_2O (9:1 v/v, 3 mL). The reaction mixture was stirred under reflux for 15-90 min to produce the desired products **3a**-**3t** (Scheme 6B).



Scheme 6B. Synthesis of 2-oxindoles from isatin-*p*-tosylhydrazones

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APPENDICES

List of Publications

Published

1. Rongalite Mediated Transition Metal and Hydride-Free Chemoselective Reduction of *α*-Keto Esters and *α*-Keto Amides

   Sivaparwathi Golla, Hari Prasad Kokatla. *J. Org. Chem.* **2022**, *87*, 9915–9925.

2. Transition Metal-Free Functionalization of 2-Oxindoles via Sequential Aldol and Reductive Aldol Reactions Using Rongalite as C1 Reagent

   Sivaparwathi Golla, Swathi Jalagam, Soumya Poshala, Hari Prasad Kokatla. *Org. Biomol. Chem.* **2022**, *20*, 4926-4932.

3. Rongalite-Induced Transition-Metal and Hydride-Free Reductive Aldol Reaction: A Rapid access to 3,3´- Disubstituted Oxindoles and Its Mechanistic Studies

   Sivaparwathi Golla, Naveenkumar Anugu, Swathi Jalagam, Hari Prasad Kokatla. *Org. Biomol. Chem.* **2022**, *20*, 808-816.

4. Rongalite-Promoted Metal-Free Aerobic ipso-Hydroxylation of Arylboronic Acids Under Sunlight: DFT Mechanistic Studies

   Sivaparwathi Golla, Soumya Poshala, Ravinder Pawar, Hari Prasad Kokatla. *Tetrahedron Lett.* **2020**, *61*, 151539.

5. Iodine Catalyzed C2-H Formamidation of Quinoline *N*-Oxides using Isocyanides: A Metal-Free Approach

   Naveenkumar Anugu, Sanjeeva Thunga, **Sivaparwathi Golla**, Hari Prasad Kokatla. *Adv. Synth. Catal.* **2022**, *364*, 149-157.

6. A Facile One-Pot Synthesis of 2,2,2-Trichloroacetates Through Acid-Catalyzed Deimination and Its Applications.

   Soumya Poshala, Sanjeeva Thunga, **Sivaparwathi Golla**, Vanaparthi Satheesh, Hari Prasad Kokatla. *ChemistrySelect* **2019**, *4*, 10466-10470.

Manuscripts under preparation

1. Chemoselective Reduction of 3-Phenacylidene-2-oxindoles Using Thiourea Dioxide
   Sivaparwathi Golla, Hari Prasad Kokatla.

2. Basicities and Nucleophilicities of Rongalite and Sodium Dithionite: Application in the Synthesis of 2-Oxindoles and Diazo Compounds
   Sivaparwathi Golla, Hari Prasad Kokatla.

PAPERS PRESENTED IN INTERNATIONAL AND NATIONAL CONFERENCES

International

1. **International Conference on "Emerging Trends in Catalysis (ETC-2020)"** During 06-08, January 2020. Organized by Department of Chemistry, Vellore Institute of Technology (VIT), Vellore, Tamil Nadu.

2. **International conference on "Advances in Chemical Sciences and Technologies-2019" (ACST-2019).** During 23-25, September 2019. Organized by Department of Chemistry, National Institute of Technology. Warangal, Telangana.

3. **International conference on "Advanced Functional Materials (ICFAM-2017)**" During 18-20, December 2017. Organized by Department of Chemistry, RGUKT, Basar, Nirmal, Telangana.

National

1. **Online Faculty Development Programme on "Teaching and Learning of NMR Spectroscopy for Structure Determination"** organized by Department of Chemistry in association with Teaching Learning Centre, National Institute of Technology Warangal, during 19 – 24 February 2021.

2. **National conference on "Emerging Trends in Instrumental Methods of Chemical Analysis"** organized by Department of Chemistry, NIT-Warangal, held on 30-31 January, 2019.

3. **Teaching and Learning of "Green Chemistry: Nurturing a New Generation of Chemists"** Organized by Department of Chemistry, National Institute of Technology, Warangal, during 26th Feb-3rd March-2021.

BRIEF BIOGRAPHY OF THE AUTHOR

Miss. Golla Sivaparwathi was born in Machavaram, Guntur district of Andhra Pradesh State, India. She has completed her secondary school education (G. K. Public High School) and intermediate (Sri Vijetha Junior College) in Machavaram. After completion of her B.Sc. (Andhra Loyola College, Vijayawada), and M.Sc. (Organic Chemistry) from National Institute of Technology Warangal, she has joined the Ph.D., programme under the guidance of Dr. K. Hari Prasad (Associate Professor), Department of Chemistry, National Institute of Technology Warangal with the financial assistance from the NITW in July 2017. She has published six research articles in peer reviewed international journals and presented papers in four national/international conferences. Her research interest lies in the synthesis of bio-active molecules by employing efficient and greener methodologies.