Pyridinium Ylide Assisted Highly Stereoselective One-Pot Synthesis of *trans*-2-(4-Chlorobenzoyl)-3-aryl-spiro[cyclopropane-1,2′-inden]-1′,3′-diones and Their Antimicrobial and Nematicidal Activities

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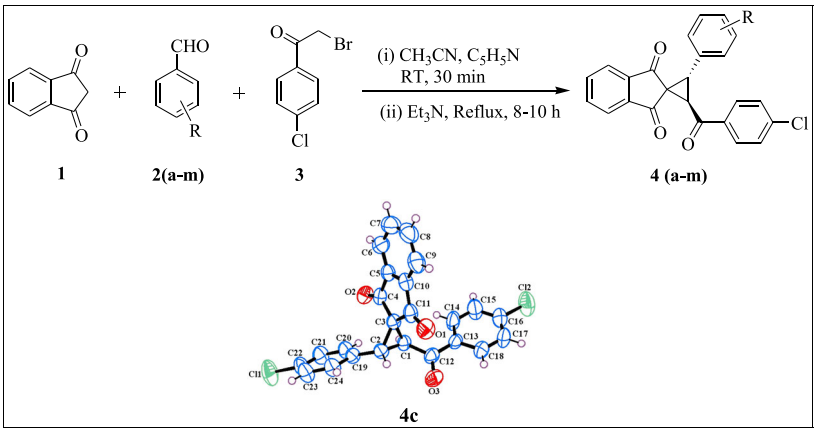

A series of highly stereoselective polysubstituted cyclopropane derivatives were synthesized *via* one-pot two-step tandem reaction starting from pyridine, 4-chloro phenacyl bromide, 1,3-indandione and aromatic aldehydes in acetonitrile using triethylamine as catalyst. Pyridinium ylide generated from 4-chloro phenacyl bromide undergo cyclopropanation with 2-arylidene-2*H*-indene-1,3-dione *in situ* afford the title compounds. Structures of all the compounds were confirmed by their analytical and spectral studies. Single crystal X-ray analysis was also performed on compound **4c** in order to determine the crystal structure. All the compounds were screened for antimicrobial and nematicidal activities. Significant antimicrobial activity was shown by the compounds derived from 2-hydroxybenzaldehyde (**4i**) and 4-(dimethylamino)benzaldehyde (**4m**) against all the tested bacterial and fungal strains. Compound **4i** has shown good activity (48% mortality) against *Meloidogyne incognita* after 48 h of exposure at 250 µg/mL concentration.

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INTRODUCTION

Nowadays, there has been a growing interest pertaining to the synthesis of bioactive compounds in the field of organic chemistry. Among them, the polysubstituted cyclopropane derivatives have attracted much attention because of their diverse pharmacological activities such as anticancer [1], antitumor [2], antibacterial, antifungal, antiviral, antimycotic, antineoplastic, antimetastatic, thyromimetic, phytotoxic, insecticidal, herbicidal and enzyme like amino acid decarboxylase, peptidase, and carboxy peptidase inhibition properties [3]. These are widely occurring in natural products [4] and used as versatile intermediates for the preparation of natural and synthetic compounds [5].

In general, cyclopropanes can be synthesized *via* Simmons–Smith reaction [6], Michael initiated ring closure of ylides with olefins [7], base-catalyzed reaction of α-halogenated compounds with olefins [8], and transition metal mediated reaction of alkene with diazo compound [9]. Among them, Michael initiated ring closure approach is highly useful for the preparation of polysubstituted cyclopropanes. Although these methods are not highly stereoselective, a mixture of *cis–trans* isomers is generally obtained. Recently, the cyclopropanation reaction of electron deficient olefins with arsonium [10], telluronium [11], sulfonium [12], ammonium [13] and pyridinium ylides [14] has been reported. Ren and co-workers [15] have reported the synthesis of *trans* spiro-cyclopropane derivatives catalyzed by triphenylarsine, which is expensive, toxic, and environmentally hazardous. Therefore, still there is a necessity to develop an efficient and highly stereoselective approach for the synthesis of spiro-cyclopropane derivatives.

As part of our research work devoted to develop an efficient methodologies toward the synthesis of biologically potent molecules [16], herein, we report an efficient and highly stereoselective synthesis of functionalized *trans* spiro-cyclopropane derivatives using triethylamine as catalyst and evaluated their antimicrobial and nematicidal activities.

RESULTS AND DISCUSSION

Highly stereoselective *trans*-2-(4-chlorobenzoyl)-3-aryl-spiro[cyclopropane-1,2′-inden]-1′,3′-diones (**4a–m**) were synthesized *via* multicomponent condensation of 1,3-indandione (**1**), aromatic aldehyde (**2a–m**), 4-chloro phenacyl bromide (**3**), and pyridine in acetonitrile using triethylamine as catalyst in acceptable yields (Scheme 1).

