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An efficient, simple and expedition synthesis of 1-amidoalkyl-2-naphthols as 'drug like' molecules for biological screening

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Abstract—An efficient and direct protocol for the preparation of amidoalkyl naphthols employing a multi-component, one-pot condensation reaction of β-naphthol, aromatic aldehydes and acetamide in the presence of ferric hydrogensulfate under solvent, solvent-free and microwave conditions is described. The thermal solvent-free and microwave green procedures offer advantages such as shorter reaction times, simple work-up, excellent yield, recovery and reusability of catalyst. It is noteworthy that 1-amidomethyl-2-naphthols can be converted into important biological 'drug like' active 1-aminomethyl-2-naphthols derivatives by amide hydrolysis.
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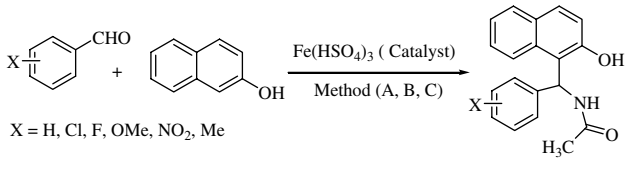
Compounds bearing 1,3-amino oxygenated functional groups are ubiquitous to a variety of biologically important natural products and potent drugs including a number of nucleoside antibiotics and HIV protease inhibitors, such as ritonavir and lipinavir.[1,2] In this research, we represent an advance in the context of synthetic methodology towards mentioned class of biologically important molecules. It is noteworthy that 1-amidomethyl-2-naphthols can be converted to important biologically active 1-aminomethyl-2-naphthol derivatives by amide hydrolysis reaction. The hypotensive and bradycardiac effects of these compounds have been evaluated.[2]

The preparation of 1-amidoalkyl-2-naphthols can be carried out by multi-component condensation of aryl aldehydes, 2-naphthol and acetonitrile or amide in the presence of Lewis or Brønsted acid catalysts such as montmorillonite K10 clay,[3] $Ce(SO_4)_2$,[4] Iodine,[5] $K_5CoW_{12}O_{40}{\cdot}3H_2O$,[6] *p*-TSA,[7] Sulfamic acid[8] and cation-exchange resins.[9] However, some of these catalysts suffer from the drawback of green chemistry such as prolonged reaction times, low yields, toxicity and recovery and reusability of the catalyst. Therefore, introducing clean processes and utilizing eco-friendly and green catalysts which can be simply recycled at the end of reactions have been under permanent attention. The demand for environmentally benign procedure with heterogeneous and reusable catalyst[10] promoted us to develop a safe alternate method for the synthesis of amidoalkyl naphthols.

Ferric(III) hydrogensulfate as a recyclable solid Brønsted acid catalyst is safe, easy to handle, environmentally benign and presents fewer disposal problems. This catalyst was prepared from the reaction of anhydrous ferric chloride (1 mmol) with concentrated sulfuric acid (3 mmol).[11,12] In continuation of our research with heterogeneous catalyst[13] in the present work, we report a new, simple, mild and effective procedure for the one-pot synthesis of amidoalkyl naphthol derivatives via a multi-component condensation reaction between aryl aldehydes, 2-naphthol and acetamide or acetonitrile in the presence of ferric hydrogensulfate as catalyst (Scheme 1).



Method A: CH_3CN (Ritter type reaction)
Method B: CH_3CONH_2 (Thermal Solvent-Free conditions)
Method C: CH_3CONH_2 (Microvawe Solvent-Free conditions)

Scheme 1.

Keywords: Amidoalkyl naphthol; Ferric hydrogensulfate; Multi-component reaction; Aminomethyl naphthol; Drug like; Biologic compound.
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To find out the optimum quantity of ferric hydrogensulfate, the reaction of 2-naphthol, benzaldehyde and acetamide was carried out under thermal solvent-free conditions (Method B) using different quantities of ferric hydrogensulfate (Table 1). Five mole percent of ferric hydrogensulfate gave excellent yield in 50 min as can be seen from Table 1. A slight excess of the acetamide was found to be advantageous and hence the molar ratio of 2-naphthol to acetamide was kept at 1:1.2.

