Sulfamic Acid-Catalyzed Multicomponent One-Pot Synthesis of Poly-Substituted Pyridines and Their Antimicrobial Activity

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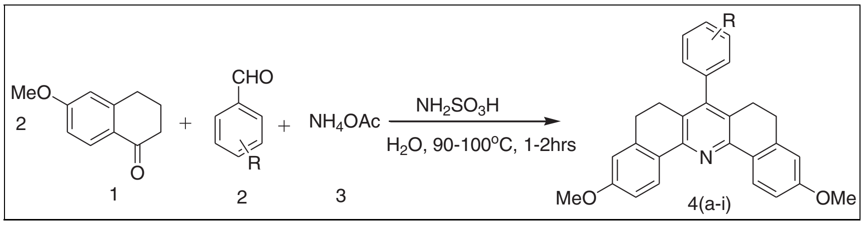

A novel series of poly-substituted pyridines (7-(substituted aryl)-3,11-dimethoxy-5,6,8,9-tetrahydrodibenzo[c,h]acridines) were synthesized via one-pot multicomponent approach using sulfamic acid as a catalyst and evaluated for their antimicrobial activity. The results indicate that the poly-substituted series (**4a–i**) showed weak to moderate antibacterial activity. However, compound (**4c**) had shown good antifungal activity against *Candida rugosa* with standard antifungal drug Amphotericin-B. Analogue (**4c**) was considered to be a lead compound for subsequent standard optimization.

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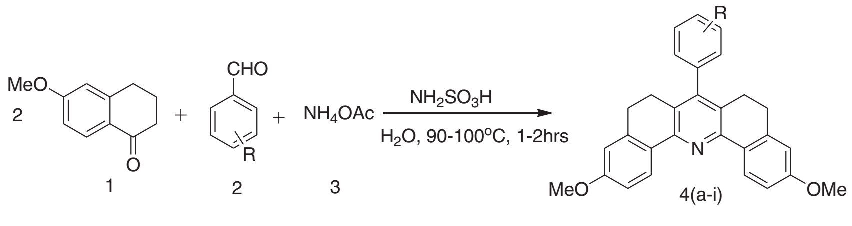
INTRODUCTION

Over a period, pyridine and its synthetic analogues are widely spread as subunit in drugs, pharmaceuticals, and natural products such as Indinavir (anti-HIV), Nexium, Ogastro (anti-ulcer), Norvasc (hypertension), Omeprazole (proton pump inhibitor) [1], and pyridine alkaloids [2]. These are also known to posses antimalarial, vasodilator, anticonvulsant, antiepileptic, anthelmintic, antibacterial, antifungal [3], antitumor [4], antiparasitic, antioxidant, topoisomerase I and II inhibitors [5], calcium antagonist activators [6,7], and agro chemicals such as fungicidal, pesticidal, and herbicidal [8] activities. Poly-substituted pyridines can be synthesized by Krohnke [9–16] and Hantzsch [17] methods, and recently several new methods have been developed containing solvent-free reactions [10,11,18], microwave irradiation [7,20], acetic acid [21], and L-proline [22] catalyzed reactions. Most of these methods suffer from one or several drawbacks such as low yield, long reaction time, tedious workup, use of toxic solvents, and expensive reagents. Moreover from the past few decades, multicomponent reactions have emerged as a powerful tool in the synthesis of complex and important biologically active molecules [17,19,23] from easily available starting materials. Therefore to overcome the aforementioned problems and fulfill the criteria, we investigated and successfully implemented the sulfamic acid (SA) as the best and cheaper catalyst (which is a common sulfur-containing amino acid with mild acidity and carries out many organic transformation under mild and user-friendly conditions) for the preparation of poly-substituted pyridines in aqueous medium and screened for antimicrobial activity (Tables 3 and 4). Among the series, compounds (**4e**) and (**4c**) have shown good antibacterial and antifungal activities against *Klebsiella pneumoniae and Candida rugosa*, respectively.

