An Efficient Green MCR Protocol for the Synthesis of New Betti Bases *via* Mannich-Type Reaction

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Abstract: An efficient solvent and catalyst-free synthesis of new Betti base derivatives *via* Mannich-type one-pot three-component condensation reaction of aminodiazines, salicylaldehyde and naphthols under solvent-free conditions is described. The reactions occur at 80 ^{o}C giving high to excellent yields of the products. The work-up procedure is very simple and the products do not require further purification with column chromatography.

Keywords: Aminodiazine, Betti base, naphthol, salicylaldehyde, solvent-free, three- component.

INTRODUCTION

Study of the chemistry of the Betti bases started at the beginning of the 20th century, when Betti reported the synthesis of 1-(α-aminobenzyl)-2-naphthol [1]. The preparation of substituted Betti base derivatives by the modified Mannich reaction has subsequently become of considerable importance because a C-C bond is formed under mild experimental conditions. The Betti procedure could be extended to different amines instead of ammonia, as shown by the earlier work of Littman and Brode [2]. In addition, a variety of amines such as $(CH_3)_2NH$ [2], piperidine [2], n-Bu-NH_2 [3], pyrrolidine [4], heteroaryl amines [5], cyclic secondary amines [6] and chiral amines [7-9] have recently been reported for the synthesis of the Betti base derivatives. Traditionally, the Betti base derivatives synthesis is carried out in organic solvents such as EtOH, MeOH, and Et_2O at room temperature for long times and microwave irradiation [6] in the presence of acid catalyst.

Preparation of the enantiomers of the Betti bases is of significance science they can serve as chiral catalyst or the nonracemic Betti base can be applied successfully as a new chiral auxiliary [10-14]. Betti base derivatives also provide convenient access to many useful synthetic building blocks because the amino and phenolic hydroxy groups can be converted into a wide variety of compounds [15, 16].

Our long interest in the chemistry of nitrogen-containing heteroaromatic systems and green chemistry, recently led us to discover that synthesis of new Betti bases was carried out from 2-naphthol, arylaldehydes and heteroarylamines in water solvent [5]. The most striking novelty of this method is the use of water as a reactin solvent. In continuation of our efforts for the development of multi-component condensation reactions [17-19] we have explored a straightforward one-pot synthesis of new Betti bases through a three-component condensation reaction of aminodiazines, salicylaldehyde and naphthols under solvent-free conditions.

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RESULTS AND DISCUSSION

Our literature survey at this stage revealed that, there is no report yet available on the synthesis of 1-(2-hydroxyphenyl(diazineamino)methyl)naphthols under solvent-free conditions. The aim of this present protocol is to highlight the synergistic effect of the combined use of multi component reactions (MCRs) and solvent-free conditions for the development of new eco-compatible strategy for aminonaphthols synthesis.

Initially, the one-pot, three-component coupling reaction of 2-aminopyrimidine, salicylaldehyde and 2-naphthol was examined under solvent-free conditions at 70–120 ^{o}C and the results demonstrated that 80 ^{o}C appeared to be the optimum temperature. Thus, the best yield in minimum time of the product **3a** was achieved under solvent-free conditions at 80 ^{o}C.

Encouraged by the remarkable results obtained with the above reaction conditions, and in order to show the generality and scope of this new protocol, we used various aminodiazines **1a-d** (2-aminopyrimidine, 2-amino-4,6-dimethylpyrimidine, 2-amino-4-methylpyrimidine and 2-amino-4-chloro-6-methylpyrimidine), naphthols **2a-d** (2-naphthol, 1-naphthol, 2,7-dihydroxynaphthalene and 2,3-dihydroxynaphthalene) and salicylaldehyde in the synthesis of new Betti bases (**3a-k**) with high to excellent yields (Scheme **1**). The results of the above mentioned reactions are shown in Table **1**.

We proposed the mechanism for the formation of these compounds. We assume that imine generated in situ from the reaction of amine and salicylaldehyde in the first step. Then, in the second step imine reacts with naphthol affording the corresponding aminonaphthol. To make insight into the reac-

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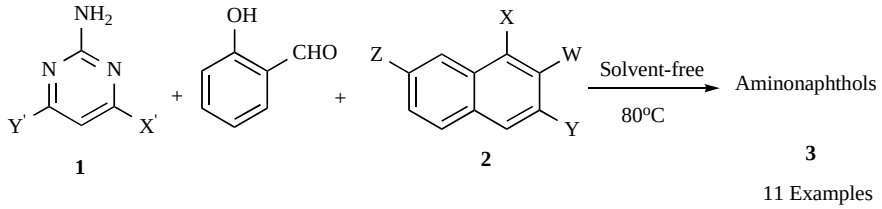


Scheme 1. Synthesis of new Betti base derivatives **3**.

