An unexpected catalytic synthesis of novel and known bis(pyrazolyl) methanes by the use of *α*-aryl-*N*-phenyl nitrones in aqueous media

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Reaction of -aryl-*N*-phenyl nitrones with 3-methyl-1-phenyl-2-pyrazoline-5-one in the presence of a catalytic amount of silica tungstic acid in EtOH/H_2O afforded, unexpectedly, high yields of bis(3-hydroxy-1-phenylpyrazolyl)-arylmethanes instead of the two possible 1,3-addition products. This is the first report of the synthesis of bis(3-hydroxy-1-phenylpyrazolyl)-arylmethanes *via* the reaction of nitrones and a pyrazolin-5-one. A possible mechanism for the process is suggested.

Keywords: *α*-aryl-*N*-phenyl nitrones, 3-methyl-1-phenyl-2-pyrazoline-5-one, bis(3-hydroxy-1-phenylpyrazolyl)-arylmethanes, silica tungstic acid catalyst

Recently, nitrones as important reactive intermediates have attracted the attention of chemists because of their applications in the synthesis of various natural and biologically active compounds.[1] Nitrones possess a highly polarised C=N bond and have many advantages due to the similarity with important functional groups such as imines, hydrazones and other nitrogen derivatives of aldehydes in reactions with nucleophiles.[2] Nitrones as intermediates have been shown to be more volatile than others such as ylids[3] and can be applied as highly reactive intermediates to the synthesis of a wide range of heterocyclic compounds.[4–6] Also, biologically these active intermediates provide a protective action against microvascular damage.[7] Pyrazole derivatives are important diaza-heterocyclic compounds found in nature and possess extensive biological activities, for example antianxiety, antipyretic, analgesic, and anti-inflammatory agents.[8–11] Several synthetic routes to bis(pyrazolyl)methanes have been reported and generally the methods involve reaction of aromatic aldehydes with pyrazolones under various conditions such as refluxing in ethanol in the presence of silica-bonded S-sulfonic acid (SBSSA) as a Bronsted acid catalyst,[12] stirring in water at room temperature using nano *n*-propylsulfonated *γ*-Fe_2O_3 (NPS-*γ*-Fe_2O_3) as a Lewis acid catalyst,[13]or stirred in the presence of 1,3-disulfonic acid imidazolium tetrachloroaluminate as acidic ionic liquid under solvent-free conditions.[14] Recently, silica tungstic acid (STA) as a highly efficient heterogeneous solid catalyst has been synthesised, characterised, and used as an efficient catalyst in organic reactions leading to benzimidazoles,[15] quinoxalines,[16] coumarins,[17,18] bis-spiro piperidines,[19] and 2-amino-4*H*-chromenes.[20]

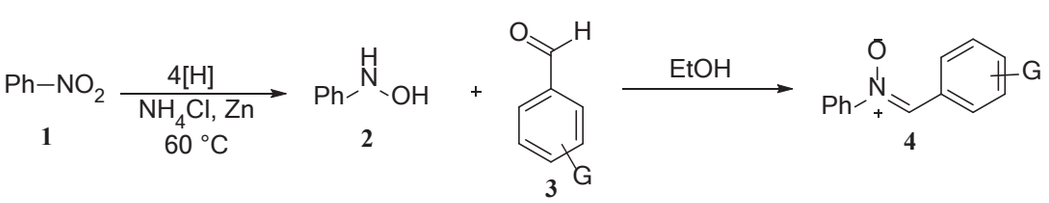
The synthesis of bis(pyrazolyl)methanes starting from nitrones has not, however, been reported. We report here a novel and unexpected route to some new and known bis(pyrazolyl) methanes based on the reaction of *α*-aryl-*N*-phenyl nitrones with 3-methyl-1-phenyl-2-pyrazoline-5-one using STA as a highly efficient heterogeneous solid catalyst.

