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L-proline catalyzed an efficient multicomponent one-pot synthesis of poly substituted pyridines

B. Janardhan[1], V. Ravibabu[1], Peter. A. Crooks [2] and B. Rajitha[1*]

[1]*Department of Chemistry, National Institute of Technology, Warangal, AP, India*

[2]*Department of Pharmaceutical Sciences, College of Pharmacy, University of Arkansas for Medical Sciences, Little Rock, AR 72205 USA*

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Abstract: A series of poly substituted pyridines (3,11-disubstituted-7-aryl-5,6,8,9-tetrahydro-dibenzo[*c*,*h*]acridines) were synthesized by the multicomponent condensation of 6-substituted-1-tetralone, aromatic aldehydes and ammonium acetate in ethanol using L-proline as an efficient organocatalyst. This methodology is mild, efficient, high yielding and the catalyst is inexpensive, easily recovered from the reaction mixture and reused for five times without losing its activity.

Keywords: Multicomponent condensation; poly substituted pyridines; L-proline; 6-substituted-1-tetralone.

1. Introduction

In recent years, multicomponent reactions (MCRs), involving three or more reactants in one-pot have been used to synthesize structurally diverse bioactive heterocyclic compounds.[1,2] The advantages of multicomponent reactions are high atom-economy, structural diversity, operational simplicity and lack of waste products in a multi-step reaction.

5,6,8,9-tetrahydro-dibenzo[*c*,*h*]acridines are comes under a class of pyridines. Pyridine and its derivatives are an important class of heterocyclic compounds, which are widely spread as subunit in drugs, pharmaceuticals and natural products.[3] They are also known to posses various biological and therapeutic properties such as antimicrobial,[4,5] antimalarial,[5] antiviral,[6] anti-inflammatory,[7] anti-Alzheimer's,[8] anticancer,[9] antitumor,[10-13] topoisomerase I and II inhibitors,[14,15] vasodilator, anticonvulsant, antiepileptic, anthelmintic, antiparasitic, antioxidant, calcium antagonist activators[16,17] and agro chemicals such as fungicidal, pesticidal and herbicidal[18] activities. Poly substituted pyridines can be synthesized by Krohnke[19-22] and Hantzsch[23] methods, recently several new methods have developed containing solvent-free reactions,[24] microwave irradiation,[25] acetic acid[26] catalyzed reactions. Mukhopadhyay and his coworkers[27] have reported the synthesis of poly substituted pyridines at room temperature using L-proline in ethanol. We also tried the same reaction using 1-

* Corresponding author: E-Mail: rajitabhargavi@yahoo.com

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tetralone as starting material, unfortunately we got maximum yield of the product at 50 ^{o}C not at room temperature. In this paper we descried the synthesis of 5,6,8,9-tetrahydro-dibenzo[*c,h*]acridines in ethanol at 50 ^{o}C employing L-proline as an efficient organocatalyst.

2. Results and Discussion

In continuation of our synthesis towards biologically important heterocyclic compounds using novel catalyst,[28,29] herein we report a simple, mild and efficient procedure for the synthesis of highly substituted pyridines by the one-pot three component condensation of 6-substituted-1-tetralone with different aryl aldehydes and ammonium acetate in excellent yields employing L-proline as an organocatalyst.