Recently, Wang and co-workers [17] have reported the synthesis of *trans*-2,3-dihydrofuran derivatives *via* one-pot, two-step tandem reaction involving phenacyl bromide/benzyl bromide, dimedone/4-hydroxy coumarin, aryl aldehyde, and pyridine using triethylamine as catalyst in acetonitrile. These attractive results encouraged us to examine the same type of reaction on 1,3-indandione and to evaluate their biological activity, especially antimicrobial activity. Therefore, we have carried out the reaction involving 1,3-indandione (1 mmol), 4-chlorobenzaldehyde (1 mmol), 4-chloro phenacyl bromide (1 mmol), and pyridine (3 mmol) using triethylamine (3 mmol) as catalyst in acetonitrile (Scheme 2). As per literature [17], we expected the product as *trans*-2,3-dihydrofuran **5c**, but actually the progress of the reaction monitored by TLC has confirmed the formation of a single product but not the mixture of *cis–trans* isomers as envisaged by us. X-ray crystal data, ^{1}H NMR, ^{13}C NMR, and mass spectral data confirmed the product as *trans* spiro-cyclopropane moiety **4c**. We have carried out the above reaction in different solvents such as, ethanol, acetic acid, and tetrahydrofuran, but we observed good yields only in acetonitrile. Further, we have carried out the reaction with simple and substituted aromatic aldehydes and observed the corresponding *trans* spiro cyclopropanes. The results are summarized in Table 1. The structures of all the synthesized compounds were characterized by analytical and spectral studies (IR, ^{1}H NMR, ^{13}C NMR, and mass).

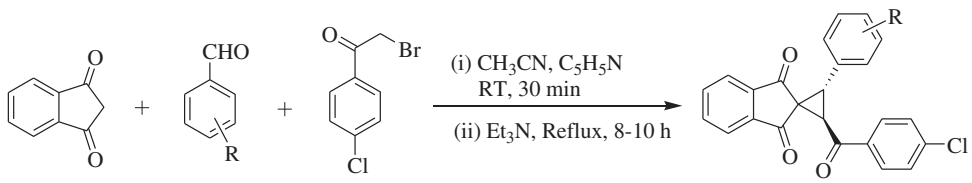
A plausible mechanism for the formation of cyclopropane derivatives has been shown in Scheme 3. Here, *N*-4-chlorophenacylpyridinium bromide **[A]** that was obtained by the reaction of 4-chloro phenacyl bromide with pyridine at ambient temperature turns into its zwitterionic form **[B]** by deprotonation from its active methylene part with the treatment of base. On the other hand, 2-arylidene-indane-1,3-dione **[C]** was formed by the Knoevenagel condensation of 1,3-indandione with arylaldehyde. Zwitterion **[B]** on reaction with 2-arylidene-indane-1,3-dione **[C]** under refluxing condition gives the desired product by the replacement of pyridine with the intramolecular substitution of the carbanion.

X-ray crystallography. Single crystal of the compound **4c** was obtained by slow evaporation of acetonitrile. Single crystal X-ray diffraction data were collected on a CCD detector based diffractometer-SMART APEX from Bruker-Nonius AXS (Karlsruhe, Germany) using Mo-Kα radiation ($\lambda = 0.71073$ Å) at 293(2) K. The crystal structure was solved by direct methods using SHELXS-97 program, and refinements of F^2 were performed using SHELXL-97 program. A summary of the crystallographic data and structure refinement details are given in Table 2. The ORTEP representation of the molecular structure of **4c** is shown in Figure 1.

EXPERIMENTAL

All the reagents were purchased from Aldrich/Merck and used without further purification. Melting points were determined in open capillaries using Stuart SMP30 apparatus and are uncorrected. The progress of the reactions as well as the purity of compounds was monitored by thin layer chromatography with F_{254} silica gel precoated sheets using hexane, ethyl acetate (8:2) as eluent; UV light and iodine vapors were used for detection. IR spectra were recorded on Perkin-Elmer 100S spectrophotometer using KBr pellet, values are expressed in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded with Bruker 400 MHz and 100 MHz spectrometer, respectively; chemical shifts are expressed in parts per million. Elemental analysis was performed on a Carlo Erba model EA1108, and the values are ±0.4% of the theoretical ones. Mass spectra were recorded on a Jeol JMSD-300 spectrometer.

Scheme 1. Multicomponent one-pot stereoselective synthesis of 2-(4-chlorobenzoyl)-3-aryl-spiro[cyclopropane-1,2′-inden]-1′,3′-diones.



1 **2(a-m)** **3** **4 (a-m)**

2a/4a : R = H; **2b/4b** : R = 2-Cl; **2c/4c**: R = 4-Cl
2d/4d : R = 4-F; **2e/4e** : R = 3-NO_2; **2f/4f**: R = 4-CH_3
2g/4g : R = 4-OCH_3; **2h/4h** : R = 3,4-$(OCH_3)_2$; **2i/4i**: R = 2-OH
2j/4j: R = 4-OH; **2k/4k**: 2-OH,3-OCH_3; **2l/4l**: 4-OH,3-OCH_3
2m/4m: 4-$N(CH_3)_2$

Scheme 2. Stereoselective synthesis of 2-(4-chlorobenzoyl)-3-(4-chlorophenyl)-spiro[cyclopropane-1,2′-inden]-1′,3′-dione.

