Solvent-Free Condensation of Phenols with Aldehydes and Amides Using 3-Methyl-1-sulfonic Acid Imidazolium Chloride

Ahmad Reza Moosavi-Zare,*[a] Mohammad Ali Zolfigol,*[b] Masoume Daraei[b]

[a] Department of Chemistry, University of Sayyed Jamaleddin Asadabadi, Asadabad 6541835583, Iran
E-mail: moosavizare@yahoo.com; E-mail: moosavi-zare@sjau.ac.ir

[b] Faculty of Chemistry, Bu-Ali Sina University, Hamedan 6517838683, Iran
Fax +98(811)8272404; E-mail: mzolfigol@yahoo.com

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Abstract: One-pot, three-component condensation of phenols, aromatic aldehydes, and amides in the presence of 3-methyl-1-sulfonic acid imidazolium chloride {[Msim]Cl} as ionic liquid and catalyst under solvent-free condition to prepare a new category of compounds, namely amido-alkyl-phenols has been described. In the presented work, all products have been reported for the first time.

Key words: amidoalkyl phenol, ionic liquid, sulfonic acid functionalized imidazolium salts, SAFIS, phenol, aldehyde, solvent-free

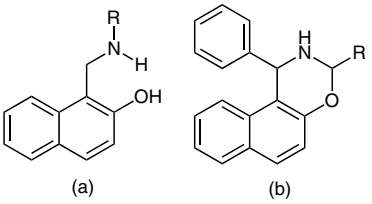


Figure 1 The general structures of 1-aminoalkyl-2-naphthols (a) and 1,3-oxazines (b)

Multicomponent reactions (MCRs) play a significant role in combinatorial chemistry due to their ability to synthesize the target compounds with more atomic economy and efficiency by the reaction of three or more compounds together in a single step. Also, MCRs improve simplicity and synthetic efficiency of the conventional organic transformations.[1–5]

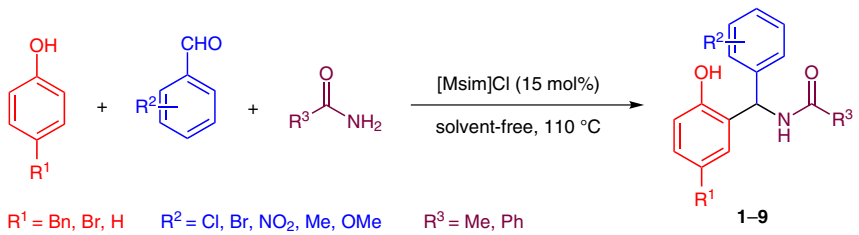
Sulfonic acid functionalized imidazolium salts (SAFIS) have been recently reported as a novel family of acidic ionic liquids and are considered as eco-friendly solvents, catalysts and reagents in green synthesis because of their interesting properties, such as low volatility, high thermal stability, nonflammability, and negligible vapor pressure. S–N bond-formation reaction yielding imidazole derivatives, as five-membered heterocyclic ring compounds, was introduced for the first time by employing such acidic ILs as catalyst.[6–15]

1-Amidoalkyl-2-naphthols are of importance as they can be easily converted to 1-aminoalkyl-2- naphthol derivatives by hydrolysis, which are biologically important compounds (Figure 1). 1-Aminoalkyl-2-naphthols have been used as bradycardiac and hypotensive agents.[16,17] Moreover, 1-amidoalkyl-2-naphthols can be converted into 1,3-oxazine derivatives (Figure 1).[18]

Some pharmaceutical properties have been reported for 1,3-oxazines, such as antibiotic,[19] antitumor,[20] and analgesic activities.[21] Having above facts in mind, we have prepared and introduced amidoalkyl phenols as a new category of compounds by the one-pot, three-component condensation of various phenols, aromatic aldehydes, and amides in the presence of 3-methyl-1-sulfonic acid imidazolium chloride {[Msim]Cl} as ionic liquid and catalyst under solvent-free condition (Scheme 1 and Scheme 2)

At first, the condensation of 4-benzylphenol (1 mmol) with benzaldehyde (1 mmol) and acetamide (1.2 mmol) was selected as the model reaction to optimize the reaction conditions. Then, different conditions such as kind of catalyst, amount of catalyst and temperature, were studied on the model reaction.