RESULTS AND DISCUSSION

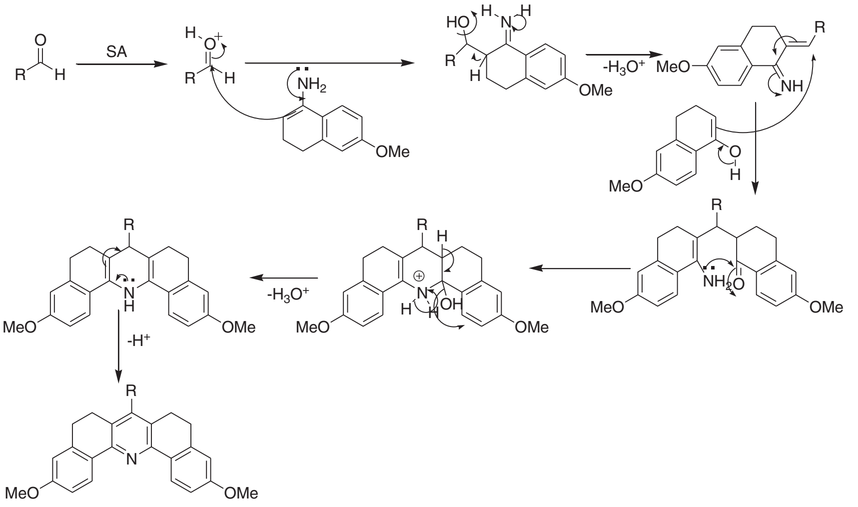
In continuation of our studies on the synthesis of biologically active heterocyclic compounds using SA as catalyst [24], herein we report a simple and efficient procedure for the synthesis of highly substituted pyridines by the condensation of 6-methoxy-1-tetralone with different aromatic aldehydes and ammonium acetate in aqueous medium in presence of SA as catalyst furnished the target compounds in excellent yields (Scheme 1). To know the optimistic conditions (temperature, amount of SA) and effect of solvent on the reaction yield, a modal reaction was performed with 6-methoxy-1-tetralone, benzaldehyde, and ammonium acetate in different solvents (MeOH, CH_3CN, DMF, and H_2O) at different temperatures, without and with variant amount (5, 10, 15, 20 mol%) of SA, and observations are as follows: at room temperature in absence of catalyst, no progress was observed; after adding 5 mol% of catalyst, only trace amount of compound was formed; as the temperature increased to 90–100°C, the yield has drastically increased from 58 to 93% depending on solvent and amount of SA; and as further increment of temperature and amount of SA, there is no appreciable change in the yields (Table 1). From these results, we deduce that 15 mol% SA in aqueous medium at 90–100°C

Scheme 1



Compound	R
4a	$-C_6H_5$
4b	$4\text{-F-}C_6H_4$
4c	$4\text{-Cl-}C_6H_4$
4d	$4\text{-}OCH_3\text{-}C_6H_4$
4e	$4\text{-}CH_3\text{-}C_6H_4$
4f	$4\text{-OH-}C_6H_4$
4g	$3\text{-}NO_2\text{-}C_6H_4$
4h	$3\text{-}OCH_3\text{-4-OH-}C_6H_3$
4i	$2\text{-OH-3-}OCH_3\text{-}C_6H_3$

Plausible Mechanism:



R = Aryl

is the optimistic condition for obtaining the excellent yield. In these optimistic conditions, we performed a reaction using different aromatic aldehydes and the results are postulated in Table 2. The catalyst was recovered by evaporating the water and washed with diethyl ether, dried, and reused after activation with only a gradual decrease in activity observed. For example, the reaction of 6-methoxy-1-tetralone, benzaldehyde, and ammonium acetate gave the corresponding highly substituted pyridine (**4a**) in 93%, 91%, and 88% yields over three cycles.

All the synthesized compounds were characterized by IR, NMR, and mass spectral data. The disappearance of IR band at 1650–1780 cm^{-1}(C=O stretching) and peak at ~186 ppm (^{13}C NMR) and the presence of IR band at 1560–1620 cm^{-1}(C=N stretching) and molecular ion peak from mass spectrum confirm the formation of the substituted pyridine moiety.

A plausible mechanism for the synthesis of highly substituted pyridine catalyzed by SA has been proposed. The aldehydic carbonyl oxygen becomes activated by the acid part of SA through intermolecular H-bonding and subsequent condensation with 6-methoxy-1-tetralone followed by dehydration and rearrangement afforded the final product.

Biological activities. All the newly synthesized compounds were tested for *in vitro* antibacterial and antifungal activities (Department of Biology, Indian Institute of Chemical Technology, Hyderabad) against *Bacillus subtilis*, *Staphylococcus aureus*, *Staphylococcus epidermidis* (Gram-

Table 1

Multicomponent reaction of 6-methoxy-1-tetralone, benzaldehyde, and ammonium acetate in different solvents at different temperature and different mol % of catalyst (SA).