Results and discussion

Following our continuing interest in developing new and green strategies for organic synthesis, especially new heterocyclic compounds,[21] we turned our attention to the synthesis of new isoxazole derivatives. For this purpose, we first had to prepare *a*-aryl-*N*-phenyl nitrones **4** *via* a two-step method involving the reduction of nitrobenzene (**1**) by ammonium chloride and zinc powder to yield phenyl hydroxylamine (**2**) and then reaction of **2** with aromatic aldehydes **3** (Scheme 1).

The *α*-aryl-*N*-phenyl nitrones **4** (Scheme 1), were then reacted with 3-methyl-1-phenyl-2-pyrazoline-5-one **5** under reflux in EtOH/H_2O. We expected the reaction to produce the corresponding isoxazole derivatives **7** or isoxazolo-fused pyrazoles **8** *via* 1,3-dipolar cycloaddition, but after spectral characterisation of the products, it was found that instead only the bis(3-hydroxy-1-phenylpyrazolyl)-arylmethanes **6** were obtained (Scheme 2).

Those results were obtained without a catalyst and the yields were only about 50%, we then proceeded to see whether various acid and base catalysts could improve the yield. We used as a model the reaction between *α*-phenyl-*N*-phenyl nitrone **4** (G=H) and 3-methyl-1-phenyl-2-pyrazoline-5-one **5** to give product **6a** (G=H) and the results are shown in Table 1. Basic catalysts at 10 mol% (Na_2CO_3, K_2CO_3) gave yields in the range 25–45% (entries 2–4). Acid catalysts such as molybdate sulfuric acid (MSA), ammonium dihydrogen phosphate (ADP), $FeCl_3$ or $CrCl_3$ gave yields in the range 50–86% (entries 5–9). The best yield of 92% was obtained with 5 mol% silica tungstic acid (STA) in EtOH : H_2O (2 : 1) under reflux (entry 11). Other amounts of catalyst were tried, but 5% was optimal. Gratifyingly the use of STA reduced the reaction time from 4 h to 40 min. It should be mentioned that under all examined conditions products **7** and **8** were not synthesised and only product **6** was obtained.



Scheme 1

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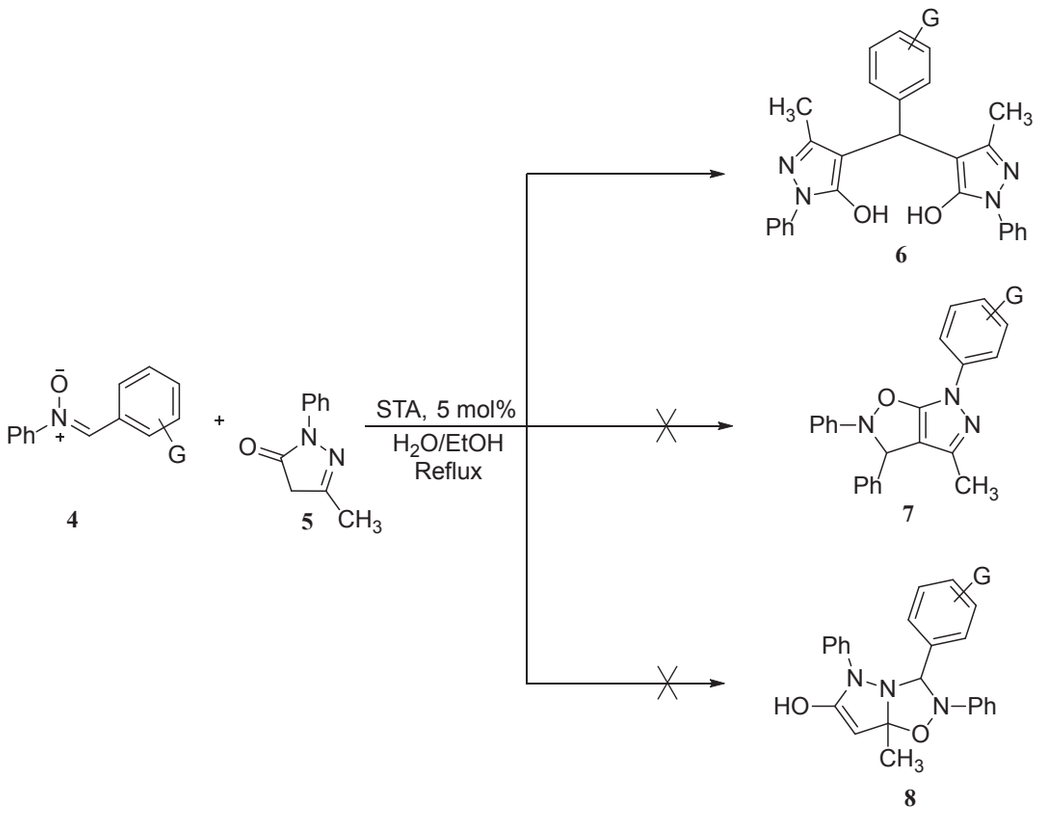