Table 1. Synthesis of Betti Base Derivatives Under Solvent-Free Conditions at 80 ºC

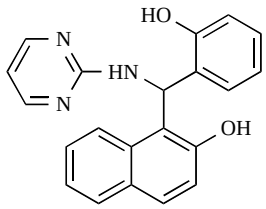
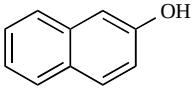
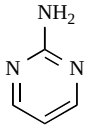
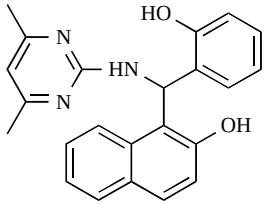
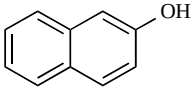
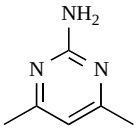
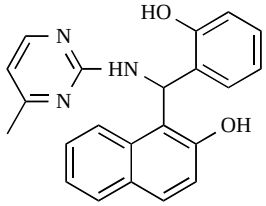
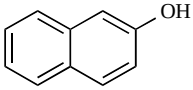
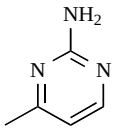
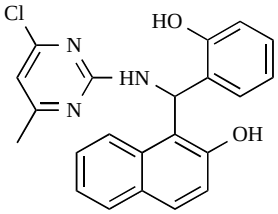
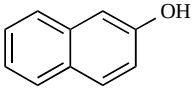
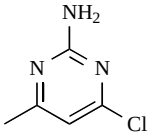
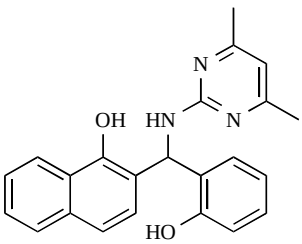
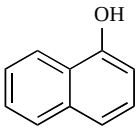
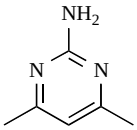
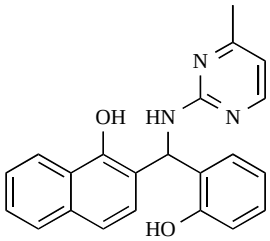
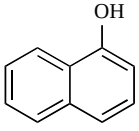
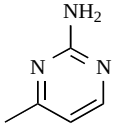
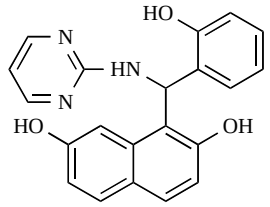
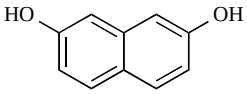
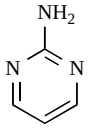
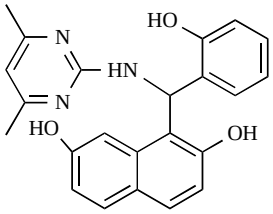
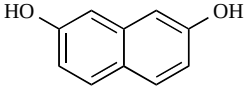
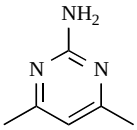
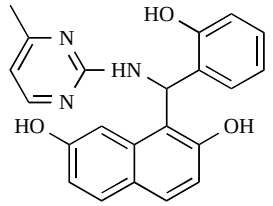
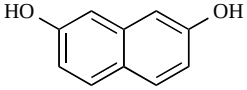
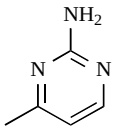
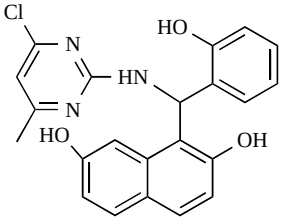
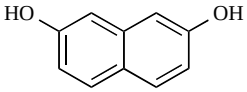
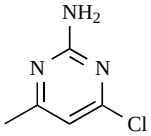
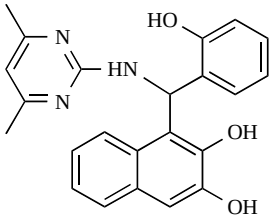
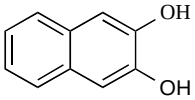
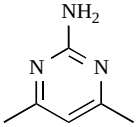
Yield (%)	Time (Min)	3	Product	Naphthol	Amine	Entry
90	25	**3a**				1
92	30	**3b**				2
87	30	**3c**				3
85	30	**3d**				4
87	25	**3e**				5
88	25	**3f**				6

Table 1. contd….