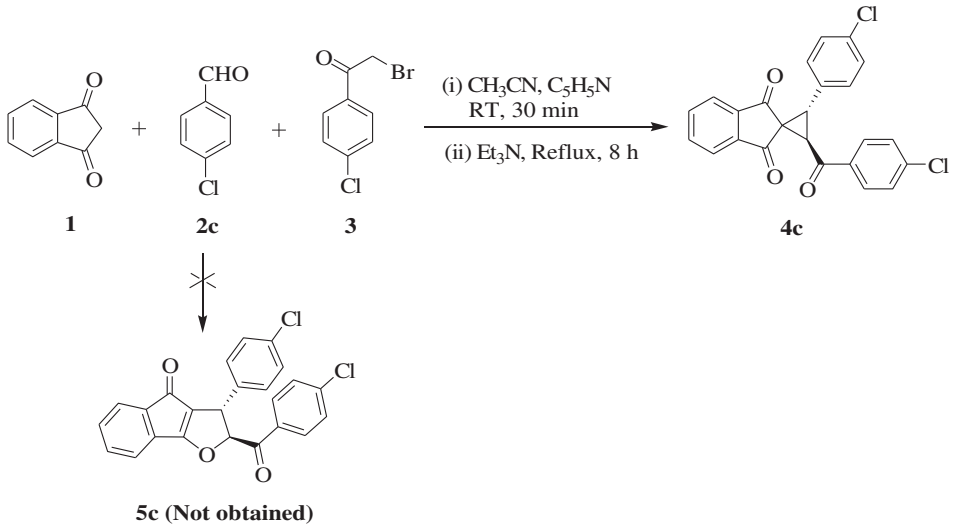


Table 1

Stereoselective synthesis of 2-(4-chlorobenzoyl)-3-aryl-spiro[cyclopropane-1,2′-inden]-1′,3′-diones.

Entry[a]	Aldehyde	Product	Time (h)	Yield[b] (%)
1	Benzaldehyde	**4a**	10	67
2	2-Chlorobenzaldehyde	**4b**	10	69
3	4-Chlorobenzaldehyde	**4c**	8	72
4	4-Fluorobenzaldehyde	**4d**	9	64
5	3-Nitrobenzaldehyde	**4e**	10	62
6	4-Methylbenzaldehyde	**4f**	10	52
7	4-Methoxybenzaldehyde	**4g**	9	62
8	3,4-Dimethoxybenzaldehyde	**4h**	9	58
9	2-Hydroxybenzaldehyde	**4i**	10	63
10	4-Hydroxybenzaldehyde	**4j**	9	55
11	2-hydroxy-3-methoxybenzaldehyde	**4k**	8	57
12	3-Methoxy-4-hydroxybenzaldehyde	**4l**	8	60
13	4-(Dimethylamino) benzaldehyde	**4m**	10	52

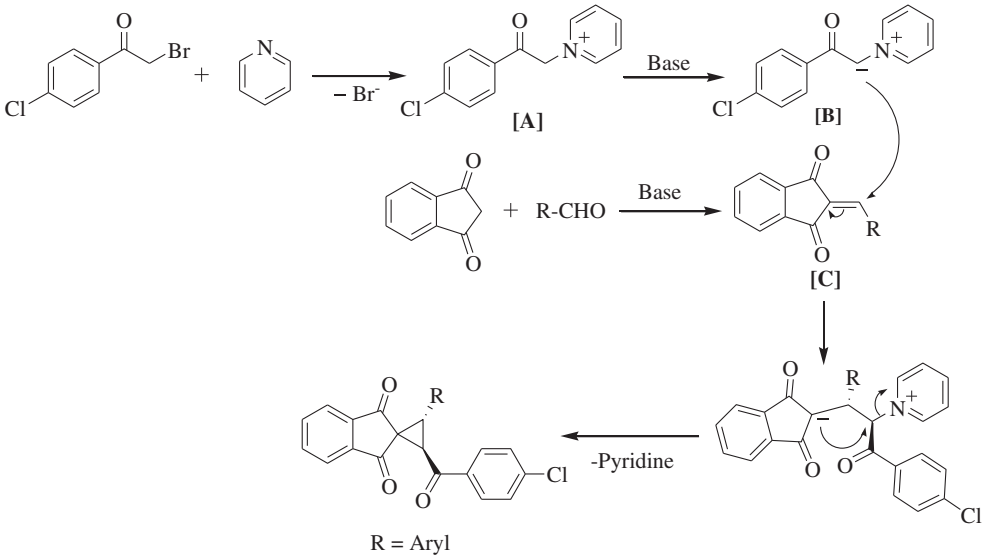
[a]Reaction conditions: 1,3-indandione (1 mmol), aryl aldehyde (1 mmol), 4-chloro phenacyl bromide (1 mmol), pyridine (3 mmol), and triethylamine (3 mmol) in 5 mL of acetonitrile and heat at refluxing temperature.
[b]Isolated yields.

