An expeditious synthesis of novel pyranopyridine derivatives involving chromenes under controlled microwave irradiation

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Abstract

An efficient synthesis of novel pyrano[2,3-*b*]pyridine derivatives has been achieved by the cyclocondensation of 2-amino-3-cyano-4*H*-chromenes and cyclohexanone in the presence of aluminium chloride under controlled microwave irradiation. The experimental conditions have been thoroughly optimized and established, allowing significant rate enhancements and excellent yields. The starting 4*H*-chromenes were obtained using one pot DBU-catalysed microwave induced multicomponent condensation of resorcinol, malononitrile and aromatic aldehydes.

Keywords: Friedländer annulation, pyranopyridines, microwave synthesis, multi-component reaction, 2-amino-3-cyano-4*H*-chromenes

Introduction

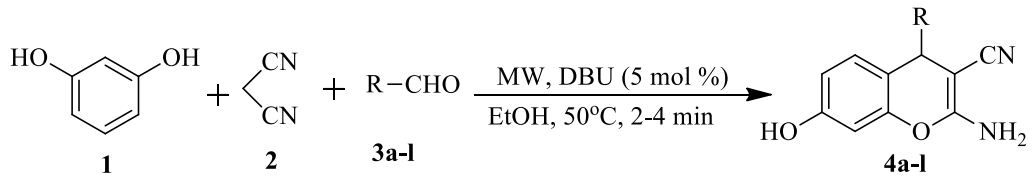
Pyranopyridines constitute an important class of heterocyclic compounds having diverse biological activities such as anti-allergic, anti-inflammatory, and estrogenic.[1,2] Among the different substitution patterns that are known, benzopyrano[2,3-*b*]pyridines exhibit anti-proliferative,[3] cancer chemopreventive,[4] anti-bacterial (including anti-tubercular),[5] antimyopic,[6] anti-histamic,[7] hypotensive,[8] anti-rheumatic,[9] and antiasthmatic activities.[10] Chromenes are important oxygenated heterocyclic compounds endowed with activities such as antidepressant, antihypertensive, anti-tubulin, antiviral, antioxidative, activator of potassium channels and inhibition of phosphodiesterase IV or dihydrofolate reductase, etc.[11-21] As a result, a number of methodologies have been developed to synthesize chromene compounds.[22-27]

Pyranopyridines have become the object of current synthetic developments and many strategies for their synthesis have been adopted.[28] The most simple and straightforward approach for the synthesis of polysubstituted pyridines and related azaheterocycles happens to be the Friedländer annulation. Among various Friedländer syntheses, cyclocondensation of o-

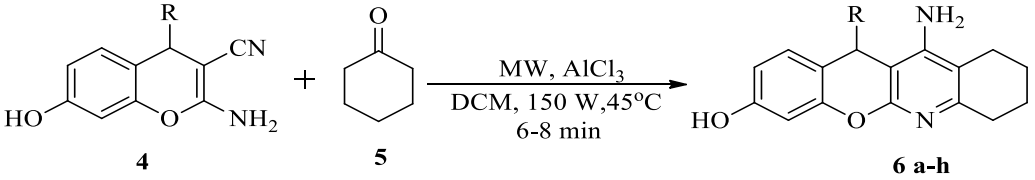
aminobenzonitrile with various ketones has been less explored. Previous investigations[29,30] on condensation of these derivatives required prolonged reaction times, use of hazardous reagents and low yields. In view of the above, the development of an efficient and convenient protocol for the synthesis of pyranopyridines is of considerable interest.

Multicomponent reactions (MCRs) have recently emerged as valuable tool in the preparation of structurally diverse chemical libraries of drug-like heterocyclic compounds.[31] There is great current interest in microwave assisted organic synthesis (MAOS),[32] because such environmentally benign chemical methodologies are strongly required in light of the paradigm shift to "Green Chemistry". According to the current synthetic requirements, environmentally benign multi-component procedures employing microwave (MW) methodology are particularly welcome due to their intrinsic advantages.[33]

In view of the above, a facile, fast and high yielding synthesis of novel 11-amino-12-aryl-7,9,10,12-tetrahydro-8*H*-5-oxa-6-aza-naphthacen-3-ols **6a-h** has been achieved by the cyclocondensation of 2-amino-3-cyano-7-hydroxy-4-aryl-4*H*-chromenes **4a-h** with cyclohexanone in the presence of $AlCl_3$ under controlled MW irradiation. The substrates 2-amino-3-cyano-4*H*-chromenes **4a-l** have been accomplished by the multicomponent reaction of resorcinol, malononitrile, and aromatic aldehydes using controlled MW irradiation in the presence of catalytic amount of DBU (5 mol%) in ethanol at an ambient temperature 50ºC. (Scheme 1).