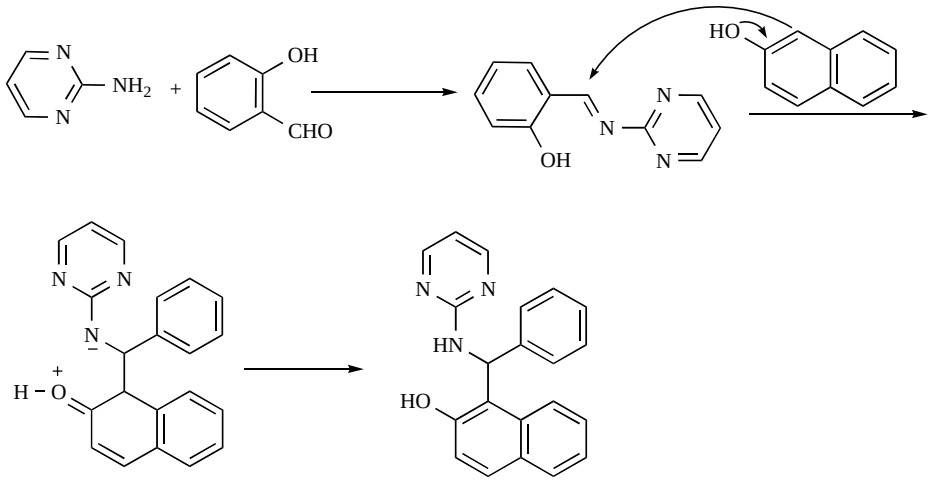
Yield (%)	Time (Min)	3	Product	Naphthol	Amine	Entry
93	30	**3g**				7
91		**3h**				8
91	30	**3i**				9
86	25	**3j**				10
89	25	**3k**				11

tion mechanism, we initially studied the reaction of 2-naphthol with salicylaldehyde. No reaction progress was observed during several hours. When the Schiff base product obtained from 2-aminopyrimidine condensation with salicylaldehyde was treated with 2-naphthol under the reaction conditions, the corresponding Betti base derivative was obtained (Scheme **2**). Notably, a wide range of heteroarylamines with electron donating and electron withdrawing groups and naphthols were well tolerated under the reaction conditions. However, negative charge on the nitrogen in the intermediate, was stabilized with heteroaryl and the reactions proceeded very fast.

Identification of products **3a–k** was carried out on the basis of spectroscopic information. For example, the ^{1}H NMR spectrum of compound **3a** the pyrimidinyl moieties are exhibited as two well-resolved AB_2 spin systems at about δ 6.57 and 8.29 ppm. The methine, amine and aromatic protons should have appeared in the region of aromatic on the basis of integration. Hydroxyl protons presented as broad signals at about δ 9.68-10.21 ppm due to the formation of hydrogen bonding. The OH and NH absorptions are observed at 3250–3400 cm^{-1} in the IR spectra. This Compound exhibits the expected parent ions with medium intensity in mass spectra.

CONCLUSION

In summary, we have successfully developed a quick, convenient, and efficient method for the synthesis of new aminonaphthol (Betti base) derivatives. This protocol is endowed with several advantages such as improved yields, clean reaction, easy operation, obtaining pure products without futhure purification by column chromatography, solvent and catalyst-free conditions, low reaction times and



Scheme 2.

obtaining high to excellent yields merits recommendation to the users. These compounds are potential chelating agents for metal ions and synthesis of novel aminoxanthene derivatives and this aspect is currently under study in our research laboratory.

EXPERIMENTAL

All commercially available chemicals and reagents were used without further purification. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 4300 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 on Bruker DRX-500 and 300 Avance spectrometers. Chemical shifts (δ) are reported in parts per million and are referenced to the NMR solvent. Mass spectra of the products were obtained with a HP (Agilent technologies) 5937 mass selective detector. Elemental analyses were carried out by a CHN–O–Rapid Heraeus elemental analyzer (Wellesley, MA).