Various catalysts such as molecular iodine, $FeCl_3$, $AlCl_3$, silica sulfuric acid (SSA), silica-supported polyphos-



Scheme 1 The synthesis and general structure of amidoalkyl phenols

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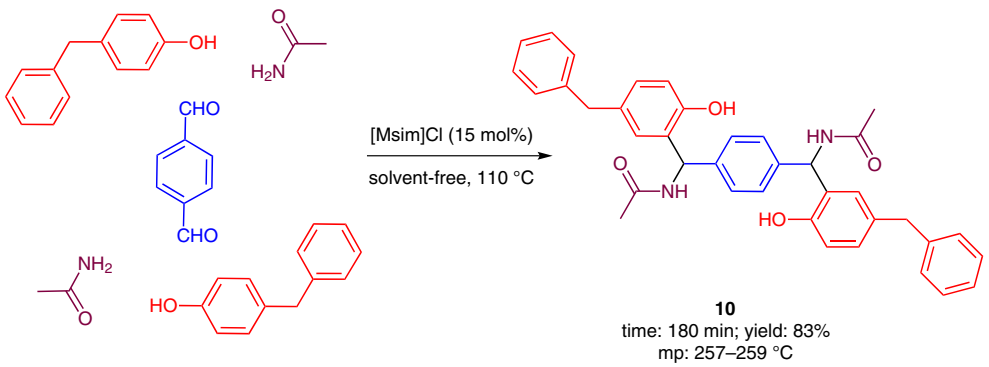


Scheme 2 The condensation between 4-benzylphenol, terephthaldehyde and acetamide

phoric acid (PPA·SiO_2) and 3-methyl-1-sulfonic acid imidazolium chloride {[Msim]Cl} were tested on the model reaction under solvent-free conditions at 110 °C. The results are tabulated in Table 1. As Table 1 indicates, higher yield and shorter reaction time were obtained in the presence of [Msim]Cl.

Table 1 The Condensation of 4-Benzylphenol (1 mmol) with Benzaldehyde (1 mmol) and Acetamide (1.2 mmol) in the Presence of Various Catalysts (15 mol%) at 110 °C under Solvent-Free Conditions

Entry	Catalyst	Time (min)	Yield (%)[a]
1	I_2	70	55
2	SSA[b]	70	50
3	$FeCl_3$	70	65
4	$AlCl_3$	70	73
5	[Msim]Cl	70	84
6	PPA·SiO_2[b]	70	60

[a] Isolated yield.
[b] In this reaction condition, the catalyst loading was 0.02 g.

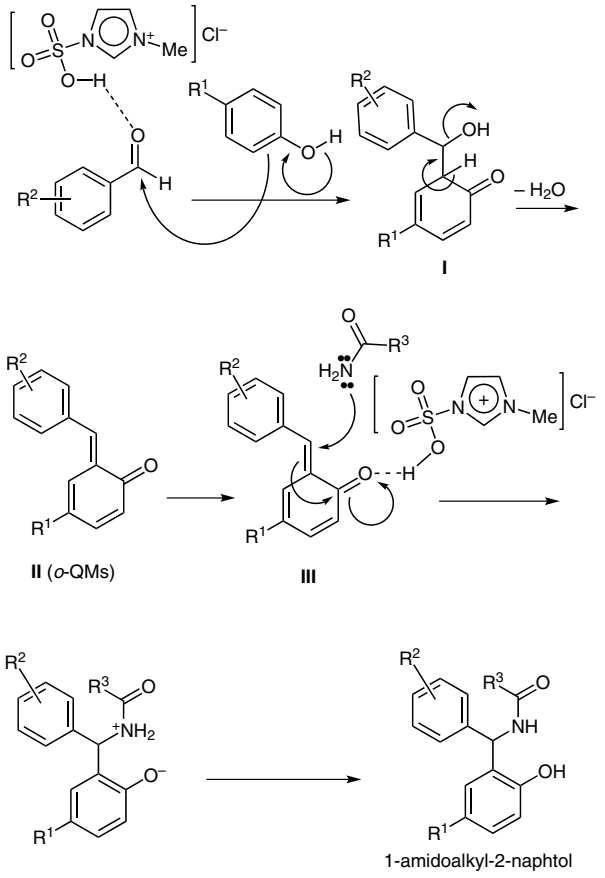
Table 2 Effect of Different Amounts of the Catalyst and Temperature on the Condensation of 4-Benzylphenol (1 mmol) with Benzaldehyde (1 mmol) and Acetamide (1.2 mmol) under Solvent-Free Conditions