Entry	Catalyst (mol%)	Solvent	Temperature (°C)	Time (h)	Yield (%)[a]
1	—	CH_3OH	RT	24	—
2	—	CH_3CN	RT	24	—
3	—	DMF	RT	24	—
4	—	H_2O	RT	24	—
5	5	CH_3OH	RT	24	Trace
6	5	CH_3CN	RT	24	Trace
7	5	DMF	RT	24	Trace
8	5	H_2O	RT	24	Trace
9	5	CH_3OH	90–100	6	58
10	5	CH_3CN	90–100	6	56
11	5	DMF	90–100	6	60
12	5	H_2O	90–100	6	65
13	10	CH_3OH	90–100	4	66
14	10	CH_3CN	90–100	4	61
15	10	DMF	90–100	4	72
16	10	H_2O	90–100	4	79
17	15	CH_3OH	90–100	2	84
18	15	CH_3CN	90–100	2	80
19	15	DMF	90–100	2	88
20	15	H_2O	90–100	2	93
21	15	H_2O	110–120	2	93
22	20	H_2O	90–100	2	93

[a] Yields refer to isolated products.

Table 2

Synthesis of highly substituted pyridine at 90–100 °C in aqueous medium using 15 mol% of catalyst (SA).

Analogue	Aldehyde	Time (min)	Yield (%)[a]
4a	Benzaldehyde	110	93
4b	4-Fluorobenzaldehyde	90	91
4c	4-Chlorobenzaldehyde	65	96
4d	4-Methoxybenzaldehyde	80	90
4e	4-Methylbenzaldehyde	85	91
4f	4-Hydroxybenzaldehyde	120	90
4g	3-Nitrobenzaldehyde	95	94
4h	3-Methoxy-4-hydroxybenzaldehyde	75	96
4i	2-hydroxy-3-methoxybenzaldehyde	80	92

[a] Yields refer to isolated products. All the compounds were characterized by spectral data (IR, NMR, and mass).

positive), *Escherichia coli*, *Pseudomonas aeruginosa*, and *K. pneumoniae* (Gram-negative) bacterial strains with respect to penicillin and streptomycin as the positive control drugs and *Aspergillus flavus*, *Saccharomyces cerevisiae*, *C. rugosa*, and *Candida albicans* fungal strains by taking Amphotericin-B as the positive control drug.

Antibacterial activity. The minimum inhibitory concentration (MIC) values for analogues and the positive control drugs penicillin and streptomycin were determined against the six bacterial strains through the use of the liquid dilution method [25,26]. Different concentrations of analogues and positive control drugs were prepared in chloroform. Inocula of the bacterial cultures were also prepared. Inoculum (0.2 mL) and sterile water (3.8 mL) were added to a series of test tubes each containing 1 mL of test solution at different concentrations. The tubes were incubated for 24 h at 37°C and carefully observed for the presence of turbidity. The minimum concentration at which no growth was observed was taken as the MIC value (Table 3).

Compound (**4e**) has shown good activity against *K. pneumoniae* Gram-negative bacteria, and the remaining compounds showed moderate activity.

Antifungal activity. Zone of inhibition (ZOI; in mm) values for analogues and positive control drug Amphotericin-B was determined against four different fungal strains by agar diffusion method. All the compounds were dissolved in chloroform. The fungal strains were

Table 3

Minimum inhibitory concentration (MIC) values for 7-(substituted aryl)-3,11-dimethoxy-5,6,8,9-tetrahydro-dibenzo[c,h]acridines (**4a–i**) and positive control drugs against different bacterial strains.

	Minimum inhibitory concentration (μg/mL)					
	Gram-positive bacteria			Gram-negative bacteria		
Analogue	*B. subtilis*	*S. aureus*	*S. epidermidis*	*E. coli*	*P. aeruginosa*	*K. pneumoniae*
4a	150	150	150	150	150	37.5
4b	150	150	150	150	150	75
4c	150	150	150	150	150	75
4d	150	150	150	150	150	37.5
4e	150	150	150	150	150	18.75
4f	150	150	150	150	150	75
4g	150	150	150	150	150	75
4h	150	150	150	150	150	37.5
4i	150	150	150	150	150	37.5
Penicillin	1.562	1.562	3.125	12.5	12.5	6.25
Streptomycin	6.25	6.25	3.125	6.25	1.562	3.125

Table 4

Zone of inhibition data for 7-(substituted aryl)-3,11-dimethoxy-5,6,8,9-tetrahydro-dibenzo[c,h]acridines (**4a–i**) against different fungal strains at 100 and 150 μg/mL concentrations.