General Procedure for the Synthesis of 1-(2-hydroxy Phenyl(diazineamino)methyl)naphthols (3a–k)

A mixture of aminodiazine **1** (1.0 mmol), salicylaldehyde (1.0 mmol) and naphthol **2** (1.0 mmol) was magnetically stirred on a preheated oil bath at 80 °C for the appropriate amount of time as indicated in Table **1**. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion, the reaction mixture was cooled to room temperature and EtOH (5 mL) was added until solid products precipitated. The precipitate was filtered, washed with cold ethanol and dried. The crude product was stirred for 5 min in boiling EtOH and the resulting white precipitate was filtered. The obtained products **3** were found to be pure upon TLC examination.

1-(2-Hydroxyphenyl(2-pyrimidinylamino)methyl)naphthalene-2-ol (3a)

M.P = 187-189 ^{o}C; IR (KBr): 3406, 3049, 2950, 1594, 1534, 1385, 1247, 804 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 6.57 (t, 1H, *J* = 4.76 Hz, *pyrimidine-H5*), 6.69-8.32 (m, 12H, Ar-H, *methine-H and NH*), 8.29 (d, 2H, *J* = 4.76 Hz, *pyrimidine-H4,6*), 9.68 (br, 1H, *OH*), 10.21 (br, 1H, *OH*) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 47.71, 111.40, 116.22, 119.54, 119.74, 120.24, 123.32, 124.22, 126.95, 128.55, 129.11, 129.13, 129.47, 129.57, 129.64, 133.33, 153.92, 155.47, 159.99, 162.23 ppm; MS (EI): m/z 343 (M^+), 279, 265, 167, 149, 113; Anal. calcd. For $C_{21}H_{17}N_3O_2$: C, 73.47; H, 4.95; N, 12.24. Found: C, 73.52; H, 4.99; N, 12.31.

1-(2-Hydroxyphenyl(2-(4,6-dimethylpyrimidinyl)amino) methyl)naphthalene-2-ol (3b)

M.P = 164-166 ^{o}C; IR (KBr): 3376, 3054, 2998, 1588, 1371, 1232, 824 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 2.21 (s, 6H, *2xCH$_3$*), 6.38 (s, 1H, *pyrimidine-H5*), 6.70-8.19 (m, 12H, *Ar-H, methine-H* and *NH*), 10.25 (br, 1H, *OH*), 10.44 (br, 1H, *OH*) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 24.18, 48.24, 110.24, 117.05, 119.79, 119.92, 120.09, 123.46, 127.13, 128.37, 128.74, 129.12, 129.15, 129.23, 129.50, 129.72, 130.14, 133.08, 153.64, 155.34, 161.77 ppm; MS (EI): m/z 371 (M^+), 247, 231, 144, 124, 115, 108, 93; Anal. calcd. For $C_{23}H_{21}N_3O_2$: C, 74.39; H, 5.66; N, 11.32. Found: C, 74.32; H, 5.72; N, 11.30.

1-(2-Hydroxyphenyl(2-(4-methylpyrimidinyl)amino)methyl) naphthalene-2-ol (3c)

M.P = 173-174 ^{o}C; IR (KBr): 3375, 3052, 2998, 1583, 1521, 1443, 1236, 801 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 2.24 (s, 3H, *CH$_3$*), 6.48 (d, 1H, *J* = 4.99 Hz, *pyrimidine-H5*), 6.69-8.27 (m, 12H, *Ar-H, methine-H* and *NH*), 8.16 (d, 1H, *J* = 4.99 Hz, *pyrimidine-H6*), 9.87 (br, 1H, *OH*), 10.30 (br, 1H, *OH*) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 24.45, 47.89, 110.91, 116.52, 119.68, 119.75, 120.24, 123.37, 124.10, 125.70, 127.01, 128.60, 129.10, 129.47, 129.62, 129.87, 130.50, 133.22, 153.79, 155.39, 158.52, 162.00 ppm; MS (EI): m/z 357 (M^+), 247, 231, 213, 144, 121, 116, 110, 94; Anal. calcd. For $C_{22}H_{19}N_3O_2$: C, 73.95; H, 5.32; N, 11.76. Found: C, 74.02; H, 5.40; N, 11.64.

1-(2-Hydroxyphenyl(2-(4-chloro-6-methylpyrimidinyl) amino)methyl)naphthalene-2-ol (3d)

M.P = 142-143 ^{o}C; IR (KBr): 3375, 3061, 2990, 1570, 1521, 1430, 1267, 812 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 2.22 (s, 3H, *CH$_3$*), 6.57 (s, 1H, *pyrimidine-H5*), 6.68-

8.33 (m, 12H, *Ar-H*, *methine-H* and *NH*), 9.55 (br, 1H, *OH*), 10.14 (br, 1H, *OH*) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 24.29, 47.79, 108.89, 109.40, 116.03, 119.39, 119.61, 119.99, 123.25, 124.39, 126.84, 128.60, 128.92, 129.07, 129.48, 129.63, 133.35, 153.97, 155.50, 160.79, 161.98, 170.73 ppm; MS (EI): m/z 391 (M^+), 248, 231, 144, 128, 115, 93; Anal. calcd. For $C_{22}H_{18}ClN_3O_2$: C, 67.43; H, 4.59; N, 10.72. Found: C, 67.50; H, 4.67; N, 10.70.

