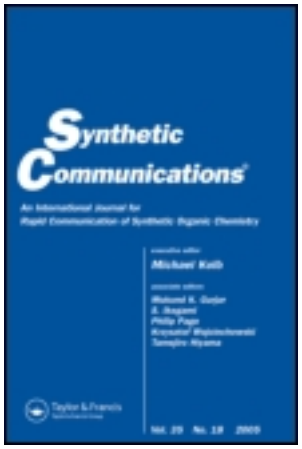

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Catalyst-Free, One-Pot, Expeditious Synthesis of Aminoalkylnaphthols at Room Temperature

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CATALYST-FREE, ONE-POT, EXPEDITIOUS SYNTHESIS OF AMINOALKYLNAPHTHOLS AT ROOM TEMPERATURE

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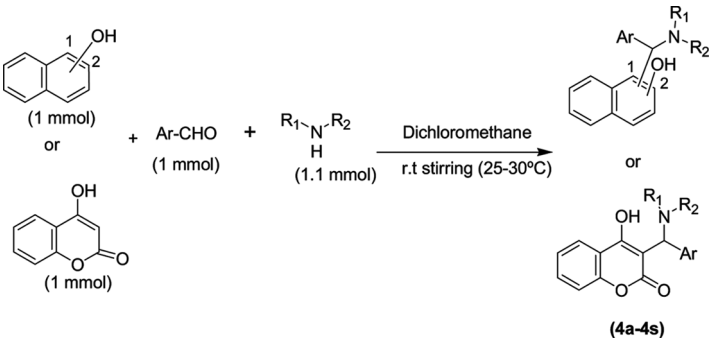
GRAPHICAL ABSTRACT



Abstract *Aminoalkylnaphthols possess several biological and catalytic activities. A methodology has been developed for the multicomponent one-pot synthesis of aminoalkylnaphthols in dichloromethane under catalyst-free conditions at room temperature. The present approach possesses several advantages such as excellent yields, quick reaction time, mild reaction conditions, and very easy purification processes. Thirteen new compounds in addition to six known compounds have been synthesized by this methodology.*

Keywords Aminoalkylnaphthols; catalyst-free; dichloromethane; one-pot synthesis; room temperature

INTRODUCTION

Recently, the synthesis of aminoalkylnaphthols has received special attention from the scientific community because of their significant biological[1] and catalytic[2] properties. These compounds, possessing multiple chelating centers, are potent inhibitors of metalloenzymes containing Fe, Cu, Zn, and Co ions as cofactors.[3–6] In addition, these compounds have the ability to act as scavengers of heavy metals (Hg, Cd, Pb, As, Sb).[7,8] They also show potent oxytocic activity.[9] A number of

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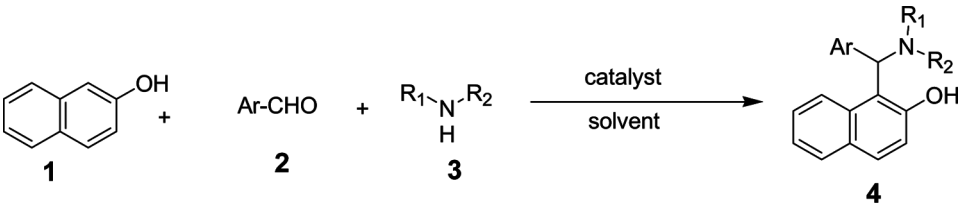


Scheme 1. Synthesis of aminoalkylnaphthols.

aminomethylphenols have been reported in the literature[10] as chelating agents in metal-catalyzed asymmetric induction in many reactions. Chiral Mannich bases are frequently used as ligands in a variety of metal-mediated enantioselective carbon–carbon bond formation reactions.[11–17] Such importance of the aminoalkylnaphthols has caused us to pursue a simple and easy method for their synthesis.

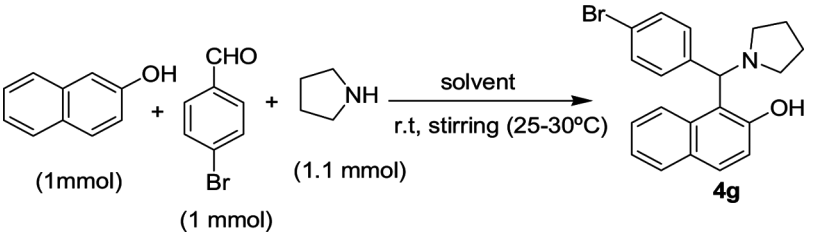
Since 1900, aminoalkylnaphthols have been synthesized by the three-component condensation of secondary amines, aromatic aldehydes, and naphthols (Scheme 1). In 1900, Mario Betti synthesized aminoalkylnaphthols (so-called Betti bases) for the first time.[18] After a long gap, Katritzky et al. in 1999 reported the synthesis of aminoalkylphenols by benzotriazole methodology using phase-transfer catalysis.[19a] Saidi et al. synthesized the compounds with lithium perchlorate.[19b] Recently, Jha et al have developed the methodology of p-toluene sulfonic acid–catalyzed microwave irradiation.[20] Kumar et al. explored the synthesis by nonionic surfactant-catalysed methodology.[21] In addition to these, a few other methodologies are also available in the literature.[22]

RESULTS AND DISCUSSION

Most of the earlier procedures for aminoalkylnaphthol synthesis[18–22] suffer from harsh reaction conditions, catalyst nonrecyclability, or a need for column chromatography for further purification. Our main aim was to synthesize aminoalkylnaphthols while avoiding expensive catalysts, using mild reaction conditions, and avoiding time-consuming column chromatography. After a thorough search for proper catalysts and reaction medium for the standard reaction of pyrrolidine, 2-naphthol, and 4-bromobenzaldehyde, we found that dichloromethane at room temperature (25–30 °C) proved to be the best reaction medium (Table 1, entry 3), and the product conversion was so high that no additional catalyst was required. This is the most important aspect of our methodology. The workup procedure is also very simple. After the completion of the reaction, checked by thin-layer chromatography (TLC), dichloromethane was pumped out by rotary evaporation. The product was purified by direct crystallization from ethylacetate and petroleum ether (60–80 °C), thus avoiding time-consuming column chromatography. This is the second important aspect of our methodology.