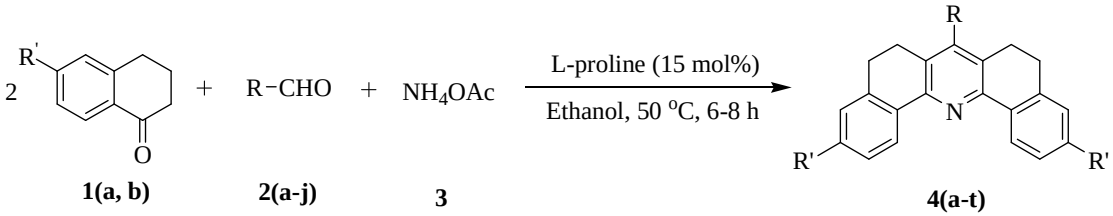
In order to set the optimistic conditions, reaction of 1-tetralone with benzaldehyde and ammonium acetate was performed as a modal reaction at different temperatures in various solvent (EtOH, CH_3CN, CH_3COOH and H_2O) without and with variant amount of catalyst (10, 15, 20 mol%) (Table-1). At room temperature without catalyst reaction dose not proceeds, but with 10 mol% of catalyst reaction slightly proceeds and observed in the range of 10-36% of product yield in different solvents. Maximum yield (36%) was observed in ethanol. As the amount of catalyst increased to 15 mol% the yield increased from 36% to 52%, further increment in amount of catalyst has not shown any affect on product yield and reaction time. As the temperature increased to 50 ^{o}C, yield of the product has enormously increased from 52% to 94%. Reaction time and product yield has not affected as the temperature further increased.

Table 1. Effect of catalyst (L-proline) concentration, type of solvent and temperature on multicomponent reaction of 1-tetralone, benzaldehyde and ammonium acetate.

Entry	Catalyst (mol%)	Solvent	Temperature	Time (h)	Yield(%)[a]
1	-	EtOH	RT	24	-
2	-	CH_3CN	RT	24	-
3	-	CH_3COOH	RT	24	-
4	-	H_2O	RT	24	-
5	10	EtOH	RT	12	36
6	10	CH_3CN	RT	12	21
7	10	CH_3COOH	RT	12	17
8	10	H_2O	RT	12	32
9	15	EtOH	RT	12	52
10	20	EtOH	RT	12	52
11	10	EtOH	50 ^{o}C	6	83
12	15	EtOH	50 ^{o}C	6	94
13	20	EtOH	50 ^{o}C	6	94
14	10	EtOH	Reflux	6	85
15	15	EtOH	Reflux	6	93
16	20	EtOH	Reflux	6	93

[a]Yields refer to pure isolated product 4a.

At these optimistic conditions (15 mol% of L-proline in ethanol at 50 ^{o}C), various substituted pyridines has synthesized (Scheme-1) in excellent yields, the results were summarized in Table-2. After completion of the reaction the catalyst was recovered and reused for subsequent reactions without losing its activity. For example, the reaction of 1-tetralone, benzaldehyde and ammonium acetate gave the corresponding highly substituted pyridine (4a) in 94%, 94%, 93%, 91% and 90% yields over five cycles.