Analogue	Zone of inhibition (in mm)							
	A. flavus		*S. cerevisiae*		*C. rugosa*		*C. albicans*	
	100 μg	150 μg	100 μg	150 μg	100 μg	150 μg	100 μg	150 μg
4a	9	12	—	—	—	—	—	—
4b	11	16	—	—	—	—	—	—
4c	11	15	—	—	15	22	—	—
4d	—	—	—	—	—	—	—	—
4e	8	11	—	—	—	—	—	—
4f	7	10	—	—	—	—	—	—
4g	—	—	—	—	—	—	—	—
4h	—	—	—	—	—	—	—	—
4i	7	11	—	—	—	—	—	—
AMP-B	25		25		22		23.5	

AMP-B, Amphotericin-B.

grown and maintained on Sabouraud glucose agar plates. The plates were incubated at 26°C for 48 h, and resulting ZOIs were measured. Antifungal screening for analogues and positive control was performed at a concentration of 100 and 150 μg/mL, and the results are illustrated in Table 4.

Compound (**4c**) has shown high ZOI against *C. rugosa* and, compounds (**4b**) and (**4c**) have shown moderate zone of inhibition against *A. flavus* fungal strain.

CONCLUSION

In conclusion, we have described an efficient, facile, and flexible multicomponent synthesis of highly substituted pyridine in aqueous medium using inexpensive SA as catalyst with excellent yields. The antimicrobial screening results reveal that electron-releasing methyl group enhanced the antibacterial activity against *K. pneumoniae* bacterial strain whereas introduction of chlorine has shown marked antifungal activity against *C. rugosa* fungal strain.

EXPERIMENTAL

The melting points were determined in open capillaries and are uncorrected. The progress of the reaction was monitored by TLC and visualized with UV light and iodine vapors. IR spectra were recorded on Thermo Nicolet Nexus 670 spectrometer (Waltham, MA) using KBr pellet, and values are expressed in cm^{-1}. The C, H, and N analysis of the compounds was performed on a Carlo Erba model EA1108 (Lakewood, NJ), NMR spectra were recorded on Bruker 300-MHz spectrometer (Billerica, MA) using TMS as an internal standard, and chemical shifts are expressed in ppm. Mass spectra were recorded on a Jeol JMSD-300 spectrometer (Tokyo, Japan).

General procedure for the synthesis of (4a–j). To a mixture of 6-methoxy-1-tetralone (2 mmol), appropriate aromatic aldehyde (1 mmol), and ammonium acetate (2 mmol) in 10 mL of distilled water, SA (15 mol %) was added and heated at 90–100°C for 1–2 h. After completion of the reaction indicated by TLC, the solid obtained was filtered, washed with water, and recrystallized from ethanol-furnished pure product with excellent yields. The recovered catalyst was washed with diethyl ether, dried, and reused for subsequent runs.

3,11-Dimethoxy-7-phenyl-5,6,8,9-tetrahydro-dibenzo[c,h] acridine (4a). A white solid, mp 162–164°C; IR (KBr) υ_{max} (cm^{-1}): 2940, 2835, 1610, 1548, 1510, 1465, 1074; ^1H NMR (300 MHz, $CDCl_3$): 2.91 (t, 4H), 3.04–3.09 (m, 4H), 3.86 (s, 6H), 6.70 (d, 1H), 6.86–6.90 (m, 2H), 7.34–7.37 (m, 5H), 7.75 (s, 1H), 8.10 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 160.0, 149.8, 146.5, 139.5, 137.8, 129.9, 128.9, 127.3, 127.2, 126.7, 112.4, 111.3,. 56.1, 55.2, 28.7, 25.8; MS(ESI), *m/z*: 420 (M + H); *Anal.* Calcd. for $C_{29}H_{25}NO_2$: C, 83.03; H, 6.01; N, 3.34; Found: C, 83.01; H, 6.04; N, 3.32.