R=Ph, 4-FC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, 2-furyl, 4-MeC_6H_4, 3,4,5-$(OMe)_3C_6H_2$, 4-$N(Me)_2C_6H_4$, 2-thienyl, 3-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 2-FC_6H_4



R=Ph, 4-FC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, 2-furyl, 4-MeC_6H_4, 3,4,5-$(OMe)_3C_6H_2$, 4-$N(Me)_2C_6H_4$

Scheme 1

Results and Discussion

Although different synthetic strategies have been used for the synthesis of 2-amino-4*H*-chromenes employing some bases, however, these methods suffer from the drawbacks such as low product yield, cumbersome isolation of the product and long reaction time. In order to develop a viable alternative, a variety of catalysts were first investigated for the typical multicomponent reaction of benzaldehyde **3a**, malononitrile and resorcinol under conventional as well as microwave irradiation conditions. The outcome is given in Table 1. The data reveals that DBU under conventional conditions brings about the reaction to afford the product **4a** in 76% yield (Table 1, entry 14). The use of KF/Alumina also promoted the reaction to a reasonable extent (62%, Table 1, entry 12), but the other catalysts such as PTSA, TBAB, $NaHCO_3$, guanidine did not work well (Table 1, entries 4, 6, 8 and 10). It is interesting to note that the afore mentioned reaction in the presence of DBU, when carried out in ethanol at room temperature, gave rise to 45% yield of the product **4a** in 60 minutes. At 50 ºC, however, the conversion was found to be the optimum; a further increase in temperature could not improve the yield further. Application of monomode MW irradiation at the same temperature, however, brought about a commendable increase in the yield as well as a dramatic reduction in the reaction time, the best result being obtained using 100W at 50ºC in just 3 minutes in the presence of 5 mol% DBU (*cf*. entry 14). A further increase in the MW power and temperature starts diminishing the yield (entries 15-16).

Under the optimized set of MW reaction conditions (100W and 50 ºC), a number of aromatic aldehydes **3a-l** were allowed to undergo multicomponent reaction with malononitrile and resorcinol in a molar ratio of 1:1:1 with DBU (5 mol%) in ethanol affording 2-amino-4*H*-chromenes **4a-l** in excellent yields in 2 to 4 minutes (Table 2). The physical and spectral data of all the products are in full agreement with the assigned structures.

In another endeavor, we optimized the reaction of **4a** with cyclohexanone **5** using various Lewis acid catalysts in different solvents (methanol, ethanol, acetonitrile, and dichloromethane) at reflux and under microwave conditions (Scheme 1 and Table 3). When the reaction was carried out using anhydrous $AlCl_3$ (1.2 equiv) as a catalyst in CH_2Cl_2 under reflux as well as under MW, the desired pyranopyridine **6a** was formed in 58% under conventional heating (reflux) in 1.0 hour and 91% under MW at 45 ºC in 8 min. (Table 3, entry 1). Decreasing the molar proportion of $AlCl_3$ decreases the yield of the product **6a** considerably (Table 3, entries 2-3), whereas an increased equivalent of $AlCl_3$ did not improve the yield further (Table 3, entry 4). Switching to other Lewis acids such as $FeCl_3$, $ZnCl_2$, $Yb(OTf)_3$, $Sc(OTf)_3$, $InCl_3$, I_2 and Montmorillonite K10 (Table 3, entries 8-14) and solvents such as ethanol, methanol and acetonitrile gave rise to no measurable products (Table 3, entries 5-7). It is concluded from the table that $AlCl_3$ in CH_2Cl_2 under microwave irradiation (150W, 45 ºC) affords the best result with considerable reduction in the reaction time. Further increase of MW power as well as temperature did not improve the product yield.