1-(2-Hydroxyphenyl(2-(4,6-dimethylpyrimidinyl)amino) methyl)naphthalene-1-ol (3e)

M.P = 170-171 ^{o}C; IR (KBr): 3382, 3058, 2996, 1585, 1384, 1249, 809 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): 2.26 (s, 6H, *2xCH$_3$*), 6.30 (s, 1H, *pyrimidine-H5*), 6.35-8.22 (m, 12H, *Ar-H*, *methine-H* and *NH*), 9.70 (br, 1H, *OH*), 10.26 (br, 1H, *OH*) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): 23.69, 48.46, 109.82, 115.78, 119.10, 119.38, 122.84, 124.38, 125.22, 125.93, 126.21, 126.79, 127.66, 128.33, 128.44, 128.50, 128.55, 133.70, 150.41, 154.41, 161.52 ppm; MS (EI): m/z 371 (M^+), 247, 231, 207, 160, 124, 107, 91; Anal. calcd. For $C_{23}H_{21}N_3O_2$: C, 74.39; H, 5.66; N, 11.32. Found: C, 74.44; H, 5.60; N, 11.35.

1-(2-Hydroxyphenyl(2-(4-methylpyrimidinyl)amino)methyl) naphthalene-1-ol (3f)

M.P = 188-189 ^{o}C; IR (KBr): 3377, 3055, 2990, 1581, 1520, 1243, 802 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): 2.27 (s, 3H, *CH$_3$*), 6.41 (d, 1H, *J* = 4.80 Hz, *pyrimidine-H5*), 6.50-8.19 (m, 12H, *Ar-H*, *methine-H*, *pyrimidine-H6* and *NH*), 9.41 (br, 1H, *OH*), 9.71 (br, 1H, *OH*) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): 23.96, 48.54, 110.43, 115.70, 117.69, 119.21, 119.34, 122.67, 124.49, 125.22, 125.78, 126.13, 126.77, 127.76, 128.25, 128.58, 128.80, 133.71, 150.15, 154.58, 158.03, 161.67 ppm; MS (EI): m/z 357 (M^+), 248, 247, 231, 189, 165, 144, 110, 94; Anal. calcd. For $C_{22}H_{19}N_3O_2$: C, 73.95; H, 5.32; N, 11.76. Found: C, 73.91; H, 5.25; N, 11.71.

1-(2-Hydroxyphenyl(2-pyrimidinylamino)methyl)naphthalene-2,7-diol (3g)

M.P = 180-181 ^{o}C; IR (KBr): 3364, 3052, 2995, 1600, 1531, 1218, 817 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 6.56 (t, 1H, *J* = 4.72 Hz, *pyrimidine-H5*), 6.67-7.62 (m, 11H, *Ar-H*, *methine-H* and *NH*), 8.29 (d, 2H, *J* = 4.72 Hz, *pyrimidine-H4,6*), 9.64 (s, 1H, *OH*), 9.75 (br, 1H, OH), 10.09 (br, 1H, *OH*) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 48.12, 106.19, 111.34, 115.88, 116.10, 116.29, 118.29, 119.46, 123.89, 128.58, 129.43, 129.48, 130.69, 135.09, 154.32, 155.75, 156.57, 158.88, 158.97, 162.19 ppm; MS (EI): m/z 359 (M^+), 264, 247, 199, 160, 131, 95; Anal. calcd. For $C_{21}H_{17}N_3O_3$: C, 70.19; H, 4.73; N, 11.70. Found: C, 70.25; H, 4.65; N, 11.78.