Once the optimum condition was reached for the model reaction, various aromatic aldehydes and secondary amines were tried for this reaction. Aromatic aldehydes with slightly electron-withdrawing groups yielded the best results, while electron-donating groups slightly decreased the yield. Aromatic aldehydes with

Table 1. Choice of reaction medium for the synthesis of the aminoalkylnaphthols at room temperature taking the standard reaction of 2-naphthol, 4-bromobenzaldehyde, and pyrrolidine



Entry	Solvents (5 ml)	Time (h)	Yield (%) (isolated)
1	Methanol	2	55
2	Ethanol	2	60
3	Dichloromethane	2	92
4	Dichloroethane	2	67
5	Acetonitrile	2	45
6	DMF	2	55
7	Water	2	58
8	DMSO	2	40
9	1,4-Dioxane	2	35
10	THF	2	53

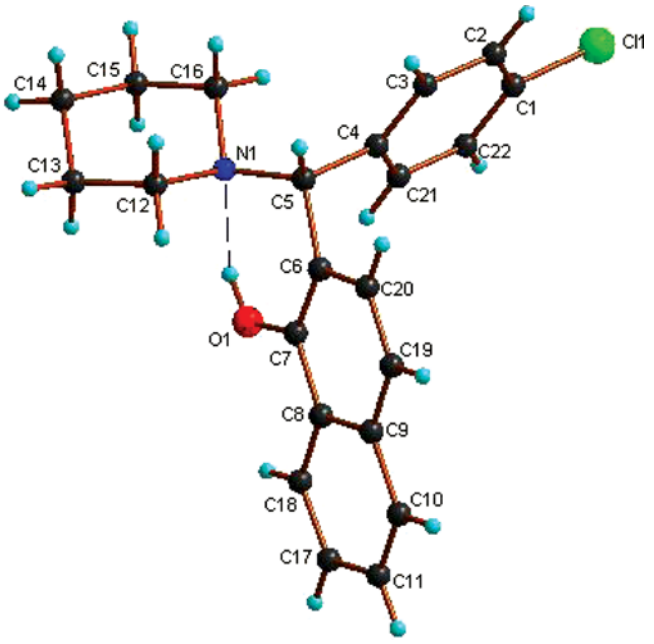


Figure 1. X-ray structural analysis of a single crystal of 2-[(4-chlorophenyl)-piperidine-1-yl-methyl]-naphthalen-1-ol (**4q**) (Table 2, entry 17) showing the crystallographic numbering (CCDC 800110). (Figure is provided in color online.)

ortho-substitution also decrease the yield slightly. This may be due to the steric effect. Of the secondary amines, piperidine, pyrrolidine, morpholine, N-methyl piperazine, and dimethylamine were used. In all cases, the yields of the desired products were moderate to excellent. We further extended the scope of the reaction by using 4-hydroxycoumarin and 1-naphthol as nucleophiles in place of 2-naphthol, with good yields. With 1-naphthol, the substitution occurs specifically at the 2-position (and not at 4) because of the stability of the product by intramolecular six-membered hydrogen-bond formation (further evidence in Fig. 1).

All the products are well characterized by melting points, infrared (IR), ^{1}H NMR, ^{13}C NMR, and CHN analysis. In ^{1}H NMR, the -NCH_2 protons and in ^{13}C NMR, the -N*C*H_2 carbons appear as broad peaks. This is due to electrical quadruple moment of nitrogen. The crystal structure of 1-[(4-bromophenyl)-pyrrolidin-1-yl-methyl]-naphthalen-2-ol (Table 2, entry 7) is given in Fig. 2. which shows a strong hydrogen bonding between OH of 2-naphthol and N of the pyrrolidine moiety.

The crystal structure of 2-[(4-chlorophenyl)-piperidine-1-yl-ethyl]-naphthalen-1-ol (Table 2, entry 17) is given in Fig. 1, which conclusively proves that 1-naphthol reacts through its 2 position.

Probably, the mechanism goes through the iminium ion formation followed by the attack of 2-naphthol at the 1-position for the specific reaction shown in Scheme 2.