Various substituted chromenes **4** were made to react with cyclohexanone **5** using a molar ratio of 1:1.3 with $AlCl_3$ (1.2 equivalent) in dry CH_2Cl_2 using safe pressure regulation 10-mL pressurized vials with "snap-on" cap under microwave (150W, 45 ºC) heating for 6-8 minutes. The results are given in Table 4. The progress of the reaction was monitored by TLC. After completion of reaction, the mixture was poured into a beaker containing ice cold water and was extracted with CH_2Cl_2 (3 × 15 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified through column chromatography (40% ethyl acetate in hexane) to afford pure product **6** in good yield. It is important to mention that under the investigated set of reaction conditions, pyranopyridines **6** are exclusively obtained as the only isolable product with no measurable side product.

Table 1. Optimization of reaction conditions for the multi-component synthesis of **4a**

Entry	Catalyst	Microwave				Conventional		
		MW (Watt)	Temp. (ºC)	Time (min.)	Yield (%)[a]	Temp. (ºC)	Time (min.)	Yield (%)[a]
1	-	80	50	20	25	RT	120	-
2	-	100	50	10	42	Reflux	120	38
3	PTSA	80	50	10	20	RT	120	Trace
4	PTSA	100	50	10	32	50	90	12
5	TBAB	80	50	15	28	RT	120	-
6	TBAB	100	50	10	44	50	120	20
7	$NaHCO_3$	80	50	10	68	RT	120	25
8	$NaHCO_3$	100	50	15	79	50	90	56
9	Guanidine	80	50	15	35	RT	120	-
10	Guanidine	100	50	10	48	50	120	15
11	KF/Al_2O_3	80	50	15	68	RT	120	30
12	KF/Al_2O_3	100	50	10	75	50	120	62
13	DBU	80	50	10	85	RT	60	45
14	DBU	100	50	03	94	50	40	76
15	DBU	150	50	05	90	Reflux	30	78
16	DBU	150	80	05	87	-	-	-

[a] Isolated mass yield based on resorcinol

Table 2. Synthesis of 2-amino-4*H*-chromenes **4a-l**

Product	R	Microwave (100W, 50 ºC)		DBU, 50 ºC	
		Time (min.)	Yield (%)[a]	Time(min.)	Yield (%)[a]
4a	Ph	3	94	40	76
4b	4-FC_6H_4	2	89	35	62
4c	4-BrC_6H_4	3	93	35	74
4d	4-$MeOC_6H_4$	3	90	35	60
4e	2-furyl	2	92	45	63
4f	4-MeC_6H_4	4	91	50	65
4g	3,4,5-$(MeO)_3C_6H_2$	4	90	45	60
4h	4-$N(Me)_2C_6H_4$	4	88	45	62
4i	2-thienyl	3	96	45	70
4j	3-$NO_2C_6H_4$	3	87	40	72
4k	2-$NO_2C_6H_4$	4	89	30	62
4l	2-FC_6H_4	3	87	35	72

[a] Isolated mass yield based on resorcinol

Table 3. Optimization of the reaction conditions using compound **4a** as reference

Entry	Lewis Acid	Reaction Condition			
		Reflux		MW[a]	
		Time (h)	Yield (%)	Time (min)	Yield (%)
1	$AlCl_3$ (1.2 equiv)	2.0	58	8	91
2	$AlCl_3$ (0.5 equiv)	2.0	15	10	25
3	$AlCl_3$ (1.0 equiv)	2.0	45	10	78
4	$AlCl_3$ (1.5 equiv)	2.0	57	8	91
5	$AlCl_3$ (1.2equiv)[b]	2.5	-	10	Trace
6	$AlCl_3$ (1.2 equiv)[c]	2.5	-	10	Trace
7	$AlCl_3$ (1.2 equiv)[d]	2.5	-	10	-
8	$FeCl_3$(1.5 equiv)	1.5	-	8	-
9	$ZnCl_2$(1.5 equiv)	2.0	-	8	-
10	$Sc(OTf)_3$	2.5	-	10	-
11	$Yb(OTf)_3$	2.0	-	8	-
12	$InCl_3$	2.0	-	8	-
13	I_2	2.5	-	10	-
14	MontmorilloniteK10	2.0	-	10	-

