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A simple and efficient method for the synthesis of amidophenols using iodine as catalyst under neat condition

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Abstract

A convenient and efficient one-pot synthesis of substituted amidophenols using iodine as catalyst at room temperature under neat condition is described.

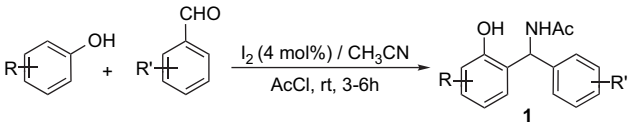
1. Introduction

In recent years there has been considerable interest in the one-pot multicomponent reaction due to their diversity, efficiency and rapid access to complex and highly functionalized organic molecules. Pioneering work by several research groups in this area has already established the versatility and uniqueness of one-pot multicomponent coupling protocols as a powerful methodology for the synthesis of diverse structural scaffolds required in the search of novel therapeutic molecules.[1] They also have considerable advantages in terms of user and environmental friendliness because of the step reduction and atom economy associated to their use.[2] In the past decade there have been tremendous developments in three- and four-component reactions and great efforts have been and still are being made to find and develop new MCRs.[3]

2. Results and discussion

The use of molecular iodine has received considerable attention as an inexpensive, non-toxic, readily available catalyst for various organic transformations, affording the corresponding products with high selectivity in excellent yields.[4] The mild Lewis acidity associated with iodine has enhanced its usage in organic synthesis to realize several organic transformations using catalytic amounts to stoichiometric levels. Owing to numerous advantages associated with iodine, it has been explored as a powerful catalyst for various organic transformations. Amide moieties are important constituents of many biologically significant compounds.[5]

In a broad programme of developing efficient, selective and eco-friendly synthetic methods for pharmacologically important moieties, herein, we report a simple, improved and one-pot procedure for the synthesis of substituted amidophenols catalyzed by iodine under ambient temperature with good yields (Scheme 1). In our previous communication, we demonstrated that a mixture of substituted phenol and aldehyde, when heated at 85 °C in acetonitrile in the presence of stoichiometric amount of anhydrous ceric sulfate for 24 h, afforded acetamidophenols in moderate yields.[6] For further



Scheme 1.

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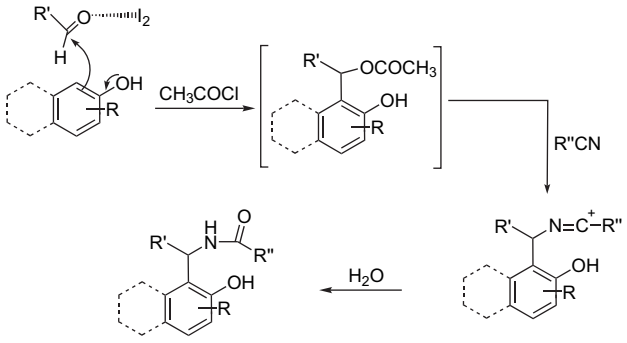


Scheme 2.

optimization and to extend the generality of this methodology, we explored an alternative procedure, which resulted in an operationally efficient process. Thus, instead of heating the reaction in acetonitrile, we stirred the reaction at room temperature for 6 h in the presence of catalytic amount of iodine and acetyl chloride.

Initially, we evaluated the catalyst required for the synthesis of amidophenols. After systematic screening, iodine/acetyl chloride under neat condition was found to be the best. Next, we evaluated the amount of iodine required for the transformation and found 4 mol % to be the optimum. We also monitored the reaction with iodine in the absence of acetyl chloride. With iodine alone, there was no progress in the reaction. The role of acetyl chloride for the formation of product is not clear. We have not yet established a mechanism for the formation of amidophenols, but a reasonable possibility[7] is indicated in Scheme 2.

The isolation of product is very simple and easy as quenching the reaction with minimum amount of saturated sodium thiosulfate resulted in the precipitation of desired acetamidophenol. The precipitated solid was filtered, dried and washed with diethyl ether to afford the corresponding pure product.

The interesting feature of this method is that no acetylated product was observed in any case. The reaction with salicylaldehyde also gave the corresponding acetamidophenol and not the –OH acetylated product and the product was confirmed by ^{1}H NMR and X-ray analysis [Fig. 1 (entry 19, Table 1)].[10] The formation of non-acetylated product is in contrast to the observation made in the corresponding iodine catalyzed reactions.[4h,i] We have no definite explanation for the formation of this anomaly.

The scope and generality of the reaction were studied with various phenols and aldehydes under optimized condition and the results are summarized in Table 1. The reaction was amenable to a wide variation in phenol and aldehydes. The reaction proceeded well irrespective of the presence of electron withdrawing or electron donating group on aldehydes and phenols.

The structures of all products (entries 1–19) were confirmed by IR, NMR and X-ray analysis [Fig. 2 (entry 11, Table 1)[8] and Fig. 3 (entry 2, Table 1)[9]].