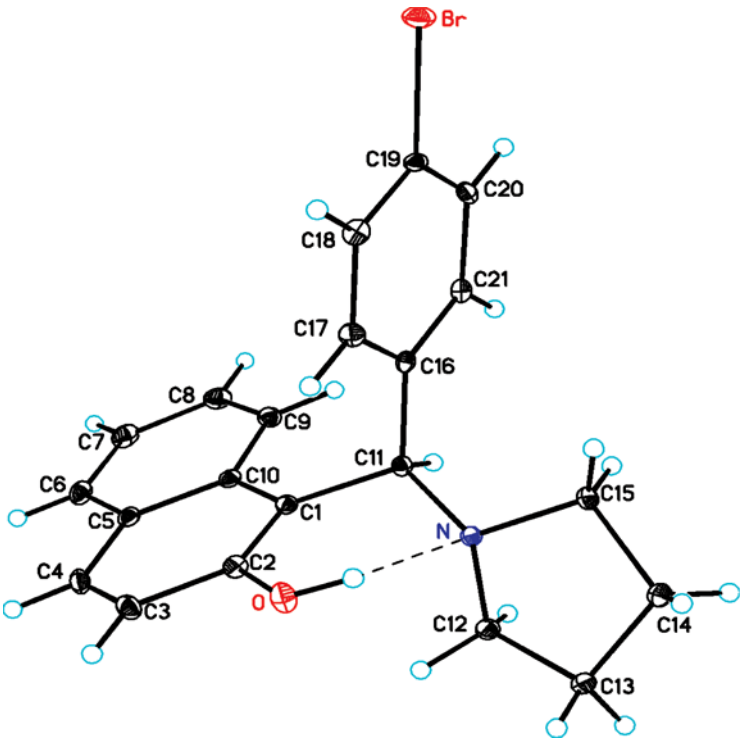
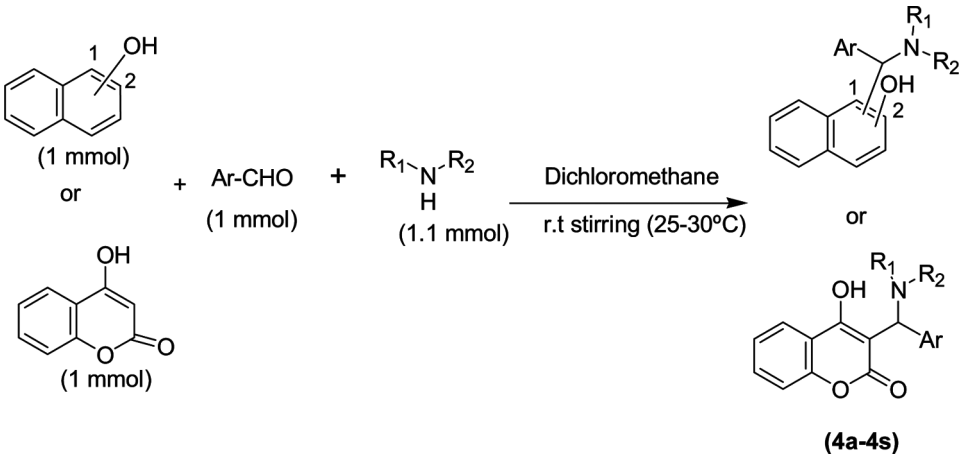
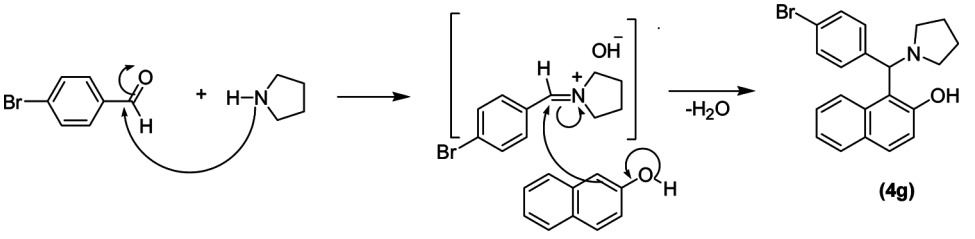


Figure 2. X-ray structural analysis of a single crystal of 1-[(4-bromo-phenyl)-pyrrolidin-1-yl-methyl]-naphthalen-2-ol (**4g**) (Table 2, entry 7) showing the crystallographic numbering (CCDC 791677). (Figure is provided in color online.)

Table 2. Synthesis of the aminoalkylnaphthols at room temperature (25–30 °C)



Entry	Starting materials: Amines	Aldehydes	Naphthols	Products[ref.] (4a–4s)	Time (h)	Yield (%), isolated
1	Piperidine	4-Chlorobenzaldehyde	2-Naphthol	**4a**[20]	2	95
2	Piperidine	4-Bromobenzaldehyde	2-Naphthol	**4b**	2	92
3	Dimethylamine	4-Chlorobenzaldehyde	2-Naphthol	**4c**[21]	2	96
4	Piperidine	3,4-dimethoxybenzaldehyde	2-Naphthol	**4d**	2	84
5	Piperidine	2-Chlorobenzaldehyde	2-Naphthol	**4e**	3	75
6	Pyrrolidine	4-Chlorobenzaldehyde	2-Naphthol	**4f**	2	90
7	Pyrrolidine	4-Bromobenzaldehyde	2-Naphthol	**4g**	2	92
8	Piperidine	2-Methoxybenzaldehyde	2-Naphthol	**4h**[21]	2	74
9	Morpholine	4-Chlorobenzaldehyde	2-Naphthol	**4i**[20]	2	90
10	Morpholine	3,4-Dimethoxybenzaldehyde	2-Naphthol	**4j**	2	83
11	Piperidine	Benzene-1,4-Dialdehyde	2-Naphthol	**4k**	2	76
12	Piperidine	4-Chlorobenzaldehyde	4-Hydroxycoumarin	**4l**	2	85
13	Piperidine	3-Nitrobenzaldehyde	4-Hydroxycoumarin	**4m**	2	78
14	Dimethylamine	4-Chlorobenzaldehyde	4-Hydroxycoumarin	**4n**	2	81
15	N-methylpiperazine	Benzaldehyde	2-Naphthol	**4o**[20]	2	76
16	Piperidine	Pyridine-4-aldehyde	2-Naphthol	**4p**[20]	2	78
17	Piperidine	4-Chlorobenzaldehyde	1-Naphthol	**4q**	2	74
18	Morpholine	Benzaldehyde	1-Naphthol	**4r**	2	83
19	N-methylpiperazine	4-Bromobenzaldehyde	1-Naphthol	**4s**	2	82



Scheme 2. Probable mechanism for the formation of aminoalkylnaphthols.