1-(2-Hydroxyphenyl(2-(4,6-dimethylpyrimidinyl)amino) methyl)naphthalene-2,7-diol (3h)

M.P = 178-180 ^{o}C; IR (KBr): 3376, 3247, 3057, 2995, 1588, 1532, 1228, 835 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): 2.28 (s, 6H, *2xCH$_3$*), 6.30 (s, 1H, *pyrimidine-H5*), 6.39-7.78 (m, 11H, *Ar-H*, *methine-H* and *NH*), 9.50 (s, 1H, *OH*), 9.65 (br, 1H, *OH*), 10.34 (br, 1H, *OH*) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): 23.74, 48.42, 105.34, 109.81, 115.58, 115.88, 116.95, 117.56, 119.52, 123.49, 128.47, 129.15, 129.21, 129.30, 129.60, 130.37, 134.41, 153.55, 155.26, 156.33, 161.27 ppm; MS (EI): m/z 387 (M^+), 247, 231, 189, 160, 131, 108, 95; Anal. calcd. For $C_{23}H_{21}N_3O_3$: C, 71.31; H, 5.42; N, 10.85. Found: C, 71.40; H, 5.32; N, 10.80.

1-(2-Hydroxyphenyl(2-(4-methylpyrimidinyl)amino)methyl) naphthalene-2,7-diol (3i)

M.P = 168-169 ^{o}C; IR (KBr): 3376, 3052, 2985, 1584, 1523, 1227, 823 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): 2.26 (s, 3H, *CH$_3$*), 6.48 (d, 1H, *J* = 4.95 Hz, *pyrimidine-H5*), 6.67-7.61 (m, 11H, *Ar-H*, *methine-H* and *NH*), 8.17 (d, 1H, *J* = 4.95 Hz, *pyrimidine-H6*), 9.65 (s, 1H, *OH*), 10.04 (br, 1H, *OH*), 10.18 (br, 1H, *OH*) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 24.42, 48.39, 106.03, 110.87, 115.92, 116.29, 116.71, 118.21, 119.65, 123.89, 128.68, 129.42, 129.52, 129.72, 130.71, 134.97, 154.15, 155.69, 156.63, 158.25, 158.52, 161.94 ppm; MS (EI): m/z 373 (M^+), 247, 213, 160, 131, 109, 94; Anal. calcd. For $C_{22}H_{19}N_3O_3$: C, 70.77; H, 5.09; N, 11.26. Found: C, 70.61; H, 5.11; N, 11.31.

1-(2-Hydroxyphenyl(2-(4-chloro-6-methylpyrimidinyl) amino)methyl)naphthalene-2,7-diol (3j)

M.P = 180-182 ^{o}C; IR (KBr): 3356, 3050, 2991, 1557, 1523, 1221, 828 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): 2.33 (s, 3H, *CH$_3$*), 6.58 (s, 1H, *pyrimidine-H5*), 6.63-7.59 (m, 11H, *Ar-H*, *methine-H* and *NH*), 9.49 (s, 1H, *OH*), 9.81 (br, 2H, *OH*) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): 23.85, 47.90, 105.80, 108.98, 115.39, 115.82, 117.57, 118.93, 123.42, 128.22, 128.39, 129.07, 129.50, 130.19, 134.68, 153.95, 155.34, 156.11, 160.52, 161.52, 163.64, 170.28 ppm; MS (EI): m/z 407 (M^+), 247, 218, 189, 160, 143, 128, 108, 93; Anal. calcd. For $C_{22}H_{18}ClN_3O_3$: C, 64.78; H, 4.41; N, 10.30. Found: C, 64.80; H, 4.50; N, 10.33.

1-(2-Hydroxyphenyl(2-(4,6-dimethylpyrimidinyl)amino) methyl)naphthalene-2,3-diol (3k)

M.P = 171-172 ^{o}C; IR (KBr): 3420, 3050, 2990, 1580, 1367, 1240, 748 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): 2.22 (s, 6H, *2xCH$_3$*), 6.31 (s, 1H, *pyrimidine-H5*), 6.34-8.24 (m, 11H, *Ar-H*, *methine-H* and *NH*), 9.30 (br, 1H, *OH*), 9.68 (br, 2H, *OH*), 10.34 (br, 1H, *OH*) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): 23.75, 48.06, 109.15, 109.87, 116.84, 119.65, 120.40, 123.07, 123.48, 123.55, 123.65, 126.80, 127.00, 128.44, 129.03, 129.33, 129.73, 145.18, 146.62, 154.90, 161.28 ppm; MS (EI): m/z 387 (M^+), 315, 273, 247, 227, 160, 123, 108, 91; Anal. calcd. For $C_{23}H_{21}N_3O_3$: C, 71.31; H, 5.42; N, 10.85. Found: C, 71.24; H, 5.51; N, 10.88.

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CONFLICT OF INTEREST

Declared none.

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