7-(4-Fluoro-phenyl)-3,11-dimethoxy-5,6,8,9-tetrahydro-dibenzo[c,h]acridine (4b). A white solid, mp 112–114°C; IR (KBr) υ_{max} (cm^{-1}): 2945, 2838, 1608, 1492, 1055, 1020; ^1H NMR (300 MHz, $CDCl_3$): δ 2.93 (t, 4H), 3.06–3.09 (m, 4H), 3.89 (s, 6H), 6.74 (d, 1H), 6.88–7.02 (m, 2H), 7.39 (d, 4H), 7.77 (s, 1H), 8.15 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 162.2, 160.3, 149.9, 146.4, 139.6, 129.8, 128.7, 128.5, 127.2, 126.7, 115.4, 112.4, 111.2,. 56.0, 55.2, 28.6, 25.7; MS(ESI): 70 eV, *m/z*: 438 (M + H); *Anal.* Calcd. for $C_{29}H_{24}F\ NO_2$: C, 79.61; H, 5.53; N, 3.20; Found: C, 79.64; H, 5.51; N, 3.26.

7-(4-Chloro-phenyl)-3,11-dimethoxy-5,6,8,9-tetrahydro-dibenzo[c,h]acridine (4c). White crystals, mp 121–123°C; IR (KBr) υ_{max} (cm^{-1}): 2932, 2840, 1595, 1458, 1084, 835; ^1H NMR (300 MHz, $CDCl_3$): δ 2.92 (t, 4H), 3.05–3.09 (m, 4H), 3.87 (s, 6H), 6.71 (d, 1H), 6.87–6.90 (m, 2H), 7.37 (d, 4H), 7.76 (s, 1H), 8.12 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 160.2, 149.7, 146.6, 139.7, 135.7, 134.4, 129.8, 129.1, 128.5, 127.2, 126.7, 112.3, 111.3,. 56.5, 55.3, 28.8, 25.8; MS(ESI), 70 eV, *m/z*: 454 (M + H); *Anal.* Calcd. for $C_{29}H_{24}Cl\ NO_2$: C, 76.73; H, 5.33; N, 3.09; Found: C, 76.75; H, 5.30; N, 3.11.

7-(4-Methoxy-phenyl)-3,11-dimethoxy-5,6,8,9-tetrahydro-dibenzo[c,h]acridine (4d). A white solid, mp 196–198°C; IR (KBr) υ_{max} (cm^{-1}): 2936, 2842, 1607, 1550, 1508, 1465, 1062; ^1H NMR (300 MHz, $CDCl_3$): δ 2.90 (t, 4H), 3.05–3.08 (m, 4H), 3.75 (s, 3H), 3.82 (s, 6H), 6.70 (d, 1H), 6.82–6.90 (m, 2H), 7.36 (d, 4H), 7.74 (s, 1H), 8.11 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 161.0, 159.9, 149.8, 146.5, 139.6, 129.9, 129.7, 128.3, 127.2, 126.7, 114.6, 112.5, 111.2,. 56.2, 55.3, 28.8, 25.6; MS(ESI), 70 eV, *m/z*: 450 (M + H); *Anal.* Calcd. for $C_{30}H_{27}NO_3$: C, 80.15; H, 6.05; N, 3.12; Found: C, 80.12; H, 6.08; N, 3.15.

7-(4-Methyl-phenyl)-3,11-dimethoxy-5,6,8,9-tetrahydro-dibenzo[c,h]acridine (4e). A white solid, mp 140–142°C; IR (KBr) υ_{max} (cm^{-1}): 2951, 2846, 1615, 1548, 1508, 1455, 1075; ^1H NMR (300 MHz, $CDCl_3$): δ2.37 (s, 3H), 2.91 (t, 4H), 3.04–3.08 (m, 4H), 3.86 (s, 6H), 6.72 (d, 1H), 6.87–6.91 (m, 2H), 7.35 (d, 4H), 7.75 (s, 1H), 8.10 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 160.2, 149.9, 146.5, 139.5, 138.7, 134.6, 129.8, 129.4, 127.3, 127.2, 126.7, 112.4, 111.1,. 56.0, 55.2, 28.6, 26.3, 25.7; MS(ESI), 70 eV, *m/z*: 434 (M + H); *Anal.* Calcd. for $C_{30}H_{27}NO_2$: C, 83.11; H, 6.28; N, 3.23; Found: C, 83.15; H, 6.26; N, 3.20.