CONCLUSION

We have developed a very simple, catalyst-free protocol for the synthesis of aminoalkylnaphthols by a one-pot, three-component methodology. The advantages of the methodology include (a) mild catalyst-free reaction condition, (b) shorter reaction time, (c) very easy purification procedure that avoids column chromatography, and (d) applicability to large-scale preparation.

EXPERIMENTAL

Ethyl acetate, petroleum ether (boiling range 60–80 °C), dichloromethane were distilled before use. All the chemicals were purchased from Aldrich Chemical Company and Spectrochem, Pvt. Ltd. (Mumbai, India). Silica gel G with binder from Spectrochem, Pvt. Ltd., Mumbai, India, was used for TLC. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker 300-MHz instrument at 300 and 75 MHz respectively. $CDCl_3$ and dimethylsulfoxied (DMSO-d_6) were purchased from Aldrich Chemical Company. Melting points were determined on an electrical melting-point apparatus with an open capillary. IR spectra were recorded on a Perkin-Elmer spectrophotometer RX/FT-IR system. The C-H-N-analyses were carried out on a 2400 series II CHNS analyzer, (Perkin-Elmer, USA).

General Experimental Procedure for Aminoalkylnaphthol Formation

Aromatic aldehydes (1 mmol), secondary amine (1.1 mmol), (naphthol/4-OH-coumarin) (1 mmol), and dichloromethane (5 ml) were added in a 25-ml, round-bottomed flask. The resulting mixture was stirred vigorously with a magnetic bar on a magnetic stirrer for 2h at room temperature (25–30 °C). The progress of the reaction was monitored by TLC. After the completion of the reaction as checked by TLC, dichloromethane was pumped out by rotary evaporation. The crude product was purified directly by crystallization from ethyl acetate and petroleum ether (60–80 °C).

Spectral and Analytical Data of the Compounds (4a–4q)

In ^{13}C spectra, most of the compounds show one extra peak in the completely saturated carbon region. The nonequivalence of the similar type of carbons may occur because of the restricted rotation of the C-N bond.

1-[(4-Chlorophenyl)-piperidin-1-yl-methyl]naphthalen-2-ol (4a) (Table 2, Entry 1). White solid. Mp 164–166 °C (EtOAc), lit.[20] Mp 165–166 °C; IR (KBr): 3050, 2939, 2854, 1590, 1475, 1408, 1352, 1262, 1233, 1152, 1091, 942 and 823 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ_H 13.80 (s, 1H, O*H*), 7.76 (d, $J = 8.4$ Hz, 1H, ArH), 7.69–7.58 (m, 2H, ArH), 7.48–7.45 (m, 2H, ArH), 7.38–7.32 (m, 1H, ArH), 7.23–7.17 (m, 3H, ArH), 7.14 (d, $J = 9.0$ Hz, 1H, ArH), 5.03 (s, 1H, CH), 3.28 (br, 1H, -NCH), 2.62 (br, 1H, -NCH), 2.06–1.50 (m, 8H, -NCH, -CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_c 155.4, 138.2, 133.6, 132.1, 130.3, 129.5, 128.9, 128.6, 126.4, 122.4, 120.7, 119.9, 115.7, 71.2, 54.6, 51.9, 26.0 and 24.0.

1-[(4-Bromophenyl)-piperidin-1-yl-methyl]naphthalen-2-ol (4b) (Table 2, Entry 2). White solid. Found: C, 66.79; H, 5.52; N, 3.45%. $C_{22}H_{22}BrNO$ requires C, 66.67; H, 5.60; N, 3.53%. Mp 158–160 °C (EtOAc); IR (KBr): 3056, 2937, 2852, 2592, 1589, 1515, 1475, 1449, 1408, 1352, 1261, 1233, 1152, 1079, 1009, 943, 822 and 740 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ_H 13.79 (s, 1H, O*H*), 7.90 (d, $J = 8.7$ Hz, 1H, ArH), 7.69–7.61 (m, 2H, ArH), 7.45–7.30 (m, 5H, ArH), 7.23–1.12 (m, 2H, ArH), 4.99 (s, 1H, CH), 3.25 (br, 1H, -NCH), 2.61 ((br, 1H, -NCH), 2.02–1.20 (m, 8H, -NCH, $-CH_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_c 155.3, 138.7, 132.1, 131.8, 130.6, 129.5, 128.9, 128.6, 126.4, 122.4, 121.7, 120.7, 119.9, 115.6, 71.2, 54.4, 51.9, 25.9 and 23.9.

1-[(4-Chlorophenyl)-dimethylamino-methyl]naphthalen-2-ol (4c) (Table 2, Entry 3). White solid. Mp 128–130 °C (EtOAc), lit.[21] Mp 129–131 °C; IR (KBr): 3129, 3061, 2976, 2848, 1629, 1462, 1240 and 758 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MH_Z): δ_H 10.01 (s, 1H, OH), 7.65–7.83 (m, 3H, ArH), 7.50–7.53 (m, 3H, ArH), 7.08–7.45 (m, 4H, ArH), 4.95 (s, 1H, CH), 2.34 (s, 6H, NCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 155.2, 142.4, 131.2, 129.7, 128.9, 128.8, 128.7, 128.5, 127.7, 126.4, 122.4, 121.1, 119.8, 116.3, 72.8 and 41.5.