Thus, we prepared a range of amidoalkyl naphthols under the optimized reaction conditions: 2-naphthol (1 mmol), arylaldehydes (1 mmol) and acetamide (1.2 mmol) or acetonitrile (reactant as well as solvent, 5 mL) in the presence of ferric hydrogensulfate (5 mol%). A series of amidoalkyl naphthols were prepared in high to excellent yields by three methods (A, B, C) (Table 2).

As shown in Table 2 and Method A,[14] the three-component reaction of 2-naphthol, arylaldehydes and acetonitrile (reactant as well as solvent, 5 mL) was performed in the presence of ferric hydrogensulfate (5 mol%). Aromatic aldehydes with substituents carrying either electron-donating or electron-withdrawing groups gave the desired products in Ritter type reaction with yields of 47–74% after 20 h.

A mechanistic rationale portraying the probable sequence of events is given in Scheme 2. The formation of product can be explained by the Ritter reaction.[4] It is suggested that the benzaldehyde is first reacted with 2-naphthol and raised to 1-(hydroxyl (aryl) methyl) naphthalene-2-ol **I** whose benzylic protonated hydroxyl group then reacts with the acetonitrile and produces intermediate **II** in Ritter type reaction. Hydrolysis of **II** accompanied by tautomerization gave the desired 1-amidoalkyl-2-naphthol.

In addition we conducted the reaction of 2-naphthol, aromatic aldehydes and acetamide (instead of toxic acetonitrile) in the presence of catalyst under thermal solvent-free (Table 2, Method B)[15] and microwave solvent-free (Table 2, Method C)[16] conditions. The experimental procedure is remarkably simple and requires no toxic acetonitrile as organic solvent.

In all cases, aromatic aldehydes with substituents carrying either electron-donating or electron-withdrawing groups reacted successfully and gave the products in high yields. It was shown that the aromatic aldehydes with electron withdrawing groups reacted faster than the aromatic aldehydes with electron releasing group as would be expected. As reported in the literatures,[5–7]

Table 1. The effect of amount of ferric hydrogensulfate on the reaction of 2-naphthol, benzaldehyde and acetamide under thermal solvent free conditions

Entry	Catalyst (mol%)	Time (min)	Yield[a] (%)
1	20	38	92
2	15	40	93
3	10	46	91
4	5	50	94
5	2.5	67	86

[a] Yields refer to the pure isolated products.

Table 2. Preparation of 1-amidoalkyl-2-naphthols

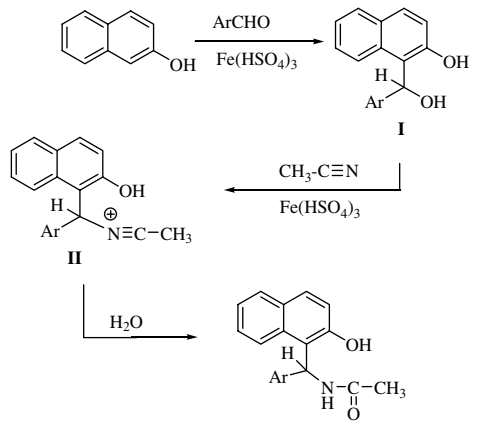
Entry	Aldehyde	Method A[a] Time/yield (%)	Method B[b] Time/yield (%)	Method C[c] Time/yield (%)	Mp[d] (lit. mp)[ref.]
1	Benzaldehyde	(20 h/56)	(65 min/83)	(7 min/90)	245–246 (241–243)[4]
2	4-(*N*,*N*-Dimethylamino)benzaldehyde	(20 h/47)	(80 min/74)	(14 min/84)	123–125 (78–79)[4]
3	4-Methoxybenzaldehyde	(20 h/53)	(55 min/84)	(11 min/87)	183–185 (184–186)[4]
4	4-Chlorobenzaldehyde	(20 h/63)	(45 min/88)	(6 min/90)	223–225 (224–227)[4]
5	4-Bromobenzaldehyde	(20 h/61)	(45 min/89)	(6 min/89)	227–229 (228–230)[8]
6	3-Nitrobenzaldehyde	(20 h/74)	(25 min/97)	(5 min/97)	241–242 (182–184)[4]
7	4-Fluorobenzaldehyde	(20 h/52)	(60 min/84)	(6 min/89)	230–232 (209–210)[4]
8	2,4-Dichlorobenzaldehyde	(20 h/68)	(45 min/90)	(6 min/90)	201–203 (198–199)[4]
9	2-Chlorobenzaldehyde	(20 h/57)	(50 min/86)	(8 min/89)	213–215 (194–196)[8]
10	3-Methoxybenzaldehyde	(20 h/55)	(55 min/81)	(11 min/84)	201–204 (203–205)[3]
11	2-Nitrobenzaldehyde	(20 h/63)	(30 min/89)	(5 min/94)	179–182 (180–182)[4]
12	2-Methylbenzaldehyde	(20 h/50)	(70 min/76)	(10 min/87)	199–202 (200–202)[8]
13	3,4-Dimethoxybenzaldehyde	(20 h/61)	(35 min/88)	(5 min/96)	235–237 (235–236)[4]
14	4-Methylbenzaldehyde	(20 h/51)	(70 min/79)	(9 min/88)	222–223
15	4-Nitrobenzaldehyde	(20 h/73)	(25 min/92)	(5 min/96)	248–250
16	3-Fluorobenzaldehyde	(20 h/51)	(50 min/87)	(6.5 min/91)	248–249
17	2,5-Dimethoxybenzaldehyde	(20 h/59)	(35 min/87)	(5 min/94)	251–253
18	Propionaldehyde	20 h/—	60 min/—	8 min/—	—