1(a, b) **2(a-j)** **3** **4(a-t)**

Scheme 1. Synthesis of highly substituted pyridines catalyzed by L-proline

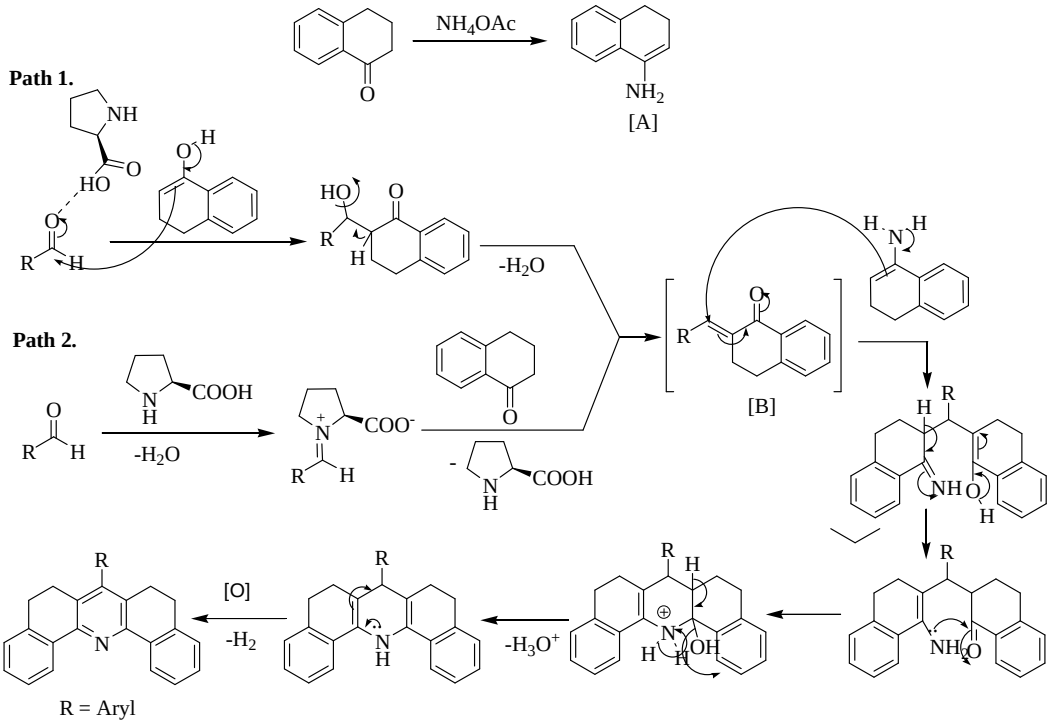
Table 2. L-proline (15 mol%) catalyzed synthesis of highly substituted pyridines in absolute ethanol at 50 °C.

Analog	R'	R	Time (h)	Yield[b] (%)
4a	H	Benzaldehyde	6	94
4b	H	4-Fluorobenzaldehyde	6	91
4c	H	4-Chlorobenzaldehyde	6	96
4d	H	4-Methylbenzaldehyde	6	90
4e	H	4-Methoxybenzaldehyde	6	92
4f	H	3,4-Dimethoxybenzaldehyde	6	89
4g	H	4-Hydroxybenzaldehyde	7	88
4h	H	3-Nitrobenzaldehyde	8	90
4i	H	3-Methoxy-4-hydroxybenzaldehyde	7	92
4j	H	2-hydroxy-3-methoxybenzaldehyde	7	90
4k	OCH_3	Benzaldehyde	8	93
4l	OCH_3	4-Fluorobenzaldehyde	8	92
4m	OCH_3	4-Chlorobenzaldehyde	6	96
4n	OCH_3	4-Methylbenzaldehyde	7	94
4o	OCH_3	4-Methoxybenzaldehyde	8	91
4p	OCH_3	3,4-Dimethoxybenzaldehyde	8	90
4q	OCH_3	4-Hydroxybenzaldehyde	8	88
4r	OCH_3	3-Nitrobenzaldehyde	8	89
4s	OCH_3	3-Methoxy-4-hydroxybenzaldehyde	7	90
4t	OCH_3	2-hydroxy-3-methoxybenzaldehyde	7	88

[b] Yields refer to isolated products.

The structures of all the synthesized compounds were confirmed on the basis of their analytical and spectroscopic data. The disappearance of IR band at 1650-1780 cm^{-1} (C=O stretching) and peak at ~186 ppm (^{13}C NMR), presence of IR band at 1560-1620 cm^{-1} (C=N stretching) and molecular ion peak from mass spectrum confirm the formation of the pyridine moiety.

A plausible mechanism for the synthesis of highly substituted pyridine catalyzed by L-proline has been proposed (Scheme-2) in which the reaction proceeds in two different pathways. In path 1, the aldehydic carbonyl oxygen gets activated by the acid part of L-proline through intermolecular H-bonding and subsequent condensation with 1-tetralone gives the intermediate (chalcone) B. Path 2 gives the same intermediate B via iminium catalysis which condenses with 3,4-dihydronaphthalen-1-amine followed by cyclisation, dehydration and rearmament afforded the final product.



Scheme 2. Plausible Mechanism for the formation of highly substituted pyridines catalyzed by L-proline.