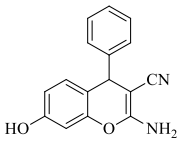
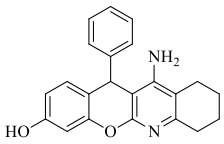
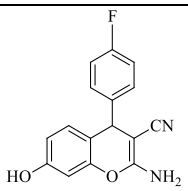
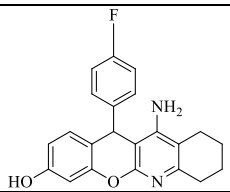
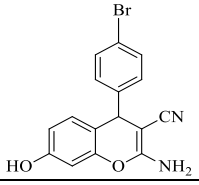
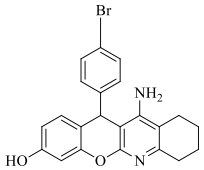
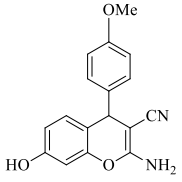
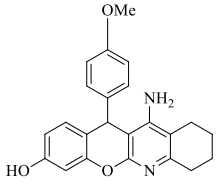
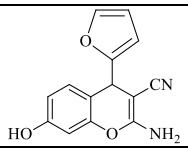
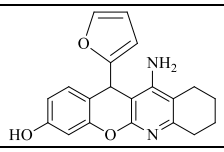
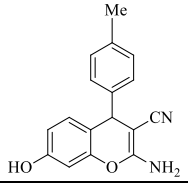
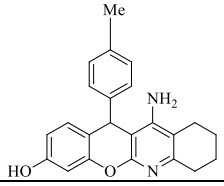
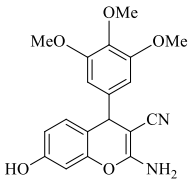
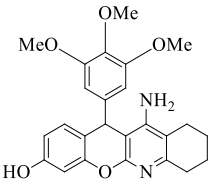
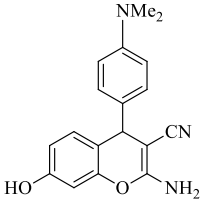
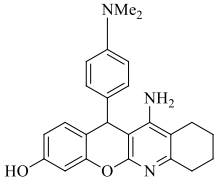
[a]MW heating performed on 150 Watt power and 45°C temperature

[b]Reaction was carried out in ethanol

[c]Reaction was carried out in methanol

[d]Reaction was carried out in acetonitrile

Table 4. Microwave assisted synthesis[a] of pyrano[2,3-*b*]pyridine **6a-h**

Entry	Reactant **4**	Product **6**	Time (min.)	Yield (%)[b]	Mp (°C)
a			8	91	313-315
b			7	89	292-294
c			8	93	281-282
d			6	92	295-297
e			8	89	318-320
f			7	90	282-284
g			8	87	285-287
h			8	85	>320

[a] Microwave heating performed on 150 Watt power and 45ºC temperature

[b] Isolated mass yield based on chromenes 4

In conclusion, the present report demonstrates a facile DBU-catalysed multicomponent condensation of resorcinol, malononitrile and aromatic aldehydes to afford 2-amino-4*H*-3-cyano-chromenes, which are subsequently made to react with cyclohexanone to furnish novel pyranopyridine derivatives in the presence of aluminium chloride. The advantages include improved yield, easier work-up, shorter reaction time and mild reaction conditions.

Experimental Section

General. IR spectra were recorded on a JASCO FT/IR-5300 spectrophotometer, whereas NMR was run on a JEOL AL300 FTNMR spectrometer. The chemical shifts are given in δ ppm with respect to TMS as internal standard. Elemental analysis (C, H, N) for final compounds were performed on a model CE-440 CHN analyzer. The tlc spots were detected using iodine chamber. Microwave irradiation was made using a CEM Discover single mode microwave reactor (Benchmate Model, USA) with infrared temperature probe and adjustable 0-300 W output power. All commercially available chemicals were purchased from Aldrich and Merck.

General microwave procedure for the preparation of 2-amino-3-cyano-4*H*-chromenes 4a-l
An equimolar mixture of resorcinol **1** (1 mmol), malononitrile **2** (1 mmol) and aromatic aldehyde **3a-l** (1 mmol) was placed in a sealed pressure regulation 10-mL pressurized vial containing ethanol (2 mL) and DBU (5 mol%) with "snap-on" cap and was irradiated in the single-mode microwave synthesis system at 100W power and 50 ºC temperature for 2-4 minutes. After completion of the reaction (TLC), the mixture was poured into ice cold water. The resulting precipitate was filtered, dried and recrystallized from ethanol to afford pure 2-amino-4*H*-chromenes **4a-l**.