[a] Method A: the reaction was carried out with 5 mol% of $Fe(HSO_4)_3$, acetonitrile (reactant as well as solvent, 5 mL) under reflux conditions at 85 °C; reaction time 20 h; molar ratio aldehydes/2-naphthol (1/1).

[b] Method B: the reaction was carried out under thermal solvent-free conditions in an oil bath at 85 °C; molar ratio aldehydes/2-naphthol/acetamide/catalyst (1/1/1.2/0.05).

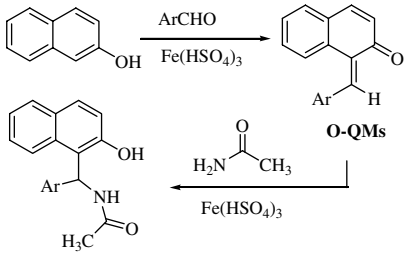
[c] Method C: the reaction was carried out in a microwave oven at 450 W under solvent-free conditions; molar ratio aldehydes/2-naphthol/acetamide/catalyst (1/1/1.2/0.05).

[d] Yields refer to the pure isolated products. All known products have been reported previously in the literature and were characterized by comparison of IR and NMR spectra with authentic samples.[3–9]



Scheme 2.

the reaction of 2-naphthol with aromatic aldehydes in the presence of acid catalyst is known to give *ortho*-quinone methides (O-QMs). The same O-QMs, generated *in-situ*, have been reacted with acetamide to form 1-amidoalkyl-2-naphthol derivatives. A reasonable explanation for this result can be given by considering the nucleophilic addition to O-QM intermediate favourable via conjugate addition on α,β-unsaturated carbonyl group that aromatizes ring of this intermediate. The electron withdrawing groups (EWD) substituted on benzaldehyde in O-QM intermediate increase the rate of 1,4-nucleophilic addition reaction because of alkene LUMO is at lower energy in the neighbouring withdrawing groups than electron donating groups (EDG).[17] The reactions of aliphatic aldehydes (Table 2, entry 18) instead of aromatic aldehydes would fail to give the desired products as well as the known catalysts, such as $K_5CoW_{12}O_{40}{\cdot}3H_2O$,[6] *p*-TSA,[7] Sulfamic acid[8] and cation-exchange resins.[9]



Scheme 3.

To find the specific effect of microwave irradiation on the reaction, these reactions were carried out under the same conditions in the microwave oven (Table 2, Method C). It was observed that the reaction time decreased considerably and also the yields of the products increased in the absence of solvent. Thus, microwave was found to have beneficial effect on the reaction. Thus, solvent-free MW conditions were found to have beneficial effect on the reaction.