3. Conclusion

In conclusion, we have developed an efficient, facile and flexible multicomponent synthesis of poly substituted pyridines (5,6,8,9-tetrahydro-dibenzo[*c*,*h*]acridines) in absolute ethanol using inexpensive L-proline as an efficient organocatalyst with excellent yields. The catalyst can be easily recovered from the reaction mixture and reused over five cycles without losing its activity.

4. Experimental

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 vapours. IR spectra were recorded on Thermo Nicolet Nexus 670 spectrometer using KBr pellets. The C, H and N analysis of the compounds were done on a Carlo Erba modal EA1108; ^{1}H NMR and ^{13}C NMR spectra were obtained at 300 MHz and 75 MHz, respectively, on a Bruker spectrometer using TMS as an internal standard. Mass spectra were recorded on a Jeol JMSD-300 spectrometer.

4.1. General Procedure for the synthesis of highly substituted pyridines 4(a-t)

L-proline (15 mol%) was added to a mixture of 1-tetralone/6-methoxy-1-tetralone (2 mmol), aryl aldehyde (1 mmol) and ammonium acetate (2 mmol) in 3 mL of absolute ethanol. Reaction mixture was stirred at 50 ^{o}C for an appropriate time as indicated in Table-2. After completion of the reaction (monitored by TLC), 5 mL of water was added and the solid separated out was filtered (if solid not separates out extract with diethyl ether, dried over anhydrous sodium sulfate and concentrate under reduced pressure), washed with water, dried and recrystallized with ethanol. Aqueous layer containing catalyst was evaporated and reused for subsequent reactions.

4.2. Characterization data

7-Phenyl-5,6,8,9-tetrahydro-dibenzo[c,h]acridine 4(a): White solid, mp 104-105 ^{o}C; IR (cm^{-1}): 1607 (C=N stretching); ^{1}H NMR (300 MHz, $CDCl_3$): 2.92 (t, *J* = 5.4 Hz, 4H), 3.02-3.06 (m, 4H), 7.24-7.67 (m, 7H), 7.72 (d, *J* = 6.9 Hz, 2H), 7.95 (d, *J* = 6.9 Hz, 2H), 8.19 (d, *J* = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 150.2, 146.1, 137.7, 134.8, 134.6, 129.3, 129.1, 128.4, 127.7, 127.4, 127.3, 126.9, 124.5, 28.5, 26.3; MS(ESI): 70ev, *m/z*: 360 (M+H); Anal. Calcd. For $C_{27}H_{21}N$: C, 90.21; H, 5.89; N, 3.90; Found: C, 90.52; H, 5.64; N, 4.07.

7-(4-Fluoro-phenyl)-5,6,8,9-tetrahydro-dibenzo[c,h]acridine 4(b): White solid, mp 174-175 ^{o}C; IR (cm^{-1}): 1610 (C=N stretching), 1015 (C-F stretching); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.90 (t, *J* = 4.8 Hz, 4H), 3.06-3.10 (m, 4H), 6.86 (d, *J* = 6.6 Hz, 2H), 7.02-7.54 (m, 6H), 7.77 (d, *J* = 6.6 Hz, 2H), 8.15 (d, *J* = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): 163.2, 149.4, 147.6, 137.9, 134.6, 130.6, 129.2, 128.9, 128.3, 127.7, 126.4, 124.5, 114.6, 29.1, 26.7; MS(ESI): 70ev, *m/z*: 378 (M+H); Anal. Calcd. For $C_{27}H_{20}F$ N: C, 85.92; H, 5.34; N, 3.71; Found: C, 86.34; H, 5.73; N, 3.48.