Scheme 2

To demonstrate the generality of reaction, a wide range of α-aryl-*N*-phenyl nitrones were reacted with 3-methyl-1-phenyl-2-pyrazoline-5-one and the results are summarised in Table 2.

It was observed that the process can tolerate both electron-withdrawing and electron-donating groups on the benzene ring. All novel products were characterised by FTIR, ^{1}H and ^{13}C NMR spectroscopy and the results for known compounds compared with authentic samples.[12,22,23] The data were in good agreement with the expected structures. A plausible mechanism for the STA-catalysed synthesis of bis(pyrazolyl) methanes **6** is been depicted in Scheme 3. It is assumed that initially a Knoevenagel-type condensation between **4** and **5** generates Int.1. Subsequent addition of another equivalent of **5** to Int.1 followed by elimination of phenylhydroxylamine and 1,3-proton shift leads to the formation of product **6**.

Table 1 Optimisation of reaction conditions for synthesis of bis(3-hydroxy-1-phenyl-pyrazolyl)-phenylmethane **6a** (G=H) from α-phenyl-*N*-phenyl nitrone **4a** (G=H) and 3-methyl-1-phenyl-2-pyrazoline-5-one **5** (Scheme 2)

Entry	Catalyst/mol%	Solvent/temp./C	Time/min	Yield of **6a**
1	–	None/80	240	50
2	Na_2CO_3 (10)	None/80	240	45
3	Na_2CO_3 (10)	$CHCl_3$/Reflux	240	25
4	K_2CO_3 (10)	THF/Reflux	240	25
5	MSA (5)	None/80	180	70
6	MSA (5)	MeOH/Reflux	60	78
7	ADP (10)	THF/Reflux	240	50
8	$FeCl_3$ (10)	MeOH/Reflux	60	65
9	$CrCl_3.6H_2O$ (5)	EtOH:H_2O (2:1)/80	60	80
10	STA (5)	EtOH/Reflux	60	86
11	STA (5)	EtOH:H_2O (2:1)/Reflux	40	92