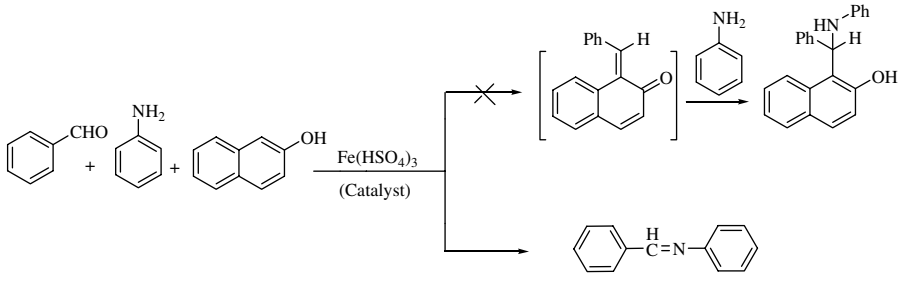
The proposed mechanism for the ferric hydrogensulfate catalyzed preparation of amidoalkyl naphthols from the reaction of 2-naphthol, aromatic aldehydes and acetamide under thermal and microwave conditions is shown in Scheme 3.

We also studied the reaction of aniline instead of acetamide with 2-naphthol and benzaldehyde in the presence of catalyst. The experiment showed that Schiff base was prepared from the reaction of aldehydes and amine and O-QMs were not formed in the reaction conditions. Thus, the preparation of 1-aminomethyl-2-naphthols from condensation reaction of O-QMs with amines was unsuccessful (Scheme 4).

To show the merit of the present work in comparison with reported results in the literature, we compared results of ferric hydrogensulfate with montmorillonite K10 clay,[3] $Ce(SO_4)_2$,[4] I_2[5] and $K_5CoW_{12}O_{40}{\cdot}3H_2O$[6] in the synthesis 1-amidomethyl-2-naphthols of derivatives. As shown in Table 3, ferric hydrogensulfate can act as effective catalyst with respect to reaction times, yields and the obtained products.

The separated catalyst can be reused after washing with $CHCl_3$ and drying at 100 °C. The reusability of the catalyst was checked by the reaction of benzaldehyde and 2-naphthol in the presence of acetamide using 5 mol% of $Fe(HSO_4)_3$ under solvent-free condition at 85 °C. The results indicate that the catalyst can be used five times without any loss of its activity (Table 4).

In conclusion, we have elaborated an efficient and expeditious synthesis of 1-amidoalkyl-2-naphthol derivatives accomplished via three-component reactions of aryl aldehydes, 2-naphthol and acetonitrile or acetamide in the presence of $Fe(HSO_4)_3$ by three methods A, B and C.



Scheme 4.

Table 3. Comparison result of ferric hydrogensulfate with montmorillonite K10 clay,[3] $Ce(SO_4)_2$,[4] I_2[5] and $K_5CoW_{12}O_{40}{\cdot}3H_2O$[6] in the synthesis of 1-amidoalkyl-2-naphthol

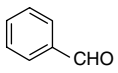
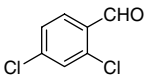
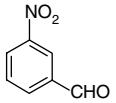
Entry	Aldehyde	Catalyst	Molar ratio Aldehyde/2-naphthol/(catalyst mol%); conditions	Time	Yield (%)
1		$Ce(SO_4)_2$	1/1/(100 mol%); under reflux	36 h	72
		I_2	1/1/(5 mol%); solvent-free, 125 °C	5.5 h	85
		Montmorillonite K10 clay	1/1/(0.1 g); solvent-free, 125 °C	1.5 h	89
		$K_5CoW_{12}O_{40}{\cdot}3H_2O$	1/1/(1 mol%); solvent-free, 125 °C	2 h	90
		$Fe(HSO_4)_3$	1/1/(5 mol%); Method B	50 min	93
		$Fe(HSO_4)_3$	1/1/(5 mol%); Method C	7 min	90
2		$Ce(SO_4)_2$	1/1/(100 mol%); under reflux	36 h	56
		I_2	—		
		Montmorillonite K10 clay	1/1/(0.1 g); solvent-free, 125 °C	1 h	84
		$K_5CoW_{12}O_{40}{\cdot}3H_2O$	1/1/(1 mol%); solvent-free, 125 °C	3 h	82
		$Fe(HSO_4)_3$	1/1/(5 mol%); Method B	45 min	90
		$Fe(HSO_4)_3$	1/1/(5 mol%); Method C	6 min	90
3		$Ce(SO_4)_2$	1/1/(100 mol%); under reflux	16 h	65
		I_2	1/1/(5 mol%); solvent-free, 125 °C	5 h	81
		Montmorillonite K10 clay	1/1/(0.1 g); solvent-free, 125 °C	0.5 h	96
		$K_5CoW_{12}O_{40}{\cdot}3H_2$	1/1/(1 mol%); solvent-free, 125 °C	3 h	78
		$Fe(HSO_4)_3$	1/1/(5 mol%); Method B	25 min	97
		$Fe(HSO_4)_3$	1/1/(5 mol%); Method C	5 min	97