General procedure for the synthesis of *trans*-2-(4-chlorobenzoyl)-3-aryl-spiro [cyclopropane-1,2′-inden]-1′,3′-diones (4a–m). In 5 mL of acetonitrile, 4-chloro phenacyl bromide (1 mmol) and pyridine (3 mmol) were added and stirred at room temperature for 30 min. A white solid, *N*-4-chlorophenacylpyridinium bromide (pyridinium ylide) is separated out; to this 1,3-indandione (1 mmol), aromatic aldehyde (1 mmol) and triethylamine (3 mmol) were added and refluxed for 8–10. After completion of the reaction shown by TLC, cooled the reaction mixture, the solid separated out was filtered and purified the compounds **4a–d** and **4f** by crystallization from ethanol and the remaining compounds over column chromatography using silica gel (230–400 mesh) with n-hexane and ethyl acetate (8:2) as eluent.

Spectral data. ***2-(4-Chlorobenzoyl)-3-phenyl-spiro[cyclopropane-1,2′-inden]-1′,3′-dione (4a).*** Colorless solid; mp 212–214°C; IR (KBr) υ_{max} (cm^{-1}): 1739, 1709, 1687, 1587, 742; ^1H NMR (400 MHz, DMSO-d_6): δ 3.97 (d, J = 8.8 Hz, 1H), 4.65 (d, J = 8.8 Hz, 1H), 7.31 (d, J = 6.8 Hz, 3H), 7.47 (t, J = 6.4 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 7.85–7.93 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 194.2, 193.0, 190.2, 141.3, 141.1, 138.6, 135.8, 134.5, 132.4, 129.8, 129.4, 129.0, 127.9, 127.7, 122.6, 122.5, 46.8, 41.3, 38.9; MS (ESI) *m/z*: 386 (M^+); *Anal*. Calcd for $C_{24}H_{15}ClO_3$: C, 74.52; H, 3.91; Found: C, 74.73; H, 3.86.

2-(4-Chlorobenzoyl)-3-(2-chlorophenyl)-spiro[cyclopropane-1,2′-inden]-1′,3′-dione (4b). Colorless solid; mp 166–167°C; IR (KBr) υ_{max} (cm^{-1}): 1735, 1709, 1688, 1590, 745; ^1H NMR (400 MHz, DMSO-d_6): δ 3.81 (d, J = 8.4 Hz, 1H), 4.61 (d,

Scheme 3. Proposed mechanism for the formation of *trans* spiro-cyclopropane derivatives.



J = 8.4 Hz, 1H), 7.38–7.43 (m, 3H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 7.2 Hz, 1H), 7.86–7.96 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 194.5, 192.8, 189.9, 141.1, 140.9, 138.8, 136.2, 136.0, 134.7, 134.4, 131.4, 131.2, 129.9, 129.2, 128.8, 127.1, 122.7, 45.7, 41.2, 38.7, MS (ESI) *m/z*: 444 (M + Na); *Anal*. Calcd for $C_{24}H_{14}Cl_2O_3$: C, 68.43; H, 3.35; Found: C, 68.59; H, 3.44.

2-(4-Chlorobenzoyl)-3-(4-chlorophenyl)-spiro[cyclopropane-1,2′-inden]-1′,3′-dione (4c). Colorless solid; mp 222–224°C; IR (KBr) υ_{max} (cm^{-1}): 1739, 1707, 1689, 1590, 743; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.14 (d, *J* = 8.8 Hz, 1H), 4.18 (d, *J* = 8.8 Hz, 1H), 7.29–7.39 (m, 6H), 7.79–7.89 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.9, 193.8, 189.1, 141.9, 141.8, 140.4, 135.5, 135.4, 134.3, 134.2, 130.6, 130.4, 129.7, 129.2, 128.6, 123.1, 122.9, 47.1, 41.2, 40.3; MS (ESI) *m/z*: 421 (M^+); *Anal*. Calcd for $C_{24}H_{14}Cl_2O_3$: C, 68.43; H, 3.35; Found: C, 68.61; H, 3.45.

2-(4-Chlorobenzoyl)-3-(4-fluorophenyl)-spiro[cyclopropane-1,2′-inden]-1′,3′-dione (4d). Colorless solid; mp 214–216°C; IR (KBr) υ_{max} (cm^{-1}): 1737, 1706, 1682, 1594, 742; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.17 (d, *J* = 8.8 Hz, 1H), 4.24 (d, *J* = 8.8 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.28–7.39 (m, 4H), 7.78–7.94 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.1, 193.9, 189.2, 159.3, 141.7, 140.4, 139.4, 135.5, 135.3, 134.5, 134.2, 130.6, 129.8, 128.8, 123.4, 122.8, 115.8, 47.3, 41.4, 40.1; MS (ESI) *m/z*: 404 (M^+); *Anal*. Calcd for $C_{24}H_{14}ClFO_3$: C, 71.21; H, 3.49; Found: C, 71.40; H, 3.38.