1-[(3,4-Dimethoxyphenyl)-piperidin-1-yl-methyl]naphthalen-2-ol (4d) (Table 2, Entry 4). White solid. Found: C, 76.59; H, 7.13; N, 3.62%. $C_{24}H_{27}NO_3$ requires C, 76.36; H: 7.21; N; 3.71%. Mp 120–122 °C (EtOAc); IR (KBr): 3056, 2934, 2841, 1595, 1513, 1455, 1418, 1355, 1264, 1145, 1027, 942 and 816 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ_H 14.0 (s, 1H, O*H*), 7.83 (d, $J = 8.4$ Hz, 1H, ArH), 7.69–7.61 (m, 2H, ArH), 7.35 (t, $J = 8.4$ Hz, 1H, ArH), 7.24–7.11 (m, 3H, ArH), 7.06 (d, $J = 8.1$ Hz, 1H, ArH), 6.73 (d, $J = 8.1$ Hz, 1H, ArH), 5.01 (s, 1H, CH), 3.79 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.30 (br, 1H, NCH), 2.65 (br, 1H, NCH), 2.20–1.50 (m, 8H, NCH, $-CH_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_c 155.4, 148.6, 132.3, 132.1, 129.2, 128.8, 128.6, 126.2, 122.2, 121.7, 121.0, 119.8, 116.2, 110.8, 71.7, 54.6, 51.7, 26.0, 24.1.

1-[(2-Chlorophenyl)-piperidin-1-yl-methyl]naphthalen-2-ol (4e) (Table 2, Entry 5). White solid. Found: C, 75.24; H, 6.21; N, 3.88%. $C_{22}H_{22}ClNO$ requires C, 75.09; H, 6.30; N, 3.98%. Mp 136–138 °C (EtOAc); IR (KBr): 3060, 2933, 2821, 2607, 1590, 1516, 1447, 1352, 1265, 1239, 1151, 1093, 1033, 978, 821 and 745 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ_H 14.28 (s, 1H, O*H*), 7.84 (d, $^3J = 8.4$ Hz, 1H, ArH), 7.72–7.64 (m, 3H, ArH), 7.42–7.37 (m, 2H, ArH), 7.26–7.09 (m, 4H, ArH), 5.88 (s, 1H, CH), 3.35 (d, $J = 11.4$ Hz, 1H, NCH), 2.66 (d, $J = 10.8$ Hz, 1H, NCH), 2.41–2.27 (m, 2H, NCH), 1.78–1.25 (m, 6H, $-CH_2$), ^{13}C NMR ($CDCl_3$, 75 MHz): δ_c 156.5, 136.9, 134.2, 132.8, 130.9, 129.5, 129.3, 129.1, 128.7, 128.5, 127.9, 126.6, 122.4, 121.2, 120.0, 115.8, 66.2, 54.7, 49.3, 26.3, 25.9 and 24.0.

1-[(4-Chlorophenyl)-pyrrolidin-1-yl-methyl]naphthalen-2-ol (4f) (Table 2, Entry 6). White solid. Found: C: 74.94; H, 5.86; N, 4.06%. $C_{21}H_{20}ClNO$ requires C, 74.66; H, 5.97; N, 4.15%. Mp 118–120 °C (EtOAc); IR (KBr): 3059, 2963, 2829, 1592, 1451, 1400, 1347, 1228, 1100, 949, 889, 820 and 741 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ_H 13.69 (s, 1H, O*H*), 7.92 (d, $^3J = 9.0$ Hz, 1H, ArH), 7.74–7.63 (m, 2H, ArH), 7.53 (d, $^3J = 8.4$ Hz, 2H, ArH), 7.37 (dt, $^3J = 8.4$ Hz and $^4J = 1.5$ Hz, 1H, ArH), 7.28–7.20 (m, 3H, ArH), 7.14 (d, $^3J = 8.7$ Hz, 1H, ArH),

5.07 (s, 1H, CH), 3.50–3.10 (br, 1H, NCH), 2.80–2.10 (m, 3H, NCH), 1.91 (br, 4H, -CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_c 155.4, 139.7, 133.5, 131.6, 129.8, 129.6, 128.9, 128.8, 128.6, 126.4, 122.4, 120.8, 119.9, 116.2, 69.9, 53.3 and 23.3.

1-[(4-Bromophenyl)-pyrrolidin-1-yl-methyl]naphthalen-2-ol (4g) (Table 2, Entry 7). White solid. Found: C, 66.19; H, 5.16; N, 3.76%. $C_{21}H_{20}BrNO$ requires C, 65.98; H, 5.27, N, 3.66%. Mp 140–142 °C (EtOAc); IR (KBr): 3068, 2967, 2818, 2568, 1589, 1451, 1407, 1236, 1107, 1010, 951 and 820 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ_H 13.68 (s, 1H, O*H*), 7.79 (d, $^3J = 8.7$ Hz, 1H, ArH), 7.70–7.62 (m, 2H, ArH), 7.44 (d, $^3J = 8.4$ Hz, 2H, ArH), 7.36–7.31 (m, 3H, ArH), 7.20 (t, $^3J = 7.5$ Hz, 1H, ArH), 7.15 (d, $^3J = 8.7$ Hz, 1H, ArH), 5.03 (s, 1H, CH), 3.17 (br, 1H, -NCH), 2.70–2.10 (m, 3H, -NCH, -NCH_2), 1.77 (s, 4H, -CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_c 155.4, 140.2, 132.1, 131.7, 130.0, 129.6, 128.8,128.5, 126.4, 122.4, 121.6, 120.7, 119.8, 116.1, 69.9, 53.4 and 23.3.