Table 4. Recyclability of the catalyst in the reaction of benzaldehyde and 2-naphthol in the presence of acetamide using 5 mol% of $Fe(HSO_4)_3$ under solvent-free condition at 85 °C

Run no.	Yield (%)
1	93
2	90
3	89
4	90
5	89

Acknowledgments

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14. General procedure for the preparation of amidoalkyl naphthols (Method A): To a solution of 2-naphthol (1 mmol) and benzaldehyde (1 mmol) in acetonitrile (5 mL), ferric hydrogensulfate (5 mol%) was added, then the reaction mixture was stirred for 20 h at 85 °C under reflux condition. Reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was filtered and the heterogeneous catalyst was recovered. Then solution was concentrated to solidify. The solid product was purified by recrystallization in aqueous EtOH (15%).
15. General procedure for the preparation of amidoalkyl naphthols (Method B): To a mixture of 2-naphthol (1 mmol), aldehydes (1 mmol) and acetamide (1.2 mmol), ferric hydrogensulfate (5 mol%) was added. The mixture was stirred at 85 °C in oil bath and the reaction was followed by TLC. After completion of reaction, mass was cooled to 25 °C, then the solid residue was solved in boiling EtOH and the mixture stirred for 5 min. The catalyst was recovered. Then solution was cooled to room temperature, the solid so obtained was filtered and recrystallized from aqueous EtOH (15%).
16. General procedure for the preparation of amidoalkyl naphthols (Method C): To a mixture of aldehyde (1 mmol), 2-naphthol (1 mmol), and acetamide (1.2 mmol), $Fe(HSO_4)_3$ (5 mol%) was added and the mixture was inserted in a microwave oven (samsung model KE300R) at 450 W for the appropriate time (Table

2, Method C). The reaction was followed by TLC. After completion of reaction, mass was cooled to 25 °C, then the solid residue was solved in boiling EtOH and the mixture stirred for 5 min. The catalyst was recovered. Then solution was cooled to room temperature, the solid so obtained was filtered and recrystallized from aqueous EtOH (15%). Some physical data of these compounds are represented below:

N-[Phenyl-(2-hydroxy-naphthalen-1-yl)-methyl]-acetamide (Table 2, entry 1): [mp: 245–246 °C]; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.98 (s, 3H), 7.19–1.10 (m, 4H), 7.26–7.20 (m, 4H), 7.33 (t, J = 7.5 Hz, 1H), 7.74 (d, J = 9.2 Hz, 1H,), 7.80 (d, J = 8.0 Hz, 1H), 7.84 (s, 1H), 8.45 (d, J = 8.5 Hz, 1H), 10.02 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 23.2, 40.4, 119.2, 119.4, 122.9, 123.8, 126.6, 126.9, 128.5, 128.7, 128.9, 129.1, 129.8, 132.9, 143.1, 153.7, 169.1 ppm; IR (KBr, cm^{-1}): 3399, 3246, 3062, 1640, 1582, 1514, 1372, 1337, 1060, 808, 742, 696, 623.

N-[(3-Nitro phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-acetamide (Table 2, entry 6): [mp: 241–242 °C]; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.01 (s, 3H), 7.17 (t, J = 8.0 Hz, 1H), 7.19 (d, J = 8.6 Hz, 1H), 7.24 (t, J = 7.4 Hz, 1H), 7.38 (t, J = 7.4 Hz, 1H), 7.51 (m, 2H), 7.78 (t, J = 8.6 Hz, 2H), 7.83 (br, 1H), 7.97–7.99 (m, 2H), 8.58 (d, J = 8.0 Hz, 1H), 10.16 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 23.1, 48.2, 118.3, 118.9, 120.9, 121.8, 123.1, 127.3, 123.2, 128.9, 129.2, 130.1, 130.5, 132.7, 133.4, 145.9, 148.2, 153.9, 170.3 ppm; IR (KBr, cm^{-1}): 3373, 3088, 2598, 1645, 1524, 1350, 1232, 1158, 1063, 808, 705.