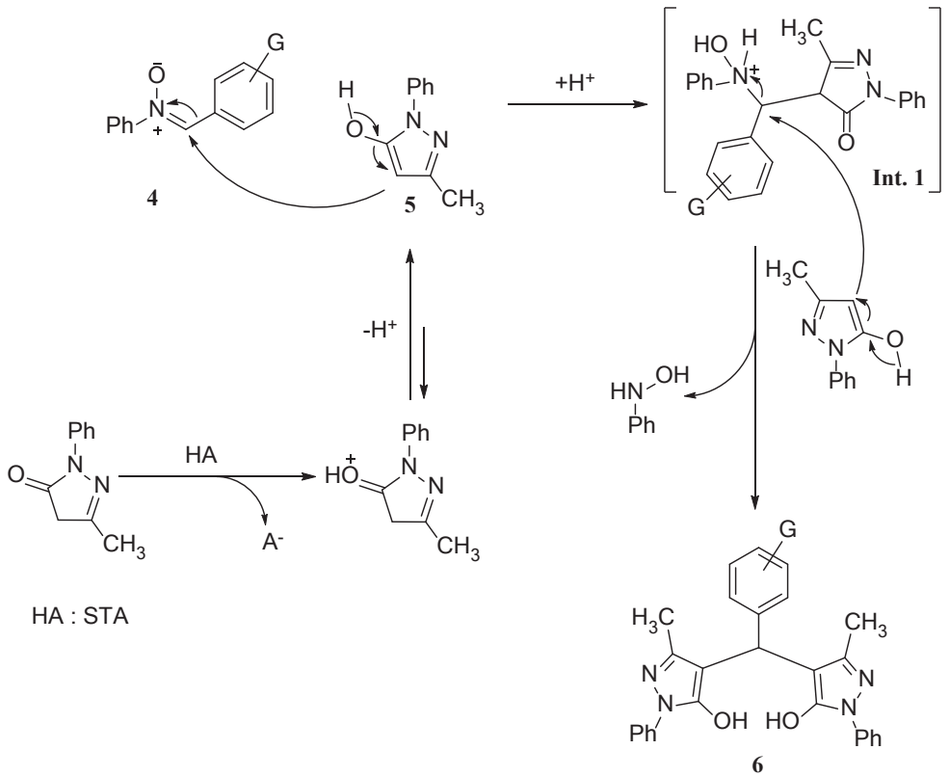
Experimental

Chemicals were purchased from Merck or Aldrich chemical companies. STA was characterised in accord with our previously method.[15] Phenylhydroxylamine and α-aryl-*N*-phenyl nitrones were prepared according to the literature.[24,25] Melting points were measured on an electro thermal KSB1N apparatus. IR spectra were recorded in the matrix of KBr with a JASCO FTIR-680 plus spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a FT-NMR Bruker Avance Ultra Shield Spectrometer at 400.13 and 100.62 MHz in DMSO-d_6 in the presence of TMS as internal standard. TLC was performed on TLC-Grade silica gel-G/UV 254 nm plates.

Table 2 Synthesis of bis(pyrazolyl)methanes **6a–m** using STA as catalyst (Scheme 2)[a]

Product	G	Time/min	Yield/%[b]	M.p./°C [lit.]
6a	H	20	92	162–164 (171–172) [22]
6b	2,4-$(OMe)_2$	20	90	190–192 (–)
6c	3-EtO-4-OH	30	88	212–213 (–)
6d	2,4-Cl_2	20	90	228–230 (227–229) [12]
6e	3-NO_2	15	90	161–163 (151–153) [22]
6f	4-NO_2	15	92	228–230 (229–231) [22]
6g	4-Me	30	88	203–205 (202–204) [22]
6h	2-Cl	15	94	238–240 (235–237) [22]
6i	3-Br	30	92	174–176 (173–175) [22]
6j	4-OMe	20	90	165–167 (176–177) [23]
6k	1-Naphthyl	30	93	228–230 (–)
6l	4-Biphenyl	15	92	218–220 (–)
6m	3-Indolyl	20	86	242–244 (–)

[a]Reaction conditions: A solution of α-aryl-*N*-phenyl nitrone **4** (1 mmol), 3-methyl-1-phenyl-2-pyrazoline-5-one **5** (2 mmol) and STA (5 mol%) in EtOH/H_2O (2:1) (10 mL) was stirred under reflux for an appropriate time.
[b]Isolated yields.