7-(4-Chloro-phenyl)-5,6,8,9-tetrahydro-dibenzo[c,h]acridine 4(c): White solid, mp 124-126 ^{o}C; IR (cm^{-1}): 1596 (C=N stretching), 847 (C-Cl stretching); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.58 (t, *J* = 4.8 Hz, 2H), 2.81 (t, *J* = 5.1 Hz, 2H), 2.94-3.06 (m, 4H), 7.26-7.68 (m, 8H), 7.96 (d, *J* = 6.3 Hz, 2H), 8.43 (d, *J* = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): 152.0, 148.2, 138.4, 135.7, 134.6, 134.1, 130.2, 128.7, 128.4, 127.8, 127.4, 126.6, 124.5, 28.2, 25.7; MS(ESI), 70ev, *m/z*: 394 (M+H); Anal. Calcd. For $C_{27}H_{20}Cl$ N: C, 82.33; H, 5.12; N, 3.56; Found: C, 82.61; H, 5.44; N, 3.15.

7-p-Tolyl-5,6,8,9-tetrahydro-dibenzo[c,h]acridine 4(d): Pale yellow solid, mp 136-138 ^{o}C; IR (cm^{-1}): 1612 (C=N stretching); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.35 (s, 3H), 2.90 (t, *J* = 5.4 Hz, 4H), 3.11-3.24 (m, 4H), 6.93 (d, *J* = 6.3 Hz, 2H), 7.18-7.64 (m, 6H), 7.75 (d, *J* = 6.3 Hz, 2H), 8.07 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): 150.0, 147.9, 138.7, 137.4, 134.8, 133.0, 129.3, 128.4, 127.7, 127.3, 127.2, 126.6, 124.5, 29.4, 27.1, 25.6; MS(ESI), 70ev, *m/z*: 374 (M+H); Anal. Calcd. For $C_{28}H_{23}N$: C, 90.04; H, 6.21; N, 3.75; Found: C, 90.38; H, 6.52; N, 3.41.

7-(4-Methoxy-phenyl)-5,6,8,9-tetrahydro-dibenzo[c,h]acridine 4(e): Pale yellow solid, mp 147-148 ^{o}C; IR (cm^{-1}): 1607 (C=N stretching), 1155 (C-O-C stretching); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.65-2.82 (m, 4H), 2.94 (t, *J* = 4.8 Hz, 2H), 3.14 (t, *J* = 4.2 Hz, 2H), 3.84 (s, 3H), 6.94 (d, *J* = 6.3 Hz, 2H), 7.23-7.47 (m, 6H), 7.84 (d, *J* = 6.3 Hz, 2H), 8.11 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 161.0, 150.1, 147.8, 138.9, 135.3, 130.0, 128.8, 124.5, 128.3, 127.5, 126.5, 124.4, 112.6, 55.4, 28.0, 26.2; MS(ESI), 70ev, *m/z*: 390 (M+H); Anal. Calcd. For $C_{28}H_{23}NO$: C, 86.34; H, 5.95; N, 3.60; Found: C, 86.12; H, 6.27; N, 3.35.

7-(3,4-Dimethoxy-phenyl)-5,6,8,9-tetrahydro-dibenzo[c,h]acridine 4(f): Gray solid, mp 171-172 ^{o}C; IR (cm^{-1}): 1598 (C=N stretching), 1186 (C-O-C stretching); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.86 (t, *J* = 4.8 Hz, 2H), 2.98 (t, *J* = 4.5 Hz, 2H), 3.10-3.19 (m, 4H), 3.78 (s, 6H), 6.83-6.92 (m, 3H), 7.35-7.54 (m, 4H), 7.74 (d, *J* = 6.6 Hz, 2H), 8.14 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): 150.1, 149.9, 149.0, 147.5, 138.3, 134.8, 129.0, 128.7, 128.3, 127.7, 126.5, 124.6, 120.6, 113.8, 112.4, 56.2, 55.8, 27.1, 26.6; MS(ESI), 70ev, *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, 83.24; H, 6.39; N, 3.16.