Entry	Catalyst (mol%)	Temp (°C)	Time (min)	Yield (%)[a]
1	–	110	240	–
2	5	110	120	60
3	10	110	60	65
4	15	110	70	84
5	15	80	180	30
6	15	100	180	75
7	15	130	70	84

[a] Isolated yield.

In the next step, to optimize the amount of the catalyst and temperature, the model reaction was examined using different amounts of [Msim]Cl at 80–130 °C under solvent-free conditions (Table 2). As Table 2 indicates, the reaction was efficiently performed in the presence of 15 mol% of [Msim]Cl at 110 °C, and afforded the desired product in high yield (Table 2, entry 4).

In a proposed mechanism that is supported by the literature,[10] the aromatic aldehyde is activated by acidic group of [Msim]Cl (Scheme 3). Then, phenolic compound attacks the activated aldehyde to give **I**. In another step, by removing one molecule of H_2O from **I**, orthoquinone me-



Scheme 3 The proposed mechanism for the synthesis of amidoalkyl phenols

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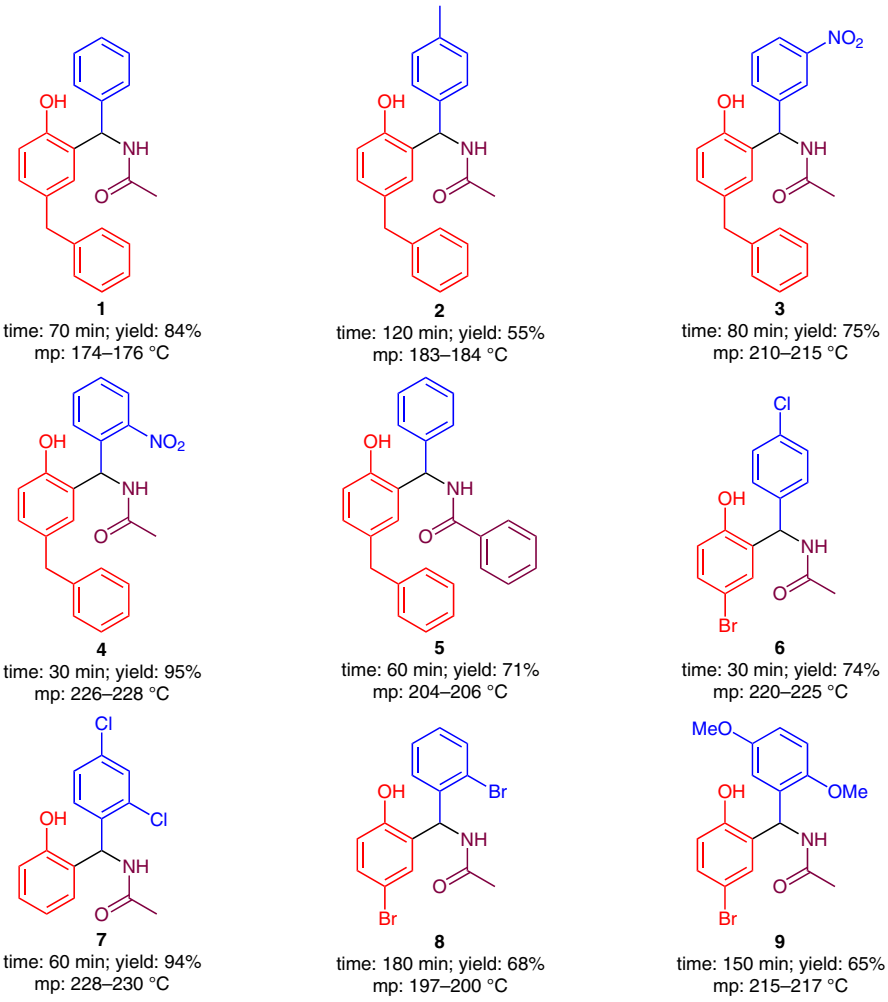
thide (o-QMs; **II**) is produced. Afterwards, **II** is activated by [Msim]Cl to prepare **III** as a Michael acceptor. Finally, Michael addition of **III** with acetamide, affords the corresponding amidoalkyl phenols.