To demonstrate the versatility of this reaction procedure, we examined the reactions with various nitriles and substituted aldehydes. Only α-hydrogenated nitriles involved in the reaction and yielded the corresponding amidophenols (Scheme 3) and the results are summarized in Table 2. Unfortunately reactions with aromatic nitriles like benzonitrile, 2-chlorobenzonitrile and 2-trifluoromethyl benzonitrile did not yield the desired product, while bisnaphthols were formed exclusively. This shows that nitrile moiety was not involved in the reaction pathway (Scheme 4).

3. Conclusion

In conclusion, this article describes a simple and efficient procedure for the synthesis of amidophenols with the use of commercially available iodine under neat condition. The methodology described here is a distinct improvement over our previous protocol in terms of scope, generality, easy product isolation with increased yield. The biological evaluation of these compounds is underway.

4. Experimental

4.1. General

Glassware was dried in hot air oven prior to use. 2-(Trifluoromethyl)benzonitrile and benzonitrile were purchased from Lancaster Research Chemicals. All other reagents were

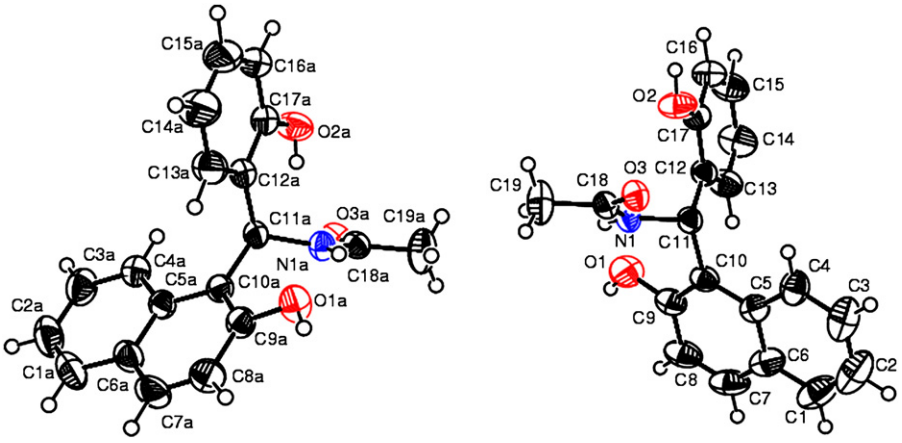
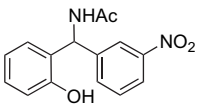
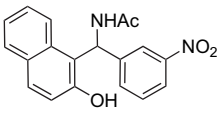
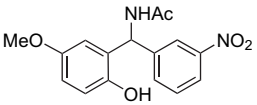
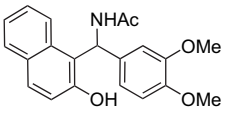
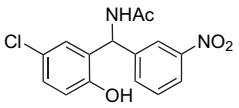
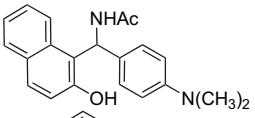
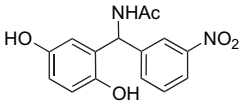
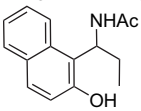
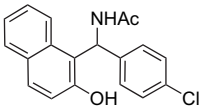
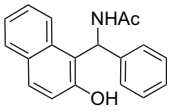
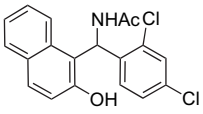
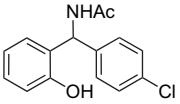
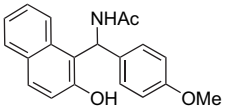
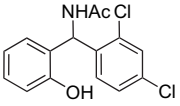
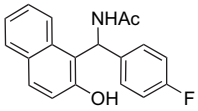
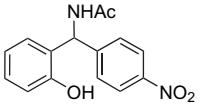
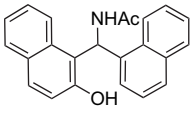
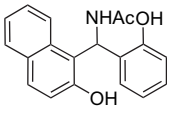
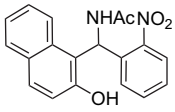


Figure 1.

Table 1
Synthesis of acetamidophenols

Entry	Product[a]	*t* (h)	Yield[b] (%)	Entry	Product[a]	*t* (h)	Yield[b] (%)
1		6	82	11		3	90
2		5	80	12		6	75
3		6	76	13		6	66
4		6	65	14		6	72
5		4	86	15		5	75
6		4	88	16		6	68
7		5	82	17		5	75
8		6	80	18		6	72
9		6	72	19		6	62
10		3	88				