2-(4-Chlorobenzoyl)-3-(3-nitrophenyl)-spiro[cyclopropane-1,2′-inden]-1′,3′-dione (4e). Colorless solid; mp 239–241°C; IR (KBr) υ_{max} (cm^{-1}): 1738, 1704, 1685, 1589, 1528, 742; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.10 (d, *J* = 8.8 Hz, 1H), 4.80 (d, *J* = 8.8 Hz, 1H), 7.55–7.65 (m, 3H), 7.85–7.95 (m, 6H), 7.99 (d, *J* = 7.6 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 8.49 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 193.8, 193.4, 189.9, 147.5, 141.5, 141.4, 138.7, 136.5, 135.9, 135.8, 135.1, 134.5, 129.9, 129.4, 129.1, 124.5, 122.7, 46.3, 41.1, 38.2; MS (ESI) *m/z*: 454 (M + Na); *Anal*. Calcd for $C_{24}H_{14}ClNO_5$: C, 66.75; H, 3.27; N, 3.24; Found: C, 66.63; H, 3.42; N, 3.37.

2-(4-Chlorobenzoyl)-3-(4-methylphenyl)-spiro[cyclopropane-1,2′-inden]-1′,3′-dione (4f). Colorless solid; mp 232–234°C; IR (KBr) υ_{max} (cm^{-1}): 1741, 1705, 1689, 1592, 744; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.29 (s, 3H), 3.92 (d, *J* = 8.8 Hz, 1H), 4.62 (d, *J* = 8.8 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.84–7.93 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 194.3, 193.0, 190.4, 141.4, 141.2, 138.6, 137.1, 135.8, 134.6, 129.8, 129.4, 129.1, 128.6, 122.6, 122.5, 47.0, 41.6, 38.8, 20.7; MS (ESI) *m/z*: 400 (M^+); *Anal*. Calcd for $C_{25}H_{17}ClO_3$: C, 74.91; H, 4.27; Found: C, 74.79; H, 4.36.

2-(4-Chlorobenzoyl)-3-(4-methoxyphenyl)-spiro[cyclopropane-1,2′-inden]-1′,3′-dione (4g). Brown solid; mp 158–160°C; IR (KBr) υ_{max} (cm^{-1}): 1739, 1706, 1690, 1583, 1214, 745; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (s, 3H), 4.16 (d, *J* = 8.8 Hz, 1H), 4.56 (d, *J* = 8.8 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.86–7.95 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.3, 194.2, 190.6, 151.1, 142.1, 140.7, 136.1, 135.4, 135.3, 134.8, 133.3, 130.4, 129.5, 128.2, 123.2, 122.9, 114.6, 55.6, 47.7, 42.6, 41.0; MS (ESI) *m/z*: 416 (M^+); *Anal*. Calcd for $C_{25}H_{17}ClO_4$: C, 72.03; H, 4.11; Found: C, 72.25; H, 4.18.

2-(4-Chlorobenzoyl)-3-(3,4-dimethoxyphenyl)-spiro[cyclopropane-1,2′-inden]-1′,3′-dione (4h). Pale yellow solid; mp 203–205°C; IR (KBr) υ_{max} (cm^{-1}): 1739, 1707, 1689, 1582, 1225, 743; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (s, 3H), 3.85 (s, 3H), 4.12 (d, *J* = 8.8 Hz, 1H), 4.60 (d, *J* = 8.8 Hz, 1H), 6.84–6.98 (m, 3H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.78–7.96 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.1, 194.0, 188.7, 150.1, 146.2, 141.8, 140.2, 137.1, 135.6, 135.2, 134.1, 133.7, 130.0, 128.8, 124.5, 122.9, 120.6, 115.6, 112.2, 55.9, 55.6, 47.1, 41.4, 40.6; MS (ESI) *m/z*: 446 (M^+); *Anal*. Calcd for $C_{26}H_{19}ClO_5$: C, 69.88; H, 4.29; Found: C, 69.97; H, 4.35.

2-(4-Chlorobenzoyl)-3-(2-hydroxyphenyl)-spiro[cyclopropane-1,2′-inden]-1′,3′-dione (4i). Yellow solid; mp 197–198°C; IR (KBr) υ_{max} (cm^{-1}): 3342, 1738, 1708, 1689, 1585, 742; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.12 (d, *J* = 8.8 Hz, 1H), 4.58 (d, *J* = 8.8 Hz, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 7.19–7.44 (m, 3H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.82–7.94 (m, 6H), 9.17 (s, 1H, OH); ^{13}C NMR

Table 2

Salient crystallographic data and structure refinement parameters of compound **4c**.