Scheme 3

Synthesis of bis(pyrazolyl)methanes **6a**–**m**

A solution of an *α*-aryl-*N*-phenyl nitrone **4** (1 mmol), 3-methyl-1-phenyl-2-pyrazoline-5-one **5** (2 mmol) and STA (5 mol%) in EtOH/H_2O (2 : 1, 10 mL) was stirred under reflux for an appropriate time. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The resulting precipitate was dried and dissolved in hot EtOH to separate the catalyst. Products **6** were obtained after recrystallisation from boiling EtOH.

bis(5-Hydroxy-3-methyl-1-phenyl-pyrazolyl)-phenylmethane (**6a**): Light yellow crystals; IR (KBr) ($\bar{\upsilon}_{max}$, cm^{-1}): 3424, 3062, 2917, 1598, 1498, 1415, 1284, 1186, 1027, 755, 692; ^{1}H NMR (400.13 MHz) δ (ppm): 13.96 (s, 1H, OH), 12.39 (s, 1H, OH), 7.71 (d, J=8.4 Hz, 4H, aromatic CH), 7.45 (t, J=7.2 Hz, 4H, aromatic CH), 7.31–7.24 (m, 6H, aromatic CH), 7.20–7.17 (m, 1H, aromatic CH), 5.00 (s, 1H, CH), 2.33 (s, 6H, CH_3); ^{13}C NMR (100.62 MHz) δ (ppm): 157.6, 146.4, 140.7, 136.9, 128.8, 128.3, 127.1, 126.4, 126.2, 121.3, 105.7, 33.6, 11.5.

bis(5-Hydroxy-3-methyl-1-phenyl-pyrazolyl)-(2,4-dimethoxyphenyl) methane (**6b**): Yellow crystals; IR (KBr) ($\bar{\upsilon}_{max}$, cm^{-1}): 3428, 2996, 2958, 2839, 1613, 1503, 1460, 1406, 1294, 1209, 1122, 1041, 839, 757, 580; ^{1}H NMR (300.13 MHz) δ (ppm): 14.35 (s, 1H, OH), 12.38 (s, 1H, OH), 7.69 (d, J=7.8 Hz, 4H, aromatic CH), 7.39–7.50 (m, 5H, aromatic CH), 7.22 (t, J=6.9 Hz, 2H, aromatic CH), 6.46 (t, J=9.6 Hz, 2H, aromatic CH), 5.09 (s, 1H, CH), 3.79 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 2.26 (s, 6H, CH_3); ^{13}C NMR (76.46 MHz) δ (ppm): 158.8, 156.7, 146.1, 137.6, 137.4, 137.3, 137.1, 136.7, 133.6, 131.9, 128.8, 125.4, 122.9, 120.5, 104.1, 98.2, 55.4, 55.0, 26.9, 11.6; Anal. calcd for $C_{29}H_{28}N_4O_4$: C, 70.15; H, 5.68; N, 11.28; found: C, 70.22; H, 5.62; N, 11.25%.

bis(5-Hydroxy-3-methyl-1-phenyl-pyrazolyl)-(3-ethoxy-4-hydroxyphenyl)methane (**6c**): Dark brown crystals; IR (KBr) ($\bar{\upsilon}_{max}$, cm^{-1}): 3420, 3219, 2985, 2927, 1596, 1498, 1400, 1275, 1214, 1126, 1043, 811, 753, 691. ^{1}H NMR (300.13 MHz) δ (ppm): 13.97 (s, 1H, OH), 12.36 (s, 1H, OH), 8.67 (s, 1H, OH), 7.69 (d, J=8.1 Hz, 4H, aromatic CH), 7.42 (t, J=7.8 Hz, 4H, aromatic CH), 7.22 (t, J=7.2 Hz, 2H, aromatic CH), 6.82 (s, 1H, CH), 6.66 (s, 2H, CH) 4.82 (s, 1H, CH), 3.90 (q, J=6.9 Hz, 2H, CH_2), 2.29 (s, 6H, CH_3), 1.25 (t, J=6.9 Hz, 3H, CH_3). ^{13}C NMR (76.46 MHz) δ (ppm): 146.1, 145.1, 142.6, 137.3, 137.0, 133.1, 131.6, 128.9, 125.5, 120.5, 119.7, 115.2, 113.4, 63.9, 32.7, 14.7, 11.6; Anal. calcd for $C_{29}H_{28}N_4O_4$: C, 70.15; H, 5.68; N, 11.28; found: C, 70.19; H, 5.57; N, 11.26%.