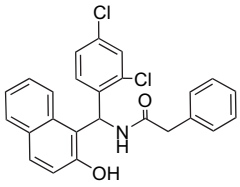
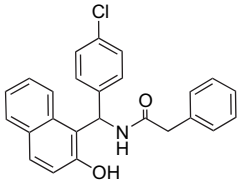
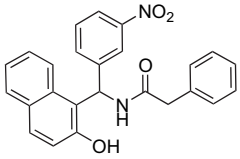
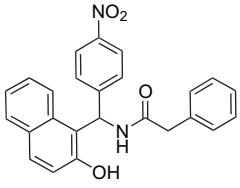
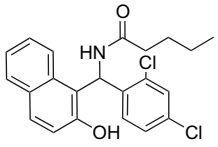
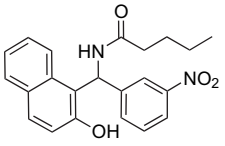
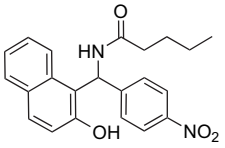
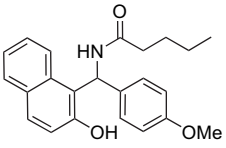
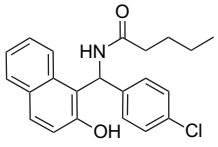
[a] All the products were characterized by IR, NMR and mass spectra.
[b] Isolated yields.

purchased from S.D. Fine. Chem. Limited and used as received. Acetonitrile was distilled from CaH_2 under nitrogen and stored over 4Å molecular sieves. DMSO-d_6 was purchased from Aldrich. IR measurements were done as KBr pellets for solids using Perkin Elmer Spectrum RXI FT-IR. The ^1H and ^{13}C NMR were recorded in DMSO-d_6 with JEOL 500 MHz and Bruker 300 MHz high resolution NMR spectrometers. DMSO-d_6 was used as the solvent for the NMR spectral measurements and spectra were recorded in parts per million with TMS as internal standards. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), multiplet (m) and broad (br). The mass was analyzed by using an Electrospray Ionisation Method with Thermo Finnigan Mass spectrometer. Melting points were determined in capillary tubes and are uncorrected. Analytical TLC was performed on precoated plastic sheets of silica gel G/UV-254 of 0.2 mm thickness (Macherey-Nagel, Germany). Elemental analysis data were recorded using a Thermo Finnigan FLASH EA 1112 CHN analyzer. Column chromatography was carried out using 100–200 mesh silica gel.

4.2. Representative procedure for the synthesis of acetamidophenols

A mixture of 4-chlorobenzaldehyde (10 mmol), β-naphthol (10 mmol) and iodine (0.4 mmol, 4 mol %) was mixed in acetonitrile (2 mL). To that suspension acetyl chloride (2.8 mmol, 0.2 mL) was added and the reaction stirred at room

Table 2

Entry	Amidophenol	Time (h)	Yield[a] (%)
1		8	62
2		8	65
3		8	70
4		10	66
5		10	58
6		10	63
7		12	60
8		14	45
9		10	62

[a] Isolated yield.

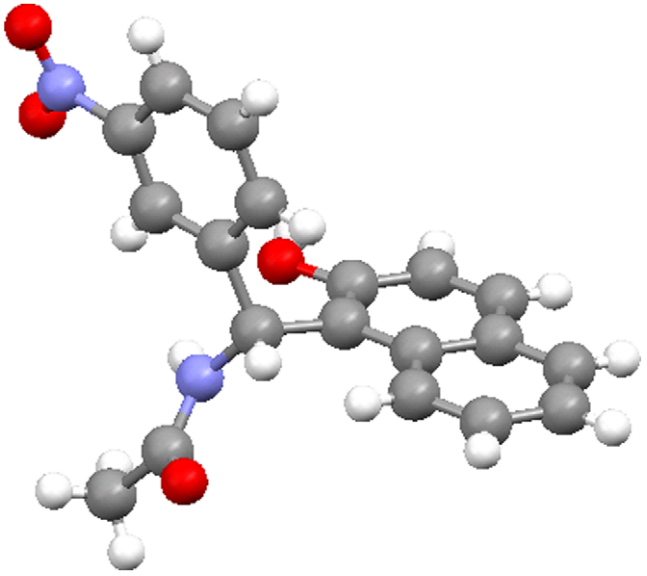


Figure 2.