To investigate the efficacy of [Msim]Cl in the synthesis of amidoalkyl phenols, various aromatic aldehydes containing electron-releasing substituents, electron-withdrawing substituents and halogens were reacted with various phenolic compounds (4-benzylphenol, 4-bromophenol and phenol) and amides (acetamide and benzamide) to furnish the expected products in moderate to high yields. The results are depicted in Figure 2.

The presented method was examined for the condensation of 4-benzylphenol, bisaldehyde (terephthalaldehyde) and acetamide in the presence of 15 mol% of [Msim]Cl (Scheme 2). The use of two equivalents of 4-benzylphenol, one equivalent of terephthalaldehyde and 2.4 equivalents of acetamide in the reaction afforded bis(acetamidoalkylphenol) **10** in 83% yield in 180 minutes.

As shown in Schemes 1 and 2, acetamidoalkyl phenols were synthesized by the one-pot multicomponent condensation between phenolic compounds, aldehydes and acetamide using [Msim]Cl as catalyst. The mixture was stirred for 30–180 minutes at 110 °C which afforded the desired products in 55–95% yield. The structures of these products were confirmed by the IR, ^{1}H NMR and ^{13}C NMR and mass analysis (experimental section). In the IR spectra, the absorbance of carbonyl group (C=O) between 1634–1656 cm^{-1}, and two strong peaks at ca. 3179 cm^{-1} and 3410 cm^{-1} related to ν_{O-H} and ν_{N-H} stretching vibrations, respectively, were useful to identify these compounds. In the ^{1}H NMR spectra of these compounds (for samples in DMSO-d_6 solution), the chemical shift of OH (phenolic hydrogen), NH (amidic hydrogen) and methyl (the hydrogens of methyl group) were displayed at about δ = 9.35, 8.5 and 1.82 ppm, respectively. Also, in the ^{13}C NMR spectra (for samples in DMSO-d_6 solution), the chemical shift of carbonyl (C=O), aliphatic CH and methyl groups were depicted at about δ = 168.4, 56.4 and 22.2 ppm, respectively. These important observations helped us to identify the structures of acetamidoalkyl phenols (experimental section, 1–10).

As we expected, all products were produced as racemic mixtures, because the reaction medium was achiral. To confirm this theory, optical activity of these compounds



1
time: 70 min; yield: 84%
mp: 174–176 °C

2
time: 120 min; yield: 55%
mp: 183–184 °C

3
time: 80 min; yield: 75%
mp: 210–215 °C

4
time: 30 min; yield: 95%
mp: 226–228 °C

5
time: 60 min; yield: 71%
mp: 204–206 °C

6
time: 30 min; yield: 74%
mp: 220–225 °C

7
time: 60 min; yield: 94%
mp: 228–230 °C

8
time: 180 min; yield: 68%
mp: 197–200 °C

9
time: 150 min; yield: 65%
mp: 215–217 °C

Figure 2 The preparation of amidoalkyl phenols using [Msim]Cl at 110 °C under solvent-free conditions; isolated yields are given

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was investigated by polarimeter, which clearly confirmed racemization of the products.