2-Amino-3-cyano-7-hydroxy-4-phenyl-4*H*-chromene (4a). Light yellow solid, mp: 231-233 °C (Lit.[26] mp: 232-234 °C). IR (KBr): 3427, 3218, 2190, 1650, 1580 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 4.61 (s, 1H, H-4), 6.85 (s, 2H, NH_2), 6.40-7.31 (m, 8H, ArH), 9.68 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 56.2, 102.1, 112.3, 113.7, 120.6, 126.6, 127.3, 128.5, 129.8, 146.3, 148.8, 157.0, 160.2. Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.45; H, 4.38; N, 10.49.

2-Amino-3-cyano-7-hydroxy-4-(4-flurophenyl)-4*H*-chromene (4b). Yellow solid, mp: 186-188 °C (Lit.[27] mp: 187-189 °C). IR (KBr): 3430, 3342, 2187, 1645, 1587 cm^{-1} ^1H NMR (300 MHz, DMSO-d_6): δ = 4.65 (s, 1H, H-4), 6.85 (s, 2H, NH_2), 6.40-7.21 (m, 7H, ArH), 9.71 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 56.6, 102.6, 112.8, 113.9, 121.0, 129.6, 129.7, 130.3, 143.0, 148.7, 157.3, 159.8, 160.6. Anal. Calcd for $C_{16}H_{11}FN_2O_2$: C, 68.08; H, 3.93; N, 9.92. Found: C, 67.94; H, 3.84; N, 10.12.

2-Amino-3-cyano-7-hydroxy-4-(4-bromophenyl)-4*H*-chromene (4c). Light yellow solid, mp: 224-226 °C (Lit.[27] mp: 225-227 °C). IR (KBr): 3471, 3336, 2194, 1641, 1578 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 4.64 (s, 1H, H-4), 6.90 (s, 2H, NH_2), 6.40-7.84 (m, 7H, ArH), 9.71 (s,

1H, OH). ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ = 56.4, 102.6, 112.0, 113.7, 120.2, 121.4, 130.1, 130.3, 132.0, 147.2, 149.5, 157.8, 160.5. Anal. Calcd for $C_{16}H_{11}BrN_2O_2$: C, 56.0; H, 3.23; N, 8.16. Found: C, 55.72; H, 3.14; N, 8.05.

2-Amino-3-cyano-7-hydroxy-4-(4-methoxyphenyl)-4*H*-chromene (4d). Yellow solid, mp: 110-112 °C (Lit.[34] mp: 112-114 °C). IR (KBr): 3424, 3333, 2190, 1651, 1587 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ = 3.51 (s, 3H, OCH_3), 4.53 (s, 1H, H-4), 6.84 (s, 2H, NH_2), 6.43-7.21 (m, 7H, ArH), 9.63 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ = 55.9, 56.0, 102.2, 112.3, 113.5, 120.6, 126.4, 129.7, 136.5, 142.0, 148.4, 152.7, 156.8, 160.4. Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.16; H, 4.54; N, 9.48.

2-Amino-3-cyano-7-hydroxy-4-(2-furyl)-4*H*-chromene (4e). Yellow solid, mp: 189-191 °C. IR (KBr): 3420, 3331, 2193, 1651, 1589 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ = 4.75 (s, 1H, H-4), 6.92 (s, 2H, NH_2), 6.13-7.50 (m, 6H, ArH), 9.74 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ = 53.2, 102.3, 105.4, 110.2, 111.0, 112.2, 120.3, 129.5, 142.3, 149.1, 156.9, 157.3, 160.9. Anal. Calcd for $C_{14}H_{10}N_2O_3$: C, 66.14; H, 3.96; N, 11.02. Found: C, 65.93; H, 3.84; N, 10.87.

2-Amino-3-cyano-7-hydroxy-4-(4-methylphenyl)-4*H*-chromene (4f). Yellow solid, mp: 184-186 °C. IR (KBr): 3409, 3332, 2194, 1656, 1589 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ = 2.24 (s, 3H, CH_3), 4.56 (s, 1H, H-4), 6.81 (s, 2H, NH_2), 6.38-7.10 (m, 7H, ArH), 9.66 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ = 20.5, 56.4, 102.1, 112.3, 113.8, 120.6, 127.2, 129.5, 129.8, 135.6, 143.4, 148.7, 156.9, 160.1. Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.12; H, 4.85 N, 9.86.