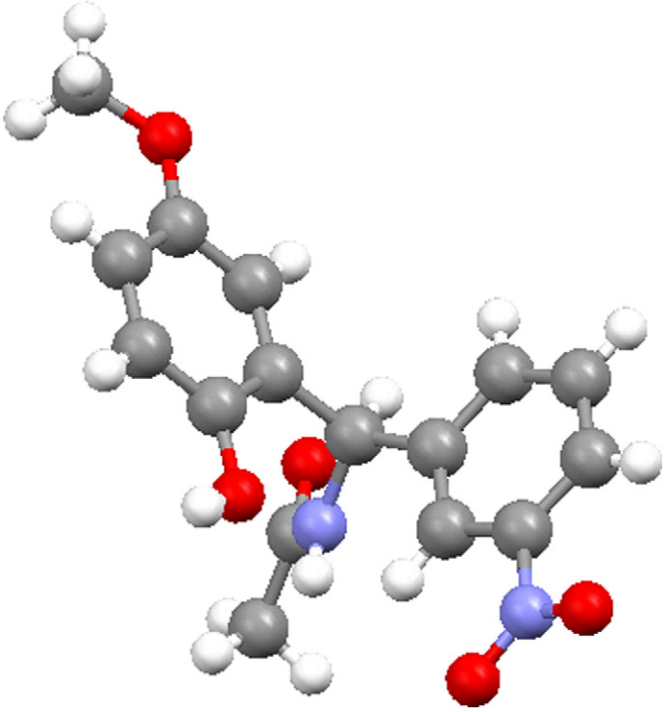
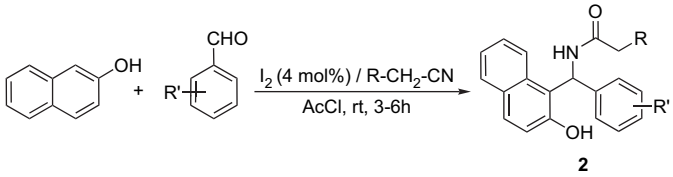


Figure 3.

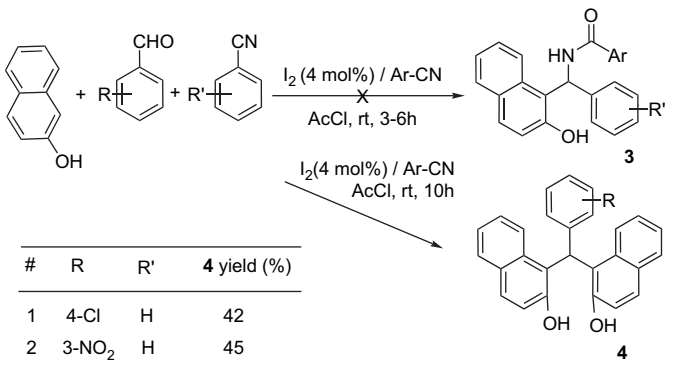


Scheme 3.

temperature for the appropriate time as mentioned in Table 1. After completion of the reaction (as monitored by TLC), saturated sodium thiosulfate in water (5 mL) was added. The precipitated solid was filtered and dried. The dried sample was washed with diethyl ether (2×10 mL) and again dried.

4.2.1. N-[(4-Chloro-phenyl)-(2-hydroxy-phenyl)-methyl]-acetamide (Table 1, entry 16)

Orange solid. Isolated yield: 68%, mp: 218–220 °C. R_f (50% EA/hexane) 0.32; ^{1}H NMR (500 MHz, DMSO-d_6) δ:



#	R	R'	4 yield (%)
1	4-Cl	H	42
2	3-NO_2	H	45
3	4-NO_2	2-CF_3	38
4	3-NO_2	2-CF_3	42
5	4-Cl	2-Cl	40
6	3-NO_2	2-Cl	42
7	4-NO_2	2-Cl	41

Scheme 4.

1.88 (s, 3H), 5.96 (d, 1H, J=8.4 Hz), 6.67 (d, 2H, J=8.4 Hz), 6.70 (d, 2H, J=8.4 Hz), 7.22 (d, 2H, J=8.4 Hz), 7.33 (d, 2H, J=8.4 Hz), 8.67 (d, 1H, J=8.4 Hz, D_2O exchangeable), 9.37 (s, 1H, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 23.1, 55.3, 115.6, 128.7, 129.1, 129.4, 131.8, 132.9, 142.8, 156.9, 169.0. IR ν_{max}: 3273, 3114, 1668, 1526, 1359, 1303, 1257, 1097, 836, 776 cm^{-1}. Mass (ESI): 274 (M−1 ion). Anal. Calcd for $C_{15}H_{14}NO_2Cl$: C, 65.34; H, 5.12; N, 5.08. Found: C, 65.10; H, 5.18; N, 5.01.

4.2.2. N-[(2,4-Dichloro-phenyl)-(2-hydroxy-phenyl)-methyl]-acetamide (Table 1, entry 17)

Off white solid. Isolated yield: 75%, mp: 230−232 °C. R_f (60% EA/hexane) 0.31; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.86 (s, 3H), 6.20 (d, 1H, J=8.4 Hz), 6.69 (d, 2H, J=9.1 Hz), 6.93 (d, 2H, J=8.4 Hz), 7.43 (s, 2H), 7.53 (s, 1H), 8.72 (d, 1H, J=8.4 Hz, D_2O exchangeable), 9.43 (s, 1H, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 23.0, 52.9, 115.7, 128.0, 129.3, 129.4, 130.1, 130.8, 132.8, 133.7, 140.0, 157.2, 169.0. IR ν_{max}: 3313, 3118, 1635, 1451, 1252, 823 cm^{-1}. Mass (ESI): 309 (M^+ ion). Anal. Calcd for $C_{15}H_{13}NO_2Cl_2$: C, 58.08; H, 4.22; N, 4.52. Found: C, 57.92; H, 4.18; N, 4.60.