4-(5,6,8,9-Tetrahydro-dibenzo[c,h]acridin-7-yl)-phenol 4(g): Gray solid, mp 120-123 ^{o}C; IR (cm^{-1}): 3385 (O-H stretching), 1610 (C=N stretching); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.99 (t, *J* = 5.4 Hz, 4H), 3.12-3.19 (m, 4H), 6.82 (d, *J* = 6.6 Hz, 2H), 6.92-7.13 (m, 4H), 7.42 (d, *J* = 6.6 Hz, 2H), 7.80 (d, *J* = 6.3 Hz, 2H), 8.12 (d, *J* = 6.0 Hz, 2H), 9.17 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): 158.8, 150.2, 148.4, 138.5, 135.5, 130.7, 128.7, 128.4, 127.6, 127.3, 126.4, 125.2, 114.4, 27.5, 25.4; MS(ESI), 70ev, *m/z*: 376 (M+H); Anal. Calcd. For $C_{27}H_{21}NO$: C, 86.37; H, 5.64; N, 3.73; Found: C, 86.75; H, 5.90; N, 3.56.

7-(3-Nitro-phenyl)-5,6,8,9-tetrahydro-dibenzo[c,h]acridine 4(h): Brown solid, mp 174-176 ^{o}C; IR (cm^{-1}): 1612 (C=N stretching), 1526 (N=O stretching); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.98 (t, *J* = 5.4 Hz, 4H), 3.02-3.09 (m, 4H), 7.04-7.41 (m, 6H), 7.78 (m, 2H), 7.94 (d, *J* = 6.3 Hz, 1H), 8.11 (d, *J* = 6.0 Hz, 2H), 8.38 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 150.3, 148.2, 147.5, 137.7, 135.9, 134.7, 133.4, 129.1, 128.2, 127.4, 126.7, 124.5, 122.2, 121.4, 30.6, 28.3; MS(ESI), 70ev, *m/z*: 405 (M+H); Anal. Calcd. For $C_{27}H_{20}N_2O_2$: C, 80.18; H, 4.98; N, 6.93; Found: C, 80.37; H, 5.25; N, 6.69.

2-Methoxy-4-(5,6,8,9-tetrahydro-dibenzo[c,h]acridin-7-yl)-phenol 4(i): White solid, mp 280-281 ^{o}C; IR (cm^{-1}): 3386 (O-H stretching), 1604 (C=N stretching), 1252 (C-O-C stretching); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.67-2.71 (m, 4H), 2.83 (t, *J* = 5.4 Hz, 4H), 3.88 (s, 3H), 6.67-6.72 (m, 2H), 7.03 (d, *J* = 6.0 Hz, 1H), 7.19-7.41 (m, 6H), 8.56 (d, *J* = 5.7 Hz, 2H), 9.17 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): 149.1, 147.6, 147.5, 146.0, 137.6, 134.7, 129.1, 128.6, 127.5, 126.7, 124.6, 121.0, 115.4, 112.8, 55.7, 27.2, 25.2; MS(ESI), 70ev, *m/z*: 406 (M+H); Anal. Calcd. For $C_{28}H_{23}NO_2$: C, 82.94; H, 5.72; N, 3.45; Found: C, 82.67; H, 5.98; N, 3.14.

2-Methoxy-6-(5,6,8,9-tetrahydro-dibenzo[c,h]acridin-7-yl)-phenol 4(j): Pale yellow solid, mp 199-202 ^{o}C; IR (cm^{-1}): 3383 (O-H stretching), 1618 (C=N stretching), 1246 (C-O-C stretching); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.62-2.68 (m, 4H), 2.83 (t, *J* = 5.4 Hz, 4H), 3.75 (s, 3H), 6.73-6.81 (m, 3H), 6.92-7.18 (m, 6H), 8.37 (d, *J* = 6.0 Hz, 2H), 9.16 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): 149.9, 147.6, 147.3, 142.4, 138.6, 134.8, 129.5, 129.1, 128.4, 127.2, 126.7, 125.8, 121.0, 116.0, 115.1, 56.8, 28.6, 25.4; MS(ESI), 70ev, *m/z*: 406 (M+H); Anal. Calcd. For $C_{28}H_{23}NO$: C, 82.94; H, 5.72; N, 3.45; Found: C, 83.15; H, 5.99; N, 3.12.