In conclusion, we have introduced the one-pot multi component synthesis of amidoalkyl phenols as new compounds by the reaction of various aromatic aldehydes, phenolic compounds (4-benzylphenol, 4-bromophenol and phenol) and amides (acetamide and benzamide) using 3-methyl-1-sulfonic acid imidazolium chloride {[Msim]Cl} as catalyst at 110 °C under solvent-free conditions.

Acknowledgement

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(22) **Experimental Materials**: All chemicals were purchased from Fluka or Merck Chemical Companies. Progress of the reactions was monitored by TLC using silica gel SIL G/UV 254 plates. The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a Bruker AVANCE- DRX FT–NMR spectrometer (δ in ppm). Melting points were determined on a Büchi B-545 apparatus in open capillary tubes. IR spectra were recorded on a Perkin–Elmer PE-1600-FTIR instrument. Mass spectra were run on Agilent Technology (HP) Network Mass Selective Detector 5973 (70 eV) apparatus. Optical rotations were studied in spectral grade solvents using a Perkin–Elmer 341 polarimeter.
General Procedure for the Synthesis of Amidoalkyl Phenols Using [Msim]Cl: To a well-ground mixture of phenolic compound (1 mmol), aldehyde (1 mmol) and amide derivative (1.2 mmol) in a 10-mL round-bottomed flask connected to a reflux condenser, was added the catalyst (15 mol%), and the resulting mixture was stirred in an oil bath at 110 °C. After completion of the reaction, as monitored by TLC, the reaction mixture was cooled to r.t., extracted with warm EtOAc (20 mL) to separate the catalyst (the product is soluble in warm EtOAc; however, the catalyst is not soluble in this solvent). Then, EtOAc was evaporated and the solid residue (crude product) was purified by plate chromatography on silica gel with *n*-hexane–EtOAc (6:4) as an eluent to give the desired amidoalkyl phenols. The recovered catalyst was washed with EtOAc (2 × 15 mL), dried at 90 °C under vacuum condition, and reused for the preparation of amidoalkyl phenols according to the mentioned procedure.
Spectral Data of the New Compounds:
***N*-[(5-Benzyl-2-hydroxyphenyl)(phenyl)methyl]-acetamide (1)**: R_f = 0.057 (EtOAc–*n*-hexane, 1:1); mp 174–176 °C. IR (KBr): 3410, 3179, 3024, 1644, 1611 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.96 (s, 3 H), 3.85 (s, 2 H), 6.48 (d, *J* = 8.4 Hz, 1 H), 6.77 (d, *J* = 8.0 Hz, 1 H), 6.99 (d, *J* = 8.0 Hz, 1 H), 7.15–7.28 (m, 7 H), 7.37–7.72 (m, 2 H), 8.09 (d, *J* = 8.0 Hz, 2 H), 8.76 (d, *J* = 8.0 Hz, 1 H), 9.56 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.09, 40.98, 50.61, 115.89, 121.83, 122.14, 126.28, 127.82, 128.79, 129.26, 130.17, 132.10, 134.41, 142.21, 145.25, 148.17, 153.08, 169.28. MS: *m/z* = 331 [M$^+$].
***N*-[(5-Benzyl-2-hydroxyphenyl)(*p*-tolyl)methyl]-acetamide (2)**: R_f = 0.057 (EtOAc–*n*-hexane, 1:1); mp 183–184 °C. IR (KBr): 3412, 3246, 3025, 1648, 1610 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.90 (s, 3 H), 2.25 (s, 3 H), 3.81 (s, 2 H), 6.31 (d, *J* = 6.0 Hz, 1 H), 6.71 (d, *J* = 5.5 Hz, 1 H), 6.87 (dd, *J* = 4.0, 1.4 Hz, 1 H), 7.07–7.28 (m, 10 H), 8.47 (d, *J* = 6.0 Hz, 1 H), 9.56 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.04, 23.10, 41.03, 50.47, 115.63, 126.23, 127.44, 128.45, 128.53, 128.76, 128.93, 129.01, 129.19, 131.66, 135.96, 140.29, 142.30, 153.04, 168.84. MS: *m/z* = 345 [M$^+$].
***N*-[(5-Benzyl-2-hydroxyphenyl)(3-nitrophenyl)methyl]-acetamide (3)**: R_f = 0.042 (EtOAc–*n*-hexane, 1:1); mp 210–215 °C. IR (KBr): 3381, 3025, 2733, 1635, 1606 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.88 (s, 3 H), 3.79 (s, 2 H), 6.44 (d, *J* = 7.6 Hz, 1 H), 6.74 (d, *J* = 8.0 Hz, 1 H), 6.81 (s,