4.2.3. N-[(4-Nitro-phenyl)-(2-hydroxy-phenyl)-methyl]-acetamide (Table 1, entry 18)

Yellowish brown solid. Isolated yield: 72%, mp: 168−170 °C. R_f (60% EA/hexane) 0.43; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.89 (s, 3H), 6.07 (d, 1H, J=7.6 Hz), 6.69 (d, 2H, J=8.4 Hz), 7.04 (d, 2H, J=8.4 Hz), 7.49 (d, 2H, J=9.2 Hz), 8.15 (d, 2H, J=9.1 Hz), 8.80 (d, 1H, J=8.4 Hz, D_2O exchangeable), 9.51 (br s, 1H, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 23.0, 55.8, 115.8, 124.1, 128.6, 129.3, 132.0, 146.8, 151.6, 157.2, 169.3. IR ν_{max}: 3413, 3203, 1636, 1516, 1346, 1234, 832, 546 cm^{-1}. Mass (ESI): 286 (M^+ ion). Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.78. Found: C, 63.20; H, 4.98; N, 9.90.

4.2.4. N-[(2-Hydroxy-naphthalen-1-yl)-(2-hydroxy-phenyl)-methyl]-acetamide (Table 1, entry 19)

White solid. Isolated yield: 62%, mp: 194−196 °C. R_f (50% EA/hexane) 0.32; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.86 (s, 3H), 6.64 (t, 1H, J=6.9 Hz), 6.69 (d, 1H, J=7.7 Hz), 6.97 (t, 1H, J=7.7 Hz), 7.12 (m, 2H), 7.20 (t, 1H, J=7.7 Hz), 7.32 (m, 2H), 7.65 (d, 1H, J=8.4 Hz), 7.72 (d, 1H, J=7.7 Hz), 8.11 (d, 1H, J=9.2 Hz), 8.36 (d, 1H, J=8.4 Hz, D_2O exchangeable), 9.42 (s, 1H, D_2O exchangeable), 9.86 (s, 1H, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 23.2, 45.4, 115.6, 118.8, 119.3, 119.6, 122.7, 124.0, 126.4, 128.1, 128.7, 128.8, 128.8, 129.1, 129.4, 133.2, 153.6, 155.2, 169.1. IR ν_{max}: 3387, 3277, 1629, 1540, 1455, 1437, 1339, 1276, 1208, 754 cm^{-1}. Mass (ESI): 307 (M^+ ion). Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.55; H, 5.52; N, 4.47.

4.3. Representative procedure for the synthesis of acetamidophenols (2)

A mixture of 4-chlorobenzaldehyde (10 mmol), β-naphthol (10 mmol) and iodine (0.4 mmol, 4 mol %) was mixed in nitrile (10 mmol). To that suspension acetyl chloride (2.8 mmol, 0.2 mL) was added and stirred at room temperature for the appropriate time as mentioned in Table 2. After completion of the reaction (as monitored by TLC), saturated sodium thiosulfate in water (5 mL) was added and the compound was extracted with ethyl acetate (4×30 mL). The organic layers were combined together and washed with water (2×25 mL) and dried over sodium sulfate, and concentrated under vacuum. The residue was purified on a column of silica gel with petroleum ether/ethyl acetate (8:2). The same procedure was repeated for all acetamidophenol derivatives.

4.3.1. N-[(2,4-Dichloro-phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-2-phenyl-acetamide (Table 2, entry 1)

Pale brown solid. Isolated yield: 62%, mp: 193−195 °C. R_f (20% EA/hexane) 0.34; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.51 (m, 2H), 7.00 (d, 1H, J=7.6 Hz), 7.09 (d, 1H, J=8.5 Hz), 7.16 (m, 1H), 7.23 (m, 5H), 7.30 (d, 1H, J=8.4 Hz), 7.38 (t, 1H, J=7.7 Hz), 7.44 (s, 1H), 7.47 (d, 1H, J=8.4 Hz), 7.71 (d, 1H, J=9.2 Hz), 7.76 (d, 1H, J=8.4 Hz), 7.93 (d, 1H, J=8.4 Hz), 8.80 (d, 1H, J=7.6 Hz, D_2O exchangeable), 9.85 (s, 1H, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 41.8, 47.4, 116.1, 118.5, 122.4, 122.4, 126.3, 126.3, 126.5, 128.1, 128.2, 128.5, 128.6, 129.0, 129.7, 131.1, 131.7, 132.7, 133.0, 136.4, 139.0, 153.7, 169.6. IR ν_{max}: 3374, 3180, 1635, 1516, 1345, 1060, 817, 746, 700 cm^{-1}. Mass (ESI): 435 (M^+ ion). Anal. Calcd for $C_{25}H_{19}NO_2Cl_2$: C, 68.82; H, 4.39; N, 3.21. Found: C, 68.54; H, 4.34; N, 3.18.