3,11-Dimethoxy-7-phenyl-5,6,8,9-tetrahydro-dibenzo[c,h]acridine 4(k): A white solid, mp 162-164 ^{o}C; IR (cm^{-1}): 1610 (C=N stretching), 1074 (C-O-C stretching); ^{1}H NMR (300 MHz, $CDCl_3$): 2.91 (t, *J* = 4.8 Hz, 4H), 3.04-3.09 (m, 4H), 3.86 (s, 6H), 6.70 (d, *J* = 6.0 Hz, 1H), 6.86-6.90 (m, 2H), 7.34-7.37 (m, 5H), 7.75(s, 1H), 8.10 (d, *J* = 6.3 Hz, 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, 55.2, 28.7, 25.8; MS(ESI): 70ev, *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 4(l): A white solid, mp 112-114 ^{o}C; IR (cm^{-1}): 1608 (C=N stretching), 1055 (C-O-C stretching) , 1020 (C-F stretching); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.93 (t, *J* = 4.8 Hz, 4H), 3.06-3.09 (m, 4H), 3.89 (s, 6H), 6.74 (d, *J* = 6.0 Hz, 1H), 6.88-7.02 (m, 2H), 7.39 (d, *J* = 6.3 Hz, 4H), 7.77 (s, 1H), 8.15 (d, *J* = 6.6 Hz, 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, 55.2, 28.6, 25.7; MS(ESI):

70ev, *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 4(m): White crystals, mp 121-123 ^oC; IR (cm^{-1}): 1595 (C=N stretching), 1260 (C-O-C stretching), 835 (C-Cl stretching); ^1H NMR (300 MHz, $CDCl_3$): δ 2.92 (t, *J* = 4.5 Hz, 4H), 3.05-3.09 (m, 4H), 3.87 (s, 6H), 6.71 (d, *J* = 6.0 Hz, 1H), 6.87-6.90 (m, 2H), 7.37 (d, *J* = 6.3 Hz, 4H), 7.76 (s, 1H), 8.12 (d, *J* = 6.6 Hz, 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, 55.3, 28.8, 25.8; MS(ESI), 70ev, *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.

3,11-Dimethoxy-7-p-tolyl-5,6,8,9-tetrahydro-dibenzo[c,h]acridine 4(n): White solid, mp 140-142 ^oC; IR (cm^{-1}): 1615 (C=N stretching), 1075 (C-O-C stretching); ^1H NMR (300 MHz, $CDCl_3$): δ 2.37 (s, 3H), 2.91 (t, *J* = 4.8 Hz, 4H), 3.04-3.08 (m, 4H), 3.86 (s, 6H), 6.72 (d, *J* = 6.0 Hz, 1H), 6.87-6.91 (m, 2H), 7.35 (d, *J* = 6.3 Hz, 4H), 7.75 (s, 1H), 8.10 (d, *J* = 6.6 Hz, 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, 55.2, 28.6, 26.3, 25.7; MS(ESI), 70ev, *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.