1-[(2-Methoxyphenyl)-Piperidin-1-yl-methyl]naphthalen-2-ol (4h) (Table 2, Entry 8). White solid. Mp 160–162 °C, lit.[21] Mp 160–161 °C; IR (KBr): 3135, 3050, 2959, 2849, 1659, 1442, 1242, 742 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 13.4 (s, 1H, O*H*), 7.82 (d, $J = 8.55$ Hz, 1H, ArH), 7.57–7.67 (m, 3H, ArH), 7.28–7.34 (m, 1H, ArH), 7.12–7.22 (m, 3H, ArH), 6.77–6.89 (m, 2H, ArH), 5.89 (s, 1H, CH), 3.99 (s, 3H -OCH_3), 3.23–3.30 (m, 1H, -NCH), 2.64–2.71 (m, 1H, -NCH), 2.29–2.40 (m, 2H, -NCH_2), 1.71–1.92 (m, 6H, -CH_2), ^{13}C NMR ($CDCl_3$, 75 MHz) δc: 23.19, 23.57, 50.13, 54.61, 55.53, 60.74, 110.47, 117.19, 119.95, 121.46, 121,54, 122.20, 126.19, 128.36, 128.52, 128.80, 129.07, 129.29, 129.67, 132.36, 156.19, 156.40.

1-[(4-Chlorophenyl)-morpholin-4-yl-methyl]naphthalen-2-ol (4i) (Table 2, Entry 9). White solid. Mp 130–132 °C, lit.[20] Mp 130–131 °C; IR (KBr): 3437, 3061, 1621, 1596, 1451, 1383, 1237 and 1118 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H 13.17 (s, 1H, OH), 7.78–7.70 (m, 3H, ArH), 7.57–7.52 (m, 2H, ArH), 7.45–7.40 (m, 1H, ArH), 7.32–7.18 (m, 4H, ArH), 5.14 (s, 1H, CH), 3.72–3.51 (s, 4H, O-CH_2), 3.19–3.14 (m, 1H, NCH), 2.55-2.33 (m, 3H, NCH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_c 154.9, 137.4, 134.5, 132.4, 131.1, 130.5, 129.9, 129.5, 129.2, 127.2, 123.3, 121.2, 120.3, 115.0, 71.6, 67.3, 67.1, 54.3 and 51.9.

1-[(3,4-Dimethoxyphenyl)-morpholin-4-yl-Methyl]naphthalen-2-ol (4j) (Table 2, Entry 10). White solid. Found: C, 72.99; H, 6.54; N, 3.66%. $C_{23}H_{25}NO_4$ requires C, 72.80; H, 6.64; N, 3.69%. Mp 68–70 °C (EtOAc); IR (KBr): 3058, 2957, 2841, 1595, 1514, 1456, 1413, 1354, 1263, 1143, 1119, 1023, 941, 870, 817 and 749 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ_H 13.16 (s, 1H, O*H*), 7.84 (d, $^3J = 8.7$ Hz, 1H, ArH), 7.74–7.64 (m, 2H, ArH), 7.37 (t, $^3J = 7.2$ Hz, 1H, ArH), 7.24–7.07 (m, 4H, ArH), 6.73 (d, $^3J = 8.4$ Hz, 1H, ArH), 5.05 (s, 1H, CH), 3.79 (s, 4H, O-CH_2), 3.76 (s, 6H, OCH_3), 3.05 (br, 1H, NCH), 2.43 (brs, 3H, NCH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_c 154.6, 149.3, 148.8, 132.2, 131.0, 129.3, 128.8, 126.4, 122.5, 121.8, 120.9, 119.6, 115.2, 111.5, 110.9, 71.6, 66.8, 55.7, 55.6 and 51.1.

1,4-Bis[1-{(Piperidin-1-yl)methyl}-2-hydroxynaphthyl]benzene (4k) (Table 2, Entry 11). White solid. Found: C, 82.16; H, 7.13; N, 5.10%. $C_{38}H_{40}N_2O_2$ requires C, 81.98; H, 7.24; N, 5.03%. Mp 190–192 °C (EtOAc); IR

(KBr): 3055, 2930, 2852, 1617, 1514, 1449, 1412, 1357, 1268, 1234, 1152, 1098, 945, 814 and 743 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ_H 13.76 (s, 2H, OH), 7.52 (t, $^3J = 10.2$ Hz, 2H, ArH), 7.68–7.59 (m, 4H, ArH), 7.44 (s, 4H, ArH), 7.36–7.24 (m, 2H, ArH), 7.17 (d, $^3J = 7.8$ Hz, 2H, ArH), 7.11 (d,$^3J = 9.0$ Hz, 2H, ArH), 4.99 (s, 2H, CH), 3.20 (br, 2H, NCH), 2.50–1.30 (m, 18H, NCH, -CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_c 155.5, 139.2, 132.4, 129.3, 128.8, 128.5, 126.3, 121.1, 119.9, 116.1, 116.1, 71.4, 52.3, 26.0 and 24.1.