	4c
Empirical formula	$C_{24}H_{14}Cl_2O_3$
Formula weight	421.25
Temperature (K)	293(2)
Crystal system, Space group	Triclinic, *P*-1
Unit cell parameters (Å,°)	
	$a = 9.1635(16)$
	$b = 9.3573(14)$
	$c = 12.6048(19)$
	$\alpha = 74.022(13)$
	$\beta = 73.425(14)$
	$\gamma = 76.641(14)$
Volume (Å^3)	982.1(3)
Z	2
D_{calc} (g/cm^3)	1.424
F (0 0 0)	432
Absorption coefficient (mm^{-1})	0.354
θ range for data collection (°)	2.88-26.37
Index ranges	$-10 \le h \le 11$
	$-11 \le k \le 11$
	$-15 \le l \le 15$
N-total	6791
N-independent	4023
N-observed	2209
Parameters	262
R_1 ($I > 2\sigma(I)$)	0.0563
wR_2 (all data)	0.1133
GOF	1.016

(100 MHz, $CDCl_3$): δ 193.9, 193.8, 190.2, 154.3, 142.2, 141.4, 135.7, 135.4, 134.6, 134.2, 133.2, 130.4, 129.6, 128.6, 126.6, 122.9, 122.6, 121.7, 116.2, 47.4, 40.7, 31.0; MS (ESI) *m/z*: 402 (M^+); *Anal*. Calcd for $C_{24}H_{15}ClO_4$: C, 71.56; H, 3.75; Found: C, 71.44; H, 3.86.

2-(4-Chlorobenzoyl)-3-(4-hydroxyphenyl)-spiro[cyclopropane-1,2′-inden]-1′,3′-dione (4j). Pale yellow solid; mp 310–312°C; IR (KBr) υ_{max} (cm^{-1}): 3345, 1739, 1705, 1692, 1586, 742; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.93 (d, *J* = 8.8 Hz, 1H), 4.60 (d, *J* = 8.8 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.82–7.96 (m, 6H), 9.19 (s 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.2, 194.1, 189.0, 154.9, 141.8, 140.5, 136.4, 135.6, 135.4, 134.1, 133.7, 130.2, 129.5, 128.3, 123.6, 122.4, 116.2, 47.3, 41.2, 40.8; MS (ESI) *m/z*: 402 (M^+); *Anal*. Calcd for $C_{24}H_{15}ClO_4$: C, 71.56; H, 3.75; Found: C, 71.42; H, 3.54.

2-(4-Chlorobenzoyl)-3-(2-hydroxy-3-methoxyphenyl)-spiro[cyclopropane-1,2′-inden]-1′,3′-dione (4k). Yellow solid; mp 180–182°C; IR (KBr) υ_{max} (cm^{-1}): 3343, 1738, 1708, 1690, 1584, 1227, 743; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.74 (s, 3H), 4.14 (d, *J* = 8.8 Hz, 1H), 4.52 (d, *J* = 8.8 Hz, 1H), 6.68–6.87 (m, 3H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.79–7.93 (m, 6H), 9.18 (s 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.3, 194.1, 189.0, 151.7, 143.5, 141.4, 140.2, 135.7, 135.1, 134.6, 134.0, 133.6, 130.1, 129.5, 123.0, 122.3, 120.9, 113.0, 112.1, 55.8, 47.9, 41.3, 31.3; MS (ESI) *m/z*: 432 (M^+); *Anal*. Calcd for $C_{25}H_{17}ClO_5$: C, 69.37; H, 3.96; Found: C, 69.54; H, 3.81.

2-(4-Chlorobenzoyl)-3-(4-hydroxy-3-methoxyphenyl)-spiro[cyclopropane-1,2′-inden]-1′,3′-dione (4l). Pale yellow solid; mp 294–296°C; IR (KBr) υ_{max} (cm^{-1}): 3347, 1739, 1704, 1689, 1586, 1232, 744; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.76 (s, 3H), 4.16 (d, *J* = 8.8 Hz, 1H), 4.55 (d, *J* = 8.8 Hz, 1H), 6.63–6.89 (m, 3H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.81–7.97 (m, 6H), 9.16 (s 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.0, 193.9, 190.3, 151.7, 142.1, 141.6, 140.4, 137.4, 135.4, 135.2, 134.3, 133.9, 130.4, 129.8, 123.1, 122.8, 120.1, 118.4, 112.6, 55.7, 47.4, 41.5, 41.1; MS (ESI) *m/z*: 432 (M^+); *Anal*. Calcd for $C_{25}H_{17}ClO_5$: C, 69.37; H, 3.96; Found: C, 69.50; H, 3.77.