bis(5-Hydroxy-3-methyl-1-phenyl-pyrazolyl)-(2,4-dichlorophenyl) methane (**6d**): Light brown crystals, m.p. 228–229 °C; IR (KBr) ($\bar{\upsilon}_{max}$, cm^{-1}): 3420, 3057, 2920, 1597, 1572, 1500, 1470, 1380, 1298, 1189, 845, 792, 752, 690; ^{1}H NMR (250.13 MHz) δ (ppm): 13.95 (s, 1H, OH), 12.67 (s, 1H, OH), 7.65–7.74 (m, 5H, aromatic CH), 7.53 (d, J=2 Hz, 1H, aromatic CH), 7.36–7.44 (m, 5H, aromatic CH), 7.22 (t, J=7.2 Hz, 2H, aromatic CH), 5.05 (s, 1H, CH), 2.26 (s, 6H, CH_3); ^{13}C NMR (62.89 MHz) δ (ppm): 148.3, 147.1, 146.0, 137.3, 134.9, 128.8, 125.4, 120.5, 119.2, 111.6, 111.5, 104.9, 104.6, 31.7, 11.6.

bis(5-Hydroxy-3-methyl-1-phenyl-pyrazolyl)-(4-nitrophenyl) methane (**6f**): Yellow crystals, m.p. 228–230 °C; IR (KBr) ($\bar{\upsilon}_{max}$, cm^{-1}): 3068, 2920, 1598, 1579, 1524, 1500, 1415, 1348, 785, 753, 691. ^{1}H NMR (400.13 MHz) δ (ppm): 13.90 (s, 1H, OH), 12.49 (s, 1H, OH), 8.18 (d, J=8.8 Hz, 2H, aromatic CH), 7.73 (d, J=8.0 Hz, 4H, aromatic CH), 7.54 (d, J=8.8 Hz, 2H, aromatic CH), 7.45 (t, J=8.0 Hz, 4H, aromatic CH), 7.25 (t, J=8.0 Hz, 2H, aromatic CH), 5.14 (s, 1H, CH), 2.37 (s, 6H, $2CH_3$); ^{13}C NMR (100.62 MHz) δ (ppm): 150.3, 146.2, 145.8, 137.1, 129.1, 128.9, 128.5, 125.6, 123.3, 120.5, 104.0, 33.1, 11.5.

bis(5-Hydroxy-3-methyl-1-phenyl-pyrazolyl)-(1-naphthyl)methane (**6k**): Orangish-white crystals; IR (KBr) ($\bar{\upsilon}_{max}$, cm^{-1}): 3419, 3062, 2922, 1608, 1542, 1497, 1402, 1370, 1132, 829, 783, 756, 689; ^{1}H NMR (300.13 MHz) δ (ppm): 13.15 (s, 1H, OH), 12.19 (s, 1H, OH), 8.10–8.00 (m, 1H, aromatic CH), 7.92 (d, J=6.6 Hz, 1H, aromatic CH), 7.80 (d, J=7.2 Hz, 1H, aromatic CH), 7.62–7.75 (m, 5H, aromatic CH), 7.34–7.57 (m, 7H, aromatic CH), 7.15–7.25 (m, 2H, aromatic CH), 5.61 (s, 1H, CH), 2.25 (s, 6H, CH_3); ^{13}C NMR (76.46 MHz) δ (ppm): 146.0, 144.1, 140.6, 137.3