N-[(4-Fluoro phenyl)-(2-hydroxy naphthalen-1-yl)-methyl]-acetamide (Table 2, entry 7): [mp: 230–232 °C]; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.96 (s, 3H), 7.04 (d, J = 8.8 Hz, 1H), 7.08 (d, J = 9.7 Hz, 2H), 7.15 (t, J = 5.6 Hz, 2H), 7.20 (d, J = 8.8 Hz, 1H), 7.25 (t, J = 7.3 Hz,1H), 7.36 (t, J = 7.3 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.82 (br d, 1H), 8.41 (d, J = 8.3 Hz, 1H), 9.97 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 22.5, 47.3, 114.6 (d, $^2J_{C-F}$ = 21.1 Hz), 118.4, 118.5, 122.3, 122.9, 126.2, 127.8 (d, $^3J_{C-F}$ = 8 Hz), 128.3, 128.4, 129.2, 132.1, 138.6, 153.0, 160.6 (d, $^1J_{C-F}$ = 240.2 Hz), 169.1 ppm; IR (KBr, cm^{-1}): 3392, 2974, 1627, 1576, 1508, 1438, 1334, 1225, 1062, 823, 748, 601, 489.

N-[(2,4-Dichloro phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-acetamide (Table 2, entry 8): [mp: 201–203 °C]; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.88 (s, 3H), 6.96 (d, J = 7.4 Hz, 1H), 7.11 (d, J = 9.2 Hz, 1H), 7.27 (t, J = 7.4 Hz, 1H), 7.34–7.32 (m, 3H), 7.54 (d, J = 8.6 Hz, 1H), 7.70 (d, J = 8.6 Hz, 1H), 7.76 (d, J = 8 Hz, 1H), 7.91 (d, J = 8.6 Hz, 1H), 8.59 (d, J = 8.0 Hz, 1H), 9.81 (br d, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 22.9, 47.8, 117.8, 119.1, 122.9, 123.1, 126.9, 127.1, 128.7, 128.9, 129.2, 130.2, 131.7, 132.1, 133.2, 133.3, 139.8, 154.2, 169.3 ppm; IR (KBr, cm^{-1}): 3404, 3116, 1649, 1579, 1516, 1438, 1279, 1162, 812, 583, 458.

N-[(2-Chloro phenyl)-(2-hydroxy naphthalen-1-yl)-methyl]-acetamide (Table 2, entry 9): [mp: 213–215 °C]; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.91 (s, 3H), 7.56–7.08 (m, 8H), 7.73 (d, J = 7.6 Hz, 1H), 7.78 (d, J = 6.1 Hz, 1H), 8.00 (d, J = 7.0 Hz, 1H), 8.50 (s, 1H), 9.75 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 22.3, 47.5, 117.0, 118.5, 122.1, 122.7, 126.1, 126.2, 127.9, 128.2, 128.4, 129.1, 129.2, 129.7, 132.1, 132.7, 139.7, 153.5, 168.4 ppm; IR (KBr, cm^{-1}): 3427, 3061, 1640, 1577, 1514, 1471, 1438, 1371, 1268, 1163, 1063, 808, 752, 711, 668. MS: m/z = 327 (3.93%), 326 (4.13%), 325 (M$^+$, 14.37%), 290 (9.69%), 232 (23.55%), 231 (100.00%), 115 (7.48%).

N-[(4-Methyl phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-acetamide (Table 2, entry 14): [mp: 222–223 °C]; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.96 (s, 3H), 2.21 (s, 3H), 7.08–7.03 (m, 5H), 7.19 (d, J = 8.8 Hz, 1H), 7.24 (t,J = 7.1 Hz, 1H), 7.34 (m, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.82 (br d, 1H), 8.36 (d, J = 8.1 Hz, 1H), 9.91 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 20.4, 22.6, 47.6, 118.4, 118.9, 122.2, 123.1, 125.9, 126.1, 128.3, 128.4, 128.9, 132.2, 134.9, 139.4, 143.3, 152.9, 168.9 ppm; IR (KBr, cm^{-1}): 3419, 3316, 3070, 1621, 1595, 1561, 1514, 1466, 1392, 1283, 1202, 1141, 1051, 939, 884, 784, 745, 712; MS: m/z = 305 (M$^+$, 21.00%), 246 (29.16%), 245 (50.55%), 231 (100.00%), 232 (31.20%), 202 (16.12%), 115 (10.04%).