4.3.2. N-[(4-Chloro-phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-2-phenyl-acetamide (Table 2, entry 2)

Off white solid. Isolated yield: 65%, mp: 208−210 °C. R_f (20% EA/hexane) 0.30; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.58 (m, 2H), 7.05 (d, 1H, J=8.5 Hz), 7.09 (d, 2H, J=8.4 Hz), 7.18 (d, 2H, J=8.4 Hz), 7.23 (m, 7H), 7.35 (t,

1H, J=7.6 Hz), 7.73 (d, 1H, J=9.2 Hz), 7.77 (d, 1H, J=8.4 Hz), 7.82 (br s, 1H), 8.57 (d, 1H, J=7.6 Hz, D_2O exchangeable), 10.04 (s, 1H, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 42.6, 48.1, 118.7, 118.9, 123.1, 127.0, 127.1, 128.4, 128.5, 128.8, 129.2, 129.7, 130.1, 131.3, 132.7, 136.9, 142.1, 153.8, 170.7. IR ν_{max}: 3396, 3160, 1633, 1510, 1264, 1090, 807, 747, 699 cm^{-1}. Mass (ESI): 402 (M+1 ion). Anal. Calcd for $C_{25}H_{20}NO_2Cl$: C, 74.72; H, 5.02; N, 3.49. Found: C, 74.60; H, 4.95; N, 3.56.

4.3.3. N-[(3-Nitro-phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-2-phenyl-acetamide (Table 2, entry 3)

White solid. Isolated yield: 70%, mp: 218–220 °C. R_f (30% EA/hexane) 0.35; ^1H NMR (500 MHz, DMSO-d_6) δ: 3.57 (m, 2H), 7.12 (d, 1H, J=8.4 Hz), 7.18 (m, 7H), 7.40 (t, 1H, J=6.4 Hz), 7.47 (m, 2H), 7.77 (m, 3H), 7.97 (m, 2H), 8.74 (d, 1H, J=8.4 Hz, D_2O exchangeable), 10.16 (s, 1H, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 42.5, 48.3, 118.0, 118.9, 120.9, 121.8, 123.1, 123.2, 127.0, 127.4, 128.8, 129.3, 129.7, 130.1, 130.5, 132.7, 133.3, 136.8, 145.7, 148.2, 153.9, 171.1. IR ν_{max}: 3380, 3220, 1645, 1525, 1439, 1349, 1273, 1064, 810, 704 cm^{-1}. Mass (ESI): 435 (M+23 ion). Anal. Calcd for $C_{25}H_{20}N_2O_4$: C, 72.80; H, 4.89; N, 6.79. Found: C, 73.08; H, 4.85; N, 6.74.

4.3.4. N-[(4-Nitro-phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-2-phenyl-acetamide (Table 2, entry 4)

Brown solid. Isolated yield: 66%, mp: 198–200 °C. R_f (30% EA/hexane) 0.42; ^1H NMR (500 MHz, DMSO-d_6) δ: 3.60 (m, 2H), 7.12 (d, 1H, J=7.7 Hz), 7.17 (d, 2H, J=9.2 Hz), 7.25 (m, 5H), 7.32 (d, 2H, J=9.2 Hz), 7.36 (t, 1H, J=7.7 Hz), 7.76 (m, 3H), 8.06 (d, 2H, J=9.2 Hz), 8.68 (d, 1H, J=8.4 Hz, D_2O exchangeable), 10.12 (s, 1H, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 42.4, 48.5, 118.1, 118.9, 123.2, 123.8, 127.0, 127.4, 127.6, 127.6, 128.8, 128.9, 129.2, 129.7, 130.5, 132.7, 136.8, 146.5, 151.5, 153.9, 171.1. IR ν_{max}: 3369, 3236, 2915, 1642, 1517, 1345, 1280, 819, 749, 701 cm^{-1}. Mass (ESI): 435 (M+23 ion). Anal. Calcd for $C_{25}H_{20}N_2O_4$: C, 72.80; H, 4.89; N, 6.79. Found: C, 72.55; H, 4.82; N, 6.86.

4.3.5. Pentanoic acid [(2,4-dichloro-phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-amide (Table 2, entry 5)

Pale brown solid. Isolated yield: 58%, mp: 86–87 °C. R_f (40% EA/hexane) 0.32; ^1H NMR (500 MHz, DMSO-d_6) δ: 0.78 (t, 3H, J=6.9 Hz), 1.15 (m, 2H), 1.40 (m, 2H), 2.12 (m, 2H), 6.97 (d, 1H, J=7.7 Hz), 7.07 (d, 1H, J=9.2 Hz), 7.23 (t, 1H, J=6.8 Hz), 7.35 (m, 2H), 7.43 (s, 1H), 7.51 (d, 1H, J=8.4 Hz), 7.70 (d, 1H, J=8.4 Hz), 7.75 (d, 1H, J=8.4 Hz), 7.92 (d, 1H, J=8.4 Hz), 8.52 (d, 1H, J=8.4 Hz, D_2O exchangeable), 9.79 (s, 1H, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 13.7, 21.8, 27.5, 34.6, 47.3, 116.4, 118.6, 122.3, 122.5, 126.3, 126.4, 128.4, 128.6, 129.6, 131.1, 131.61, 132.8, 132.9, 139.3, 153.7, 171.7. IR ν_{max}: 3416, 3182, 2957, 1641, 1514, 1468, 1438, 1237, 816, 745 cm^{-1}. Mass (ESI): 425 (M+23 ion). Anal. Calcd for $C_{22}H_{21}NO_2Cl_2$: C, 65.68; H, 5.26; N, 3.48. Found: C, 65.39; H, 5.32; N, 3.45.