2-Amino-3-cyano-7-hydroxy-4-(3,4,5-trimethoxyphenyl)-4*H*-chromene (4g). Yellow solid, mp: 208-210 °C. IR (KBr): 3473, 3335, 2199, 1647, 1589 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ = 3.62 (s, 3H, OCH_3), 3.71 (s, 6H, OCH_3), 4.57 (s, 1H, H-4), 6.86 (s, 2H, NH_2), 6.38-6.89 (m, 5H, ArH), 9.68 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ = 55.8, 56.0, 59.9, 102.2, 104.6, 112.3, 113.5, 120.6, 129.8, 136.2, 141.9, 148.6, 152.9, 157.0, 160.3. Anal. Calcd for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12; N, 7.91. Found: C, 64.15; H, 4.92. N, 7.86.

2-Amino-3-cyano-7-hydroxy-4-(4-dimethylaminophenyl)-4*H*-chromene (4h). Yellow solid, mp: 193-195 °C. IR (KBr): 3415, 3330, 2190, 1654, 1585 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ = 2.84 (s, 6H, $N(CH_3)_2$), 4.46 (s, 1H, H-4), 6.77 (s, 2H, NH_2), 6.37-6.97 (m, 7H, ArH), 9.66 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ = 40.2, 56.8, 101.9, 112.1, 112.5, 114.4, 120.7, 127.8, 129.8, 134.1, 148.7, 149.2, 156.7, 159.9. Anal. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.15; H, 5.36; N, 13.51.

2-Amino-3-cyano-7-hydroxy-4-(2-thienyl)-4*H*-chromene (4i). Yellow solid, mp: 204-205 °C (Lit.[34] mp: 202-204 °C). IR (KBr): 3422, 3332, 2193, 1653, 1568 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ = 4.97 (s, 1H, H-4), 6.91 (s, 2H, NH_2), 6.38-7.35 (m, 6H, ArH), 9.76 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ = 56.4, 102.2, 112.4, 113.4, 120.5, 124.0, 125.0, 126.7, 129.8, 148.5, 151.5, 157.4, 160.3. Anal. Calcd for $C_{14}H_{10}N_2O_2S$: C, 62.21; H, 3.73; N, 10.36. Found: C, 62.28; H, 3.70; N, 10.25.

2-Amino-3-cyano-7-hydroxy-4-(3-nitrophenyl)-4*H*-chromene (4j). Yellow solid, mp: 169-170 °C. IR (KBr): 3440, 3345, 2192, 1650, 1585 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 4.85 (s, 1H, H-4), 7.05 (s, 2H, NH_2), 6.45-8.10 (m, 7H, ArH), 9.78 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 55.2, 102.4, 111.9 112.7, 120.0, 121.0, 123.7, 128.2, 129.6, 131.4, 133.4, 139.3, 148.7, 149.0, 157.5, 160.3. Anal. Calcd. for $C_{16}H_{11}N_3O_4$: C, 62.14; H, 3.58; N, 13.59. Found: C, 61.87; H, 3.67; N, 13.25.

2-Amino-3-cyano-7-hydroxy-4-(2-nitrophenyl)-4*H*-chromene (4k). Yellow solid, mp: 162-163 °C. IR (KBr): 3417, 3342, 2187, 1650, 1590 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 5.14 (s, 1H, H-4), 7.0 (s, 2H, NH_2), 6.43-7.86 (m, 7H, ArH), 9.80 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 55.5, 102.7, 112.1, 113.0, 120.4, 121.2, 123.5, 128.0, 129.5, 131.7, 133.2, 139.5, 148.3, 149.2, 157.8, 160.4. Anal. Calcd for $C_{16}H_{11}N_3O_4$: C, 62.14; H, 3.58; N, 13.59. Found: C, 61.93; H, 3.50; N, 13.42.

2-Amino-3-cyano-7-hydroxy-4-(2-fluorophenyl)-4*H*-chromene (4l). Yellow solid, mp: 200-202 °C. IR (KBr): 3424, 3333, 2190, 1651, 1587 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 4.87 (s, 1H, H-4), 6.86 (s, 2H, NH_2), 6.38-7.25 (m, 7H, ArH), 9.69 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 54.5, 102.2, 112.4, 115.5, 115.8, 120.4, 124.7, 128.8, 129.5, 129.8, 132.7, 149.1, 157.2, 160.6. Anal. Calcd for $C_{16}H_{11}FN_2O_2$: C, 68.08; H, 3.93; N, 9.92. Found: C, 67.73; H, 3.80; N, 9.75.