N-[(4-Nitro-phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-acetamide (Table 2, entry 15): (mp: 248–250 °C); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.02 (s, 3H), 7.19 (d, J = 8.0, 1H), 7.22 (d, J = 8.8, 1H), 7.28 (t, J = 7.47 Hz, 1H), 7.41 (t, J = 7.34, 1H), 7.52–7.58 (m, 2H), 7.81 (t, J = 9.38 Hz, 2H), 7.89 (br d, 1H), 8.05–8.03 (m, 2H), 8.60 (d, J = 8.0 Hz, 1H), 10.11 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 22.5, 47.6, 117.7, 118.4, 120.3, 121.1, 122.5, 126.7, 128.6, 129.4, 129.8, 132.1, 132.7, 145.3, 147.7, 153.2, 169.5 ppm; IR (KBr, cm^{-1}): 3391, 3267, 2593, 1648, 1603, 1522, 1438, 1063, 825, 739, 447; MS: m/z = 336 (M$^+$, 26.66%), 319 (75.99%), 276 (52.02%), 260 (54.15%), 231 (63.80%), 202 (45.11%), 230 (100.00%), 115 (18.05%).

N-[(3-Fluoro phenyl)-(2-hydroxy naphthalen-1-yl)-methyl]-acetamide (Table 2, entry 16): [mp: 248–249 °C]; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.98 (s, 3H), 6.98–6.92 (m, 3H), 7.12 (d, J = 8.3 Hz, 1H), 7.27–7.19 (m, 3H), 7.37 (t, J = 7.3 Hz, 1H), 7.76 (d, J = 8.6 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.84 (br d, 1H), 8.44 (d, J = 8.2 Hz, 1H), 10.01 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 22.5, 47.5, 112.5 (d, $^2J_{C-F}$ = 22.1 Hz), 112.7 (d, $^2J_{C-F}$ = 20.9 Hz), 118.3, 118.4, 122.1 (d, $^4J_{C-F}$ = 2.5 Hz), 122.4, 122.9, 126.4, 128.3, 128.5, 129.4, 129.8 (d, $^3J_{C-F}$ = 8.1 Hz), 132.1, 145.9 (d, $^3J_{C-F}$ = 6.6 Hz), 153.1, 162.0 (d, $^1J_{C-F}$ = 241.2 Hz), 169.3 ppm; IR (KBr, cm^{-1}): 3410, 3160, 1640, 1589, 1545, 1484, 1439, 1335, 1280, 1064, 989, 814, 760, 743. MS: m/z = 310 (4.79%), 309 (M$^+$, 21.45%), 251 (9.00%), 250 (51.75%), 249 (100.00%), 231 (14.44%), 220 (16.11%), 122 (7.31%), 115 (9.01%). *N*-[(2,5-Dimethoxy phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-acetamide (Table 2, entry 17): [mp: 251–253 °C]; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.88 (s, 3H), 3.48 (s, 3H), 3.64 (s, 3H), 6.77–6.72 (m, 2H), 7.23–7.10 (m, 4H), 7.39 (s, 1H), 7.73–7.66 (m, 2H), 8.27–8.15 (m, 2H), 9.75 (s, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 22.5, 44.4, 55.2, 55.9, 111.1, 111.9, 115.7, 118.5, 118.9, 122.0, 123.2, 125.7, 128.1, 128.6, 131.7, 132.4, 150.7, 152.7, 153.1, 168.1 ppm; IR (KBr, cm^{-1}): 3365, 3174, 3002, 2939, 1614, 1577, 1497, 1436, 1370, 1317, 1277, 1218, 1084, 1052, 819, 797, 727; MS: m/z = 351 (M$^+$, 17.83%), 308 (5.82%), 276 (5.87%), 262 (36.04%), 261 (100.00%), 218 (16.71%), 144 (6.60%), 115 (7.99%).

17. Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books: Sausalito, California, 2006.