4.3.6. Pentanoic acid [(3-nitro-phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-amide (Table 2, entry 6)

Pale brown solid. Isolated yield: 63%, mp: 188–190 °C. R_f (50% EA/hexane) 0.32; ^1H NMR (500 MHz, DMSO-d_6) δ: 0.81 (t, 3H, J=6.9 Hz), 1.23 (m, 2H), 1.47 (m, 2H), 2.20 (m, 1H), 2.34 (m, 1H), 7.15 (m, 3H), 7.37 (m, 1H), 7.50 (s, 2H), 7.76 (m, 3H), 8.01 (s, 1H), 8.53 (d, 1H, J=7.7 Hz, D_2O exchangeable), 10.11 (s, 1H, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 13.7, 21.8, 27.5, 34.8, 47.6, 117.7, 118.4, 120.4, 121.2, 122.6, 122.7, 126.7, 128.4, 128.7, 129.6, 129.8, 132.2, 132.8, 145.4, 147.7, 153.3, 172.6. IR ν_{max}: 3404, 2961, 1628, 1522, 1347, 818, 744 cm^{-1}. Mass (ESI): 379 (M^+ ion). Anal. Calcd for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.72; H, 5.83; N, 7.47.

4.3.7. Pentanoic acid [(4-nitro-phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-amide (Table 2, entry 7)

Off white solid. Isolated yield: 60%, mp: 188–190 °C. R_f (40% EA/hexane) 0.39; ^1H NMR (500 MHz, DMSO-d_6) δ: 0.80 (t, 3H, J=7.6 Hz), 1.20 (q, 2H, J=7.7 Hz), 1.45 (m, 2H), 2.20 (m, 2H), 7.15 (d, 1H, J=7.7 Hz), 7.20 (d, 1H, J=9.2 Hz), 7.23 (t, 1H, J=7.7 Hz), 7.35 (d, 3H, J=8.4 Hz), 7.76 (m, 3H), 8.10 (d, 2H, J=8.4 Hz), 8.49 (d, 1H, J=7.7 Hz, D_2O exchangeable), 10.12 (s, 1H, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 13.68, 21.85, 27.47, 34.73, 47.80, 117.83, 118.37, 122.56, 122.81, 123.20, 126.68, 127.09, 128.38, 128.62, 129.80, 132.16, 145.88, 151.18, 153.28, 172.59. IR ν_{max}: 3429, 3229, 2954, 1639, 1509, 1345, 1267, 1106, 818, 734 cm^{-1}. Mass (ESI): 379 (M^+ ion). Anal. Calcd for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.86; N, 7.40. Found: C, 70.13; H, 5.92; N, 7.33.

4.3.8. Pentanoic acid [(3-methoxy-phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-amide (Table 2, entry 8)

White solid. Isolated yield: 45%, mp: 183–184 °C. R_f (40% EA/hexane) 0.43; ^1H NMR (500 MHz, DMSO-d_6) δ: 0.79 (t, 3H, J=6.9 Hz), 1.17 (m, 2H), 1.42 (m, 2H), 2.13 (m, 2H), 3.60 (s, 3H), 6.76 (d, 2H, J=9.2 Hz), 7.02 (d, 3H, J=8.4 Hz), 7.17 (d, 1H, J=8.4 Hz), 7.21 (t, 1H, J=6.9 Hz), 7.33 (m, 1H), 7.70 (d, 1H, J=9.2 Hz), 7.75 (d, 1H, J=7.7 Hz), 7.82 (s, 1H), 8.33 (d, 1H, J=8.4 Hz, D_2O exchangeable), 9.99 (s, 1H, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 13.7, 21.8, 27.5, 35.0, 47.4, 55.0, 113.4, 118.5, 118.9, 122.3, 123.2, 126.2, 127.2, 128.4, 129.0, 132.3, 134.4, 153.0, 157.7, 171.9. IR ν_{max}: 3401, 3070, 2957, 2922, 1633, 1579, 1509, 1437, 1247, 1174, 1033, 819, 657 cm^{-1}. Mass (ESI): 389 (M+23 ion). Anal. Calcd for $C_{23}H_{25}NO_3$: C, 76.01; H, 6.93; N, 3.85. Found: C, 76.32; H, 7.01; N, 3.90.