3-[(4-Chlorophenyl)-piperidin-1-yl-methyl]-4-hydroxy-Chromen-2-one (4l) (Table 2, Entry 12). White solid. Found: C, 68.41; H, 5.36; N, 3.67%. $C_{21}H_{20}ClNO_3$ requires C, 68.20; H, 5.45; N%. Mp 176–178 °C (EtOAc); IR (KBr): 3069, 2950, 2861, 1650, 1605, 1539, 1460, 1414, 1367, 1331, 1275, 1232, 1066, 951 and 758 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ_H 11.14 (s, 1H, O*H*), 7.84 (d, $^3J = 7.5$ Hz, 1H, ArH), 7.62 (d, $^3J = 8.4$ Hz, 2H, ArH), 7.45–7.37 (m, 3H, ArH), 7.22–7.05 (m, 2H, ArH), 5.13 (s, 1H, CH), 3.76 (d, $J = 11.7$ Hz, 1H, NCH), 2.93 (d, $J = 11.4$ Hz, 1H, NCH), 2.78–2.69 (m, 1H, NCH), 2.42–2.33 (m, 1H, NCH), 1.90–1.40 (m, 6H, -CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_c 173.6, 164.0, 154.0, 135.0, 134.7, 131.3, 130.3, 129.2, 124.1, 123.0, 120.6, 116.4, 94.6, 70.3, 53.6, 50.4, 24.3 and 22.4.

4-Hydroxy-3-[(3-nitrophenyl)-piperidin-1-yl-methyl]chromen-2-one (4m) (Table 2, Entry 13). White solid. Found: C, 66.56; H, 5.36; N, 7.27%. $C_{21}H_{20}N_2O_5$ requires C, 66.31; H, 5.30; N, 7.36%. Mp 184–186 °C (EtOAc); IR (KBr): 3076, 2948, 2863, 1642, 1604, 1535, 1461, 1402, 1348, 1284, 1237, 1072, 953 and 762 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ_H 11.15 (s, 1H, OH), 8.42 (s, 1H, ArH), 8.16 (d, $^3J = 8.1$ Hz, 1H, ArH), 8.01–7.95 (m, 2H, ArH), 7.53–7.43 (m, 2H, ArH), 7.24–7.18 (m, 2H, ArH), 5.24 (s, 1H, CH), 3.79 (d, $J = 10.5$ Hz, 1H, NCH), 2.91 (d, $J = 9.9$ Hz, 1H, NCH), 2.80–2.72 (m, 1H, NCH), 2.46−2.38 (m, 1H, NCH), 2.00–1.41 (m, 6H, -CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_c 173.1, 163.8, 154.0, 148.5, 138.6, 134.9, 131.7, 130.3, 124.2, 124.0, 123.3, 116.6, 95.0, 70.2, 54.2, 24.5 and 22.6.

3-[(4-Chlorophenyl)-dimethylamino-methyl]-4-hydroxy-chromen-2-one (4n) (Table 2, Entry 14). White solid. Found: C, 65.79; H, 4.82; N, 4.18%. $C_{18}H_{16}ClNO_3$ requires C, 65.56, H, 4.89; N, 4.25%. Mp 168–170 °C (EtOAc); IR (KBr): 3074, 2856, 1647, 1603, 1543, 1467, 1413, 1358, 1319, 1287, 1219, 1139, 1046, 949, 826 and 756 cm^{-1}; ^1H NMR (300 MHz; DMSO-d_6): δ_H 10.55 (s, 1H, OH), 7.84 (d, $^3J = 7.8$ Hz, 1H, ArH), 7.66 (d, $^3J = 8.4$ Hz, 2H, ArH), 7.45–7.35 (m, 3H, ArH), 7.20–7.08 (m, 2H, ArH), 5.26 (s, 1H, CH), 2.67 (s, 6H, NMe_2); ^{13}C NMR (DMSO-d_6, 75 MHz): δ_c 173.9, 163.0, 153.7, 152.6, 137.3, 133.0, 130.0, 128.6, 124.4, 124.2, 123.0, 120.0, 115.9, 93.1, 68.9 and 42.0.

1-[(4-Methyl-Piperazin-1-yl)-phenyl-methyl]naphthalen-2-ol (4o) (Table 2, Entry 15). White solid. Mp 140–142 °C (EtOAc), lit.[20] Mp 141–142 °C; IR (KBr): 3048, 2944, 2840, 2791, 2686, 1593, 1513, 1454, 1415, 1356, 1277, 1238, 1144, 1084 and 1002 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ_H 13.42 (s, 1H, OH), 7.97 (d,$^3J = 8.7$ Hz, 1H, ArH), 7.96–7.77 (m, 2H, ArH), 7.69 (d,$^3J = 7.2$ Hz, 2H, ArH), 7.50 (t, $^3J = 7.2$ Hz, 1H, ArH), 7.42–7.32 (m, 4H, ArH), 7.27 (d,$^3J = 8.7$ Hz, 1H, ArH), 5.25 (s, 1H, CH), 3.34–2.60 (m, 8H, N-CH_2); 2.43 (s, 3H, N-CH_3),

^{13}C NMR ($CDCl_3$, 75 MHz): δ_c 155.3, 139.5, 132.6, 130.1, 129.3, 129.1, 128.8, 128.6, 128.1, 127.0, 123.0, 121.5, 120.3, 116.0, 71.9, 55.6, 55.3, 53.7, 51.2 and 46.2.