General microwave procedure for the synthesis of substituted tetrahydro-8*H*-5-oxa-6-aza-naphthacen-3-ols 6a-h

A mixture of substituted 2-amino-3-cyano-4*H*-chromene **4** (1 mmol), cyclohexanone **5** (1.3 mmol) and anhydrous $AlCl_3$ (1.2 mmol) was placed in a sealed pressure regulation 10 mL pressurized vial containing dry dichloromethane (2 mL) with "snap-on" cap and was irradiated in the single-mode microwave synthesis system using 150W power at 45 ºC temperature for 6-8 minutes. After completion of reaction (TLC), the reaction mixture was poured into a beaker containing ice cold water. The mixture was extracted with CH_2Cl_2 (3 × 15 mL), dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure and the resultant crude product was purified by column chromatography (40% ethyl acetate in hexane) to afford pure product **6**.

11-Amino-12-phenyl-7,9,10,12-tetrahydro-8*H*-5-oxa-6-aza-naphthacen-3-ol (6a). White solid, mp: 313-315 °C. IR (KBr): 3456, 3380, 2928, 1624, 1462, 1238, 1172 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 1.70 (m, 4H, CH_2), 2.22 (m, 2H, CH_2), 2.50 (m, 2H, CH_2), 5.20 (s, 1H, CH), 5.49 (s, 2H, NH_2), 6.42-7.22 (m, 8H, ArH), 9.52 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 22.2, 22.4, 22.9, 32.0, 38.2, 98.6, 102.6, 111.1, 112.0, 116.0, 126.3, 127.1, 128.5, 129.5, 146.0, 151.2, 151.3, 152.3, 155.4, 156.9. Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.58; H, 5.72; N, 7.92.

11-Amino-12-(4-fluorophenyl)-7,9,10,12-tetrahydro-8*H*-5-oxa-6-aza-naphthacen-3-ol (6b). White solid, mp: 292-294 °C. IR (KBr): 3485, 3395, 2924, 1625, 1465, 1235, 1168 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 1.70 (m, 4H, CH_2), 2.10 (m, 2H, CH_2), 2.53 (m, 2H, CH_2),

5.23 (s, 1H, CH), 5.53 (s, 2H, NH_2), 6.44-7.27 (m, 7H, ArH), 9.65 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 22.1, 22.3, 22.9, 32.0, 37.7, 98.2, 102.7, 111.3, 112.1, 115.2, 119.3, 127.3, 129.3, 131.5, 145.6, 151.2, 151.3, 152.6, 155.5, 157.3. Anal. Calcd for $C_{22}H_{19}FN_2O_2$: C, 72.91; H, 5.28; N, 7.73. Found: C, 72.83; H, 5.15; N, 7.58.

11-Amino-12-(4-bromophenyl)-7,9,10,12-tetrahydro-8*H*-5-oxa-6-aza-naphthacen-3-ol (6c). Yellow solid, mp: 281-282 °C. IR (KBr): 3463, 3390, 2928, 1627, 1462, 1240, 1176 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.70 (m, 4H, CH_2), 2.22 (m, 2H, CH_2), 2.50 (m, 2H, CH_2), 5.24 (s, 1H, CH), 5.55 (s, 2H, NH_2), 6.43-7.41 (m, 7H, ArH), 9.69 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 22.1, 22.3, 22.9, 32.0, 37.8, 98.2, 102.7, 111.3, 112.0, 115.2, 119.3, 127.3 129.3, 131.32, 145.4, 151.2, 151.3, 152.4, 155.3, 157.2. Anal. Calcd for $C_{22}H_{19}BrN_2O_2$: C, 62.42; H, 4.52; N, 6.62. Found: C, 62.23; H, 4.61; N, 6.48.

11-Amino-12-(4-methoxyphenyl)-7,9,10,12-tetrahydro-8*H*-5-oxa-6-aza-naphthacen-3-ol (6d). White solid, mp: 295-297 °C. IR (KBr): 3495, 3402, 2928, 1635, 1465, 1253, 1180 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.68 (m, 4H, CH_2), 2.20 (m, 2H, CH_2), 2.54 (m, 2H, CH_2), 3.62(s, 3H, OCH_3), 5.11 (s, 1H, CH), 5.44 (s, 2H, NH_2), 6.40-7.13 (m, 7H, ArH), 9.63 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 22.2, 22.4, 23.0, 32.0, 37.7, 55.0, 98.9, 102.6, 111.1, 112.0, 113.8, 116.2, 128.1, 129.5, 138.2, 151.1, 151.3, 152.1, 155.3, 156.8, 157.7. Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.52; H, 5.80; N, 7.34.