2-(4-Chlorobenzoyl)-3-(4-(dimethylamino)phenyl)-spiro[cyclopropane-1,2′-inden]-1′,3′-dione (4m). Brown solid; mp 206–208°C; IR (KBr) υ_{max} (cm^{-1}): 1736, 1705, 1684, 1582, 740; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.98 (s, 6H), 3.96 (d, *J* = 8.8 Hz, 1H), 4.54 (d, *J* = 8.8 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 2H),

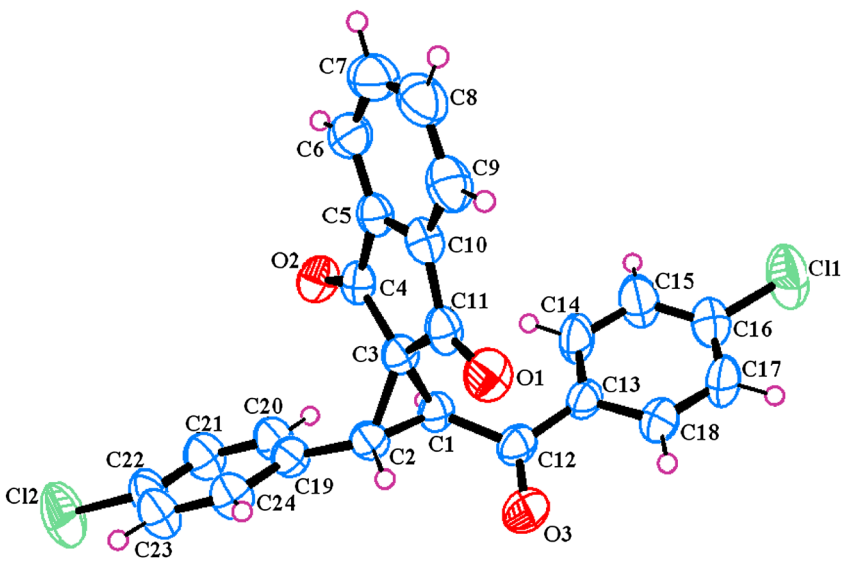


Figure 1. ORTEP representation of compound **4c**. Thermal ellipsoids are drawn at 50% probability level. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

7.29 (d, $J = 8.0$ Hz, 2H), 7.57 (d, $J = 8.4$ Hz, 2H), 7.78–7.94 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.9, 193.8, 190.2, 146.0, 141.2, 140.4, 135.7, 134.9, 134.3, 133.8, 133.3, 130.4, 129.7, 128.1, 123.2, 122.7, 114.6, 47.6, 42.2, 41.7, 41.2; MS (ESI) *m/z*: 429 (M^+); *Anal*. Calcd for $C_{26}H_{20}ClNO_3$: C, 72.64; H, 4.69; N, 3.26; Found: C, 72.57; H, 4.76; N, 3.42.

PHARMACOLOGY

Antimicrobial activity. All the newly synthesized compounds (**4a–m**) were evaluated for their *in vitro* antibacterial activity against Gram-positive bacteria (*Bacillus subtilis* and *Staphylococus aureus*), Gram-negative bacteria (*Proteus vulgaris* and *Klebsiella pneumoniae*), and antifungal activity against *Candida albicans*. The values are compared with those of standard antibiotic Kanamycin for bacteria and Clotrimazole for fungus.

Zone of inhibition. Zone of inhibition (ZOI; in mm) values for analogs (**4a–m**) and positive control drugs Kanamycin and Clotrimazole were determined against four different bacterial strains and one fungal strain by Agar disk-diffusion technique [18]. The bacterial and fungal strains were grown and maintained on Nutrient agar plates. All the compounds (100 µg) were dissolved in DMSO and transferred to each disk with the help of a micropipette, simultaneously maintained a standard Kanamycin (30 µg/disk) against bacteria and Clotrimazole (10 µg/disk) against fungus. After overnight incubation at 37°C for bacteria and 25°C for fungi, the resulting ZOIs were measured and compared with the standard drugs. Control measurements were carried out with DMSO. All the experiments were performed in triplicates, and the average zones of inhibition was recorded and depicted in Table 3.

Zone of inhibition data (Table 3) revealed that most of the tested compounds possess weak to moderate activity with variable inhibitory effects from 8 mm to 15 mm on the growth of the tested bacterial and fungal strain compared with standard drugs. Among the series **4i** and **4m** has shown moderate activity against all tested bacterial and fungal strain, it reveals that the hydroxyl group at second position and *N*,*N*-dimethylamino group at fourth position increase the activity. It was also noticed that the compound **4a** and **4b** did not show any activity against fungal strain *C. albicans* at 100 µg/disk concentration.

Minimum inhibitory concentration. The minimum inhibitory concentration (MIC) values for analogs (**4a–m**) and positive control drugs Kanamycin and Clotrimazole were also determined against four different bacterial strains and one fungal strain by broth dilution method [19]. Different concentrations (ranging from 200–0.1 µg/mL) of analogs and positive control drugs were prepared in DMSO. These diluted compounds were mixed in nutrient broth and 0.1 mL of active inoculum was added to each tube. The tubes were incubated aerobically at 37°C for bacteria and 25°C for fungi for 24 h and carefully observed for the presence of turbidity. The lowest concentration of the compound that completely inhibited bacterial or fungal growth (no turbidity) in comparison with control was taken as the MIC value.