4-(3,11-Dimethoxy-5,6,8,9-tetrahydro-dibenzo[c,h]acridin-7-yl)-phenol (4f). A white solid, mp 208–210°C; IR (KBr) υ_{max} (cm^{-1}): 3390, 2954, 2838, 1611, 1549, 1518, 1452,1133; ^1H NMR (300 MHz, $CDCl_3$): δ 2.90 (t, 4H), 3.04–3.09 (m, 4H), 3.88 (s, 6H), 6.72 (d, 1H), 6.88–6.92 (m, 2H), 7.39 (d, 4H), 7.79 (s, 1H), 8.13 (d, 2H), 9.15 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 160.1, 158.9, 149.7, 146.5, 139.5, 129.9, 130.5, 128.6, 127.2, 126.7, 115.8, 112.4, 111.1,. 56.0, 55.2, 28.6, 25.7; MS(ESI), 70 eV, *m/z*: 436 (M + H); *Anal.* Calcd. for $C_{29}H_{25}NO_3$: C, 79.98; H, 5.79; N, 3.22; Found: C, 79.94; H, 5.81; N, 3.21.

7-(3-Nitro-phenyl)-3,11-dimethoxy-5,6,8,9-tetrahydro-dibenzo[c,h]acridine (4g). Pale yellow solid, mp 138–140°C; IR (KBr) υ_{max} (cm^{-1}): 2942, 2836, 1612, 1552, 1516, 1465, 1057; ^1H NMR (300 MHz, $CDCl_3$): δ 2.98 (t, 4H), 3.06–3.11 (m, 4H), 3.89 (s, 6H), 6.75 (d, 1H), 6.89–6.98 (m, 2H), 7.34–7.39 (m, 4H), 7.78 (s, 1H), 8.15 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 160.0, 149.9, 148.6, 146.4, 139.6, 138.7, 133.3, 130.0, 129.9, 127.2, 126.7, 121.9, 121.2, 112.4, 111.2,. 56.1, 55.1, 28.7, 25.6; MS(ESI), 70 eV, *m/z*: 465 (M + H); *Anal.* Calcd. for $C_{29}H_{24}N_2O_4$: C, 74.98; H, 5.21; N, 6.03; Found: C, 74.95; H, 5.23; N, 6.06.

4-(3,11-Dimethoxy-5,6,8,9-tetrahydro-dibenzo[c,h]acridin-7-yl)-2-methoxy-phenol 4(h). White crystals, mp 202–204°C; IR (KBr) υ_{max} (cm^{-1}): 3384, 2940, 2837, 1607, 1548, 1508, 1459, 1157; ^1H NMR (300 MHz, $CDCl_3$): δ 2.58–2.64 (m, 4H), 2.77 (t, 4H), 3.76 (s, 3H), 3.80 (s, 6H), 6.64–6.66 (m, 1H), 6.80–6.96 (m, 6H), 8.31 (d, 2H), 9.17 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 160.0, 149.9, 147.1, 146.5, 144.9, 139.5, 129.9, 128.5, 127.2, 126.7, 121.6, 114.4, 112.5, 112.4, 111.1,. 56.0, 55.2, 28.6, 25.7; MS(ESI), 70 eV, *m/z*: 466 (M + H); *Anal.* Calcd. for $C_{30}H_{27}NO_4$: C, 77.40; H, 5.85; N, 3.01; Found: C, 77.38; H, 5.88; N, 3.04.

2-(3,11-Dimethoxy-5,6,8,9-tetrahydro-dibenzo[c,h]acridin-7-yl)-6-methoxy-phenol (4i). A white solid, mp 254–256°C; IR (KBr) υ_{max} (cm^{-1}): 3385, 2945, 2836, 1618, 1549, 1512, 1463, 1153; ^1H NMR (300 MHz, $CDCl_3$): δ 2.58–2.65 (m, 4H), 2.79 (t, 4H), 3.76 (s, 3H), 3.81 (s, 6H), 6.64–6.67 (m, 1H), 6.82–6.98 (m, 6H), 8.35 (d, 2H), 9.15 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 160.3, 151.7, 149.8, 146.5, 142.1, 139.5, 129.8, 129.5, 127.3, 126.7, 122.9, 121.1, 116.0, 112.4, 111.1,. 56.1, 55.6, 55.2, 28.5, 25.6; MS(ESI), 70 eV, *m/z*: 466 (M + H); *Anal.* Calcd. for $C_{30}H_{27}NO_4$: C, 77.40; H, 5.85; N, 3.01; Found: C, 77.38; H, 5.88; N, 3.02.

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