1-(Piperidin-1-yl-pyridin-4-yl-methyl)naphthalen-2-ol (4p) (Table 2, Entry 16). Off-white solid, Mp 184–186 °C (EtOAc), lit.[20] Mp 185–186 °C; IR (KBr): 3047, 2943, 2825, 2670, 1593, 1513, 1449, 1416, 1356, 1317, 1270, 1230, 1152, 1094, 1032, 945, 869, 815 and 739 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ_H 13.51 (s, 1H, OH), 8.53 (d,$^3J = 4.5$ Hz, 2H, ArH), 7.83 (d,$^3J = 8.4$ Hz, 1H, ArH), 7.75–7.69 (m, 2H, ArH), 7.54 (d,$^3J = 4.5$ Hz, 2H, ArH), 7.43 (dt, $^3J = 7.7$ Hz and $^4J = 1.3$ Hz, 1H, ArH), 7.27 (dt, $^3J = 6.2$ Hz and $^4J = 1.6$ Hz, 1H, ArH), 7.19 (d,$^3J = 9.0$ Hz, 1H, ArH), 5.09 (s, 1H, CH), 3.28 (brs, 1H, NCH), 2.61–1.69 (m, 3H, NCH), 1.69–1.25 (m, 6H, NCH_2CH_2 and $NCH_2CH_2CH_2$),^{13}C NMR ($CDCl_3$, 75 MHz): δ_c 155.4, 150.1, 148.5, 132.0, 129.9, 129.0, 128.6, 126.6, 123.6, 122.5, 120.4, 119.8, 114.6, 70.7, 53.6, 25.8 and 23.8.

2-[(4-Chlorophenyl)-piperidin-1-yl-methyl]naphthalen-1-ol (4q) (Table 2, Entry 17). White solid. Found: C, 75.35; H, 6.22; N, 3.91%. $C_{22}H_{22}ClNO$ requires C, 75.09, H; 6.30; N, 3.98%. Mp 152–154 °C (EtOAc); IR (KBr): 3050, 2930, 2826, 2659, 1628, 1576, 1450, 1380, 1311, 1216, 1150, 1091, 1015, 934, 871, 836, 800 and 753 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ_H 13.27 (s, 1H, OH), 8.33 (d,$^3J = 7.5$ Hz, 1H, ArH), 7.71 (d,$^3J = 7.5$ Hz, 1H, ArH), 7.56–7.05 (m, 7H, ArH), 6.95 (d,$^3J = 8.4$ Hz, 1H, ArH), 4.51 (s, 1H, CH), 2.43 (brs, 3H, NCH), 1.50 (brs, 5H, NCH_2-CH_2), 1.26 (brs, 2H, NCH_2-CH_2-CH_2).

2-(Morpholin-4-yl-phenyl-methyl)naphthalen-1-ol (4r) (Table 2, Entry 18). Yellow solid. Found: C, 78.75; H, 6.52; N, 4.48%. $C_{21}H_{21}NO_2$ requires C, 78.97; H, 6.63; N, 4.39%. Mp 116–118 °C (EtOAc); IR (KBr): 3421, 3052, 2938, 2798, 1631, 1577, 1456, 1387, 1297, 1145, 1007, 854, 804 and 761 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ_H 12.60 (s, 1H, OH), 8.35 (d, $^3J = 7.5$ Hz, 1H, ArH), 7.73 (dd,$^3J = 8.1$ Hz and $^4J = 1.8$ Hz, 1H, ArH), 7.53–7.44 (m, 4H, ArH), 7.38–7.24 (m, 4H, ArH), 7.05 (d, $^3J = 8.4$ Hz, 1H, ArH), 4.52 (s, 1H, CH), 3.88–3.80 (m, 4H, O-CH_2), 2.85–2.45 (m, 4H, NCH_2), ^{13}C NMR ($CDCl_3$, 75 MHz): δ_c 151.5, 139.4, 133.7, 128.9, 128.6, 128.1, 127.2, 127.0, 126.2, 125.3, 124.9, 122.3, 119.0, 117.5, 77.0, 66.9 and 52.4.

2-[(4-Bromo-phenyl)-(4-methyl-piperazin-1-yl)-methyl]-naphthalen-1-ol (4s) (Table 2, Entry 19). Yellow solid. Found: C, 64.47; H, 5.55; N, 6.88%. $C_{22}H_{23}BrN_2O$ requires C, 64.24; H, 5.64, N: 6.81%. Mp 74–76 °C (EtOAc); IR (KBr): 3421, 3052, 2938, 2798, 1631, 1577, 1456, 1387, 1297, 1145, 1085, 1007, 854, 804 and 761 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ_H 12.38 (s, 1H, OH), 8.20 (dd, $^3J = 8.1$ Hz and $^4J = 2.1$ Hz, 1H, ArH), 7.62 (dd, $^3J = 6.6$ Hz and $^4J = 2.4$ Hz, 1H, ArH), 7.39–7.34 (m, 2H, ArH), 7.31 (d, $^3J = 8.7$ Hz, 2H, ArH), 7.21 (d, $^3J = 8.7$ Hz, 2H, ArH), 7.14 (d, $^3J = 8.4$ Hz, 1H, ArH), 6.88 (d, $^3J = 8.7$ Hz, 1H, ArH), 4.35 (s, 1H, CH), 2.41 (brs, 8H, NCH_2), 2.23 (s, 3H, NCH_3) ; ^{13}C NMR ($CDCl_3$, 75 MHz): δ_c 151.7, 138.8, 133.8, 132.1, 131.6, 131.5, 130.3, 127.3, 126.7, 126.3, 125.4, 125.1, 122.4, 122.1, 119.1, 117.4, 75.7, 68.3, 55.0 and 45.5.

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