4.3.9. Pentanoic acid [(4-chloro-phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-amide (Table 2, entry 9)

White solid. Isolated yield: 62%, mp: 202–203 °C. R_f (40% EA/hexane) 0.35; ^1H NMR (500 MHz, DMSO-d_6) δ: 0.82 (t, 3H, J=7.5 Hz), 1.20 (m, 2H), 1.43 (m, 2H), 2.18 (m, 2H), 7.07 (d, 1H, J=8.4 Hz), 7.14 (d, 2H, J=8.4 Hz), 7.21 (m, 4H), 7.36 (t, 1H, J=7.5 Hz), 7.76 (m, 3H), 8.40 (d, 1H,

J=8.4 Hz, D_2O exchangeable), 10.08 (s, 1H, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 13.7, 21.8, 27.5, 34.9, 47.4, 118.36, 118.4, 122.4, 123.0, 126.4, 127.9, 128.4, 128.6, 129.4, 130.6, 132.2, 141.8, 153.2, 172.3. IR ν_{max}: 3408, 3062, 2955, 1635, 1517, 1438, 1323, 1272, 1088, 820, 751, 649 cm^{-1}. Mass (ESI): 390 (M+23 ion). Anal. Calcd for $C_{22}H_{22}NO_2Cl$: C, 71.83, H, 6.03; N, 3.81. Found: C, 72.10; H, 5.92; N, 3.76.

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References and notes

1. For recent reviews, see: (a) Ugi, I.; Domling, A.; Werner, B. *J. Heterocycl. Chem.* **2000**, *37*, 647–658; (b) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem.—Eur. J.* **2000**, *6*, 3321–3329; (c) Ugi, I.; Heck, S. *Comb. Chem. High Throughput Screen.* **2001**, *4*, 1–34.
2. Strecker, A. *Justus Liebigs Ann. Chem.* **1850**, *75*, 27–45.
3. (a) Shestopalov, A. M.; Emeliyanova, Y. M.; Shestiopolov, A. A.; Rodinovskaya, I. A.; Niazimbetova, A. I.; Evans, D. H. *Org. Lett.* **2002**, *4*, 423–425; (b) Bagley, M. C.; Cale, J. W.; Bower, J. *Chem. Commun.* **2002**, 1682–1683; (c) Bora, U.; Saikia, A.; Boruah, R. C. *Org. Lett.* **2003**, *5*, 435–438; (d) Dallinger, D.; Gorobets, N. Y.; Kappe, C. O. *Org. Lett.* **2003**, *5*, 1205–1208.
4. For the review: Wang, H. S.; Miao, J. Y.; Zhao, L. F. *Chin. J. Org. Chem.* **2005**, *25*, 615–618; For recent references: (a) Yadav, J. S.; Satyanarayana, M.; Raghavendra, S.; Balanarsh, E. *Tetrahedron Lett.* **2005**, *46*, 8745–8748; (b) Bhosale, R. S.; Sarda, S. R.; Ardhapure, S. S. *Tetrahedron Lett.* **2005**, *46*, 7183–7186; (c) Mori, N.; Togo, H. *Tetrahedron* **2005**, *61*, 5915–5925; (d) Sun, J. W.; Dong, Y. M.; Cao, L. Y. *J. Org. Chem.* **2004**, *69*, 8932–8934; (e) Ji, S. J.; Wang, S. Y.; Zhang, Y.; Loh, T. P. *Tetrahedron* **2004**, *60*, 2051–2055; (f) Lin, C.; Hsu, J. C.; Sastry, M. N. V.; Fang, H.; Tu, Z. J.; Liu, J. T.; Yao, C. F. *Tetrahedron* **2005**, *61*, 11751–11757; (g) Kosak, A. I.; Hartough, H. D. H. *J. Am. Chem. Soc.* **1947**, *69*, 3144; (h) Deka, N.; Kalita, D. J.; Borah, R.; Sarma, J. C. *J. Org. Chem.* **1997**, *62*, 1563–1564; (i) Wahlstrom, J. L.; Ronald, R. C. *J. Org. Chem.* **1998**, *63*, 6021–6022.
5. Aleman, C.; Puiggali, J. *J. Org. Chem.* **1995**, *60*, 910–924 and references therein.
6. Panneer Selvam, N.; Perumal, P. T. *Tetrahedron Lett.* **2006**, *47*, 7481–7483.
7. Pandey, G.; Singh, R. P.; Garg, A.; Singh, V. K. *Tetrahedron Lett.* **2005**, *46*, 2137–2140.
8. Crystal structure of compound (entry 11, Table 1) has been deposited at the Cambridge Crystallographic Data Center and allocated the reference no. CCDC 651834.
9. Crystal structure of compound (entry 2, Table 1) has been deposited at the Cambridge Crystallographic Data Center and allocated the reference no. CCDC 651835.
10. Crystal structure of compound (entry 19, Table 1) has been deposited at the Cambridge Crystallographic Data Center and allocated the reference no. CCDC 652214.