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1 H), 6.92 (d, *J* = 8.0 Hz, 1 H), 7.13–7.58 (m, 8 H), 7.59 (d, *J* = 4.8 Hz, 1 H (, 8.41 (s, 1 H), 9.39 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 22.89, 40.97, 51.48, 115.58, 124.14, 126.26, 127.38, 127.83, 128.76, 128.82, 128.93, 128.98, 129.25, 129.58, 131.25, 133.13, 141.85, 142.15, 153.72, 168.78. MS: *m/z* = 376 [M$^+$].

***N*-[(5-Benzyl-2-hydroxyphenyl)(2-nitrophenyl)methyl]-acetamide (4)**: R_f = 0.05 (EtOAc–*n*-hexane, 1:1); mp 226–228 °C. IR (KBr): 3403, 3271, 3027, 1656, 1614 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.79 (s, 3 H), 3.68 (s, 2 H), 6.60–6.70 (m, 3 H), 6.82 (dd, *J* = 6.2, 2.0 Hz, 1 H), 7.01–7.18 (m, 3 H), 7.32–7.34 (m, 2 H), 7.34–7.41 (m, 1 H), 7.75 (s, 1 H), 7.77 (s, 1 H), 7.78 (d, *J* = 7.4 Hz, 1 H), 8.43 (d, *J* = 8.0 Hz, 1 H), 9.36 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 22.28, 46.91, 56.00, 115.01, 124.06, 125.73, 126.80, 127.65, 128.10, 128.43, 128.48, 128.63, 129.54, 130.89, 132.63, 135.98, 141.53, 148.81, 153.00, 168.41. MS: *m/z* = 376 [M$^+$].

***N*-[(5-Benzyl-2-hydroxyphenyl)(phenyl)methyl]-benzamide (5)**: R_f = 0.11 (EtOAc–*n*-hexane, 1:1); mp 204–206 °C. IR (KBr): 3403, 3062, 3028, 1630, 1603 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.78 (s, 2 H), 6.46 (d, *J* = 8.4 Hz, 1 H), 6.67–6.92 (m, 11 H), 7.13–7.27 (m, 7 H), 8.23 (d, *J* = 8.4 Hz, 1 H), 9.25 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 41.04, 56.45, 111.91, 112.47, 115.41, 115.55, 126.21, 128.44, 128.56, 128.74, 128.87, 128.93, 131.14, 132.07, 142.39, 151.31, 153.50, 153.58, 168.59. MS: *m/z* = 393 [M$^+$].

***N*-[(5-Bromo-2-hydroxyphenyl)(4-chlorophenyl)-methyl]acetamide (6)**: R_f = 0.028 (EtOAc–*n*-hexane, 1:1); mp 220–225 °C. IR (KBr): 3309, 3074, 2980, 2739, 1649, 1631 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.85 (s, 3 H), 5.95 (d, *J* = 8.4 Hz, 1 H), 6.68 (s, 2 H), 6.99 (d, *J* = 8.0 Hz, 2 H), 7.23–7.35 (m, 3 H), 8.66 (s, 1 H), 9.35 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 24.19, 56.36, 116.70, 129.78, 130.14, 130.50, 132.84, 133.97, 143.90, 158.02, 169.99. MS: *m/z* = 354 [M$^+$].