11-Amino-12-furan-2-yl-7,9,10,12-tetrahydro-8*H*-5-oxa-6-aza-naphthacen-3-ol (6e). Brown solid, mp: 318-320 °C. IR (KBr): 3491, 3402, 2935, 1627,1462, 1241, 1172 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.69 (m, 4H, CH_2), 2.26 (m, 2H, CH_2), 2.48 (m, 2H, CH_2), 5.58 (s, 1H, CH), 5.68 (s, 2H, NH_2), 6.44- 7.19 (m, 6H, ArH), 9.57 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 22.5, 22.8, 23.4, 32.4, 34.2, 99.0, 103.1, 111.5, 112.3, 116.0, 124.2, 124.8, 126.7, 129.7, 150.7, 151.7, 151.9, 152.7, 157.6. Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.65; H, 5.38; N, 8.25.

11-Amino-12-(4-methylphenyl)-7,9,10,12-tetrahydro-8*H*-5-oxa-6-aza-naphthacen-3-ol (6f). White solid, mp: 282-284 °C. IR (KBr): 3482, 3400, 2920, 1627, 1456, 1232, 1177 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.70 (m, 4H, CH_2), 2.17(s, 3H, CH_3), 2.21 (m, 2H, CH_2), 2.56 (m, 2H, CH_2), 5.15 (s, 1H, CH), 5.44 (s, 2H, NH_2), 6.44-7.12 (m, 7H, ArH), 9.61 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.4, 22.1, 22.3, 32.0, 38.0, 98.6, 102.5, 111.0, 111.9, 115.9, 126.9, 128.9, 129.4, 135.2, 143.1, 151.1, 151.2, 152.0, 155.2, 156.8. Anal. Calcd for $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19; N, 7.82. Found: C, 76.85; H, 6.02; N, 7.65.

11-Amino-12-(3,4,5-trimethoxyphenyl)-7,9,10,12-tetrahydro-8*H*-5-oxa-6-aza-naphthacen-3-ol (6g). White solid, mp: 285-287 °C. IR (KBr): 3468, 3385, 2928, 1630, 1450, 1235, 1180 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.70 (m, 4H, CH_2), 2.25 (m, 2H, CH_2), 2.57 (m, 2H, CH_2), 3.56 (s, 3H, CH_3), 3.65 (s, 6H, CH_3), 5.10 (s, 1H, CH), 5.51 (s, 2H, NH_2), 6.44-7.00 (m, 5H, ArH), 9.54 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 22.2, 22.4, 22.9, 32.0, 55.8, 56.0, 59.8, 98.5, 102.6, 104.6, 111.1, 111.9, 115.7, 129.4, 136.0, 141.9, 151.2, 151.4, 152.2, 152.7, 155.2, 156.9. Anal. Calcd for $C_{25}H_{26}N_2O_5$: C, 69.11; H, 6.03; N, 6.45. Found: C, 68.95; H, 5.92; N, 6.23.

11-Amino-12-(4-dimethylaminophenyl)-7,9,10,12-tetrahydro-8*H*-5-oxa-6-aza-naphthacen-3-ol (6h). Brown solid, mp: >320°C. IR (KBr): 3483, 3392, 2922, 1629, 1445, 1240, 1175 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 1.70 (m, 4H, CH_2), 2.23 (m, 2H, CH_2), 2.51 (m, 2H, CH_2), 2.78 (s, 6H, $N(CH_3)_2$), 5.03 (s, 1H, CH), 5.37 (s, 2H, NH_2), 6.43-7.06 (m, 7H, ArH), 9.61 (s, 1H, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 22.1, 22.2, 22.4, 32.0, 37.5, 79.1, 99.0, 102.4, 111.0, 111.8, 112.6, 116.4, 127.6, 129.4, 134.0, 149.0, 151.0, 151.2, 151.8, 155.2, 156.7. Anal. Calcd for $C_{24}H_{25}N_3O_2$: C, 74.39; H, 6.50; N, 10.84. Found: C, 74.25; H, 6.43; N, 10.61.

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Supplementary Material

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