3,11-Dimethoxy-7-(4-methoxy-phenyl)-5,6,8,9-tetrahydro-dibenzo[c,h]acridine 4(o): White solid, mp 196-198 ^oC; IR (cm^{-1}): 1607 (C=N stretching), 1062 (C-O-C stretching); ^1H NMR (300 MHz, $CDCl_3$): δ 2.90 (t, *J* = 4.8 Hz, 4H), 3.05-3.08 (m, 4H), 3.75 (s, 3H), 3.82 (s, 6H), 6.70 (d, *J* = 6.0 Hz, 1H), 6.82-6.90 (m, 2H), 7.36 (d, *J* = 6.3 Hz, 4H), 7.74 (s, 1H), 8.11 (d, *J* = 6.6 Hz, 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), 70ev, *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-(3,4-Dimethoxy-phenyl)-3,11-dimethoxy-5,6,8,9-tetrahydro-dibenzo[c,h]acridine 4(p): White solid, mp 178-180 ^oC; IR (cm^{-1}): 1612 (C=N stretching), 1245 (C-O-C stretching); ^1H NMR (300 MHz, DMSO-d_6): δ 2.94 (t, *J* = 4.8 Hz, 4H), 3.08-3.17 (m, 4H), 3.78 (s, 6H), 3.89 (s, 6H), 6.72 (d, *J* = 6.6 Hz, 2H), 6.91-7.16 (m, 5H), 8.17 (d, *J* = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): 160.7, 150.1, 149.2, 149.0, 147.2, 140.3, 130.6, 128.2, 127.2, 126.9, 122.2, 112.8, 112.4, 112.0, 111.3, 56.6, 55.7, 28.9, 25.5; MS(ESI), 70ev, *m/z*: 480 (M+H); Anal. Calcd. For $C_{31}H_{29}NO_4$: C, 77.64; H, 6.10; N, 2.92; Found: C, 77.31; H, 6.47; N, 3.18.

4-(3,11-Dimethoxy-5,6,8,9-tetrahydro-dibenzo[c,h]acridin-7-yl)-phenol 4(q): White solid, mp 208-210 ^oC; IR (cm^{-1}): 3390 (O-H stretching), 1611 (C=N stretching), 1133 (C-O-C stretching); ^1H NMR (300 MHz, $CDCl_3$): δ 2.90 (t, *J* = 4.8 Hz, 4H), 3.04-3.09 (m, 4H), 3.88 (s, 6H), 6.72 (d, *J*= 6.0 Hz, 1H), 6.88-6.92 (m, 2H), 7.39 (d, *J* = 6.3 Hz, 4H), 7.79 (s, 1H), 8.13 (d, *J* = 6.6 Hz, 2H), 9.15 (s, 1H, OH); ^{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, 55.2, 28.6, 25.7; MS(ESI), 70ev, *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 4(r): Pale yellow solid, mp 138-140 ^oC; IR (cm^{-1}): 1612 (C=N stretching), 1516 (N=O stretching), 1057 (C-O-C stretching); ^1H NMR (300 MHz, $CDCl_3$): δ 2.98 (t, *J* = 4.8 Hz, 4H), 3.06-3.11 (m, 4H), 3.89 (s, 6H), 6.75 (d, *J* = 6.0 Hz, 1H), 6.89-6.98 (m, 2H), 7.34-7.39 (m, 4H), 7.78 (s,

1H), 8.15 (d, *J* = 6.6 Hz, 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, 55.1, 28.7, 25.6; MS(ESI), 70ev, *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(s): White crystals, mp 202-204 ^{o}C; IR (cm^{-1}): 3384 (O-H stretching), 1607 (C=N stretching), 1255 (C-O-C stretching); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.58-2.64 (m, 4H), 2.77 (t, *J* = 5.4 Hz 4H), 3.76 (s, 3H), 3.80 (s, 6H), 6.64-6.66 (m, 1H), 6.80-6.96 (m, 6H), 8.31 (d, *J* = 6.6 Hz, 2H), 9.17 (s, 1H, OH); ^{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), 70ev, *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 4(t): White solid, mp 254-256 ^{o}C; IR (cm^{-1}): 3385 (O-H stretching), 1618 (C=N stretching), 1247 (C-O-C stretching); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.58-2.65 (m, 4H), 2.79 (t, *J* = 5.4 Hz, 4H), 3.76 (s, 3H), 3.81 (s, 6H), 6.64-6.67 (m, 1H), 6.82-6.98 (m, 6H), 8.35 (d, *J* = 6.6 Hz, 2H), 9.15 (s, 1H, OH); ^{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, 55.6, 55.2, 28.5, 25.6; MS(ESI), 70ev, *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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