From the MIC values (Table 4), it was noticed that compounds **4i** and **4m** have shown good activity against all the tested bacterial strains and moderate activity against

Table 3

Zone of inhibition (mm) values of compounds **4a–m** at 100 µg/disk and positive control drugs Kanamycin at 30 µg/disk, Clotrimazole at 10 µg/disk against different bacterial and fungal strains.

	Zone of inhibition in mm				
	Gram-positive bacteria		Gram-negative bacteria		Fungi
Analog	*Bacillus subtilis*	*Staphylococcus aureus*	*Proteus vulgaris*	*Klebsiella pneumoniae*	*Candida albicans*
4a	8	8	8	8	–
4b	12	12	11	11	–
4c	8	8	8	8	8
4d	11	11	12	12	11
4e	11	12	12	12	12
4f	8	8	8	8	8
4g	10	12	12	10	10
4h	10	11	11	11	09
4i	15	14	14	14	13
4j	8	8	8	8	8
4k	9	9	9	9	9
4l	9	9	10	10	9
4m	12	12	13	13	11
Kanamycin	30	32	25	23	–
Clotrimazole	–	–	–	–	25

Table 4

Minimum inhibitory concentration (MIC) values of compound **4a–m** and positive control drugs against different bacterial and fungal strains.

	Minimum inhibitory concentration (μg/mL)				
	Gram-positive bacteria		Gram-negative bacteria		Fungi
Analog	*Bacillus subtilis*	*Staphylococcus aureus*	*Proteus vulgaris*	*Klebsiella pneumoniae*	*Candida albicans*
4a	80	80	80	80	–
4b	40	40	50	50	–
4c	80	80	80	80	80
4d	50	50	45	45	50
4e	50	45	45	45	50
4f	80	80	80	80	80
4g	60	45	45	55	50
4h	60	55	55	55	55
4i	30	35	35	35	40
4j	80	80	80	80	80
4k	75	75	75	75	80
4l	80	80	75	75	80
4m	35	35	30	30	50
Kanamycin	08	10	08	11	–
Clotrimazole	–	–	–	–	10

fungal strain. Remaining all the compounds were shown moderate activity against all the tested bacterial and fungal strains, compound **4a** and **4b** were inactive against fungal strain *C. albicans*.

Nematicidal activity. ***Culture preparation.*** Fresh egg masses of *Meloidogyne incognita* were collected from stock culture maintained on tomato (*Lycopersicon esculentum*) root tissues and kept in water for egg hatching. The eggs suspension were poured on a cotton-wool filter paper and incubated at 28 ± 2°C to obtain freshly hatched juveniles (J2). Juveniles collected within 48 h and used for screening the nematicidal activity of the derived compounds.

Mortality test. All the synthesized compounds were initially dissolved in DMSO and then prepared 250, 150, and 50 μg/mL by diluting with distilled water. About 100 freshly hatched second stage juveniles were suspended in 5 mL of each diluted compound and incubated under laboratory conditions at 28 ± 2°C. Distilled water with nematode larvae was taken as control. The dead nematodes were observed under an inverted binocular microscope after an incubation of 24 and 48 h, and the percentage of mortality were calculated. Nematodes were considered dead if they did not move when probed with a fine needle [20]

From Table 5, it was observed that the compounds **4b**, **4d**, **4e**, **4g**, **4h**, **4i**, **4l**, and **4m** were shown weak to moderate activity ranging from 4–48% mortality of the nematode larvae after an exposure of 24 and 48 h. Among these

Table 5

Effect of diluted compounds on mortality of *Meloidogyne incognita* at different time intervals.

	After 24 h			After 48 h		
Analog	250 μg/mL	150 μg/mL	50 μg/mL	250 μg/mL	150 μg/mL	50 μg/mL
4a	0	0	0	0	0	0
4b	24	17	10	36	28	15
4c	0	0	0	0	0	0
4d	22	17	9	30	24	10
4e	20	16	9	29	22	10
4f	0	0	0	0	0	0
4g	20	16	9	29	22	10
4h	19	15	9	27	20	8
4i	30	25	10	48	32	18
4j	0	0	0	0	0	0
4k	0	0	0	0	0	0
4l	15	9	4	22	13	6
4m	22	16	9	34	26	13

compounds, **4i** caused maximum mortality (48%) after 48 h of exposure at 250 μg/mL concentration. The activity was higher at high concentrations and increased with time (time dependent activity). Remaining all the compounds was inactive at all the tested concentrations under 24 and 48 h intervals. There is no mortality observed in control.

CONCLUSION

We have developed a simple and efficient method for the synthesis of *trans* spiro-cyclopropane derivatives *via* multicomponent two-step tandem reaction of 1,3-indandione, aromatic aldehydes, 4-chloro phenacyl bromide, and pyridine in acetonitrile using triethylamine as catalyst. All the compounds were confirmed by spectral data and screened for antimicrobial and nematicidal activities. Compounds **4i** and **4m** were active against all the tested bacterial and fungal strains; compound **4i** has shown good activity against *M. incognita* at 250 μg/mL.

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