***N*-[(2,4-Dichlorophenyl)(2-hydroxyphenyl)methyl]-acetamide (7)**: R_f = 0.028 (EtOAc–*n*-hexane, 1:1); mp 228–230 °C. IR (KBr): 3301, 3065, 2808, 1634, 1613 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.85 (s, 3 H), 6.33 (d, *J* = 8.0 Hz, 1 H), 6.47 (d, *J* = 8.0 Hz, 1 H), 6.71 (d, *J* = 8.0 Hz, 1 H), 6.91 (d, *J* = 7.6 Hz, 1 H), 7.14–7.81 (m, *J* = 8.0 Hz, 4 H), 7.96 (s, 1 H), 8.69 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 24.08, 58.14, 117.91, 124.91, 125.23, 127.41, 129.90, 130.08, 130.48, 133.03, 133.9, 134.12, 143.26, 154.17, 170.50. MS: *m/z* = 310 [M$^+$].

***N*-[(5-Bromo-2-hydroxyphenyl)(2-bromophenyl)-methyl]acetamide (8)**: R_f = 0.08 (EtOAc–*n*-hexane, 1:1); mp 197–200 °C. IR (KBr): 3300, 3064, 2808, 1634, 1613 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.21 (s, 3 H), 6.45 (s, 1 H), 6.61 (s, 1 H), 6.98 (s, 1 H), 7.06–7.32 (m, 5 H), 7.55 (d, *J* = 6.8 Hz, 1 H), 8.69 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 22.82, 51.72, 126.26, 127.17, 127.86, 128.09, 128.67, 128.86, 129.10, 129.34, 133.25, 141.20, 141.42, 169.66. MS: *m/z* = 399 [M$^+$].

***N*-[(5-Bromo-2-hydroxyphenyl)(2,5-dimethoxyphenyl)-methyl]acetamide (9)**: R_f = 0.08 (EtOAc–*n*-hexane, 1:1); mp 215–217 °C. IR (KBr): 3372, 3267, 2854, 1652 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.82 (s, 3 H), 3.31 (s, 3 H), 3.76 (s, 3 H), 6.30 (d, *J* = 6.0 Hz, 1 H), 6.69 (d, *J* = 8.4 Hz, 1 H), 6.87 (d, *J* = 6.4 Hz, 1 H), 7.09–7.28 (m, 4 H), 8.50 (d, *J* = 9.2 Hz, 1 H), 9.35 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.12, 41.05, 50.46, 115.68, 126.26, 127.32, 128.33, 128.48, 128.79, 128.96, 129.05, 131.78, 141.55, 142.32, 152.94, 168.75. MS: *m/z* = 380 [M$^+$].

***N*,*N*′-{1,4-Phenylenebis[(5-benzyl-2-hydroxyphenyl)-methylene]}diacetamide (10)**: R_f = 0.084 (EtOAc–*n*-hexane, 1:1); mp 257–259 °C. IR (KBr): 3402, 3026, 1639, 1604 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.88 (s, 6 H), 3.85 (s, 4 H), 6.72 (d, *J* = 8.8 Hz, 1 H), 6.81 (d, *J* = 8.0 Hz, 1 H), 6.96 (d, *J* = 8.0 Hz, 1 H), 7.15–7.57 (m, 17 H), 7.92 (d, *J* = 6.8 Hz, 2 H), 9.11 (d, *J* = 9.2 Hz, 2 H), 9.55 (s, 2 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 18.98, 41.17, 51.54, 115.17, 126.28, 127.12, 127.83, 128.02, 128.23, 128.58, 128.73, 128.75, 128.80, 129.02, 129.18, 131.70, 131.97, 135.17, 142.35, 143.02, 153.35, 166.37. MS: *m/z* = 584 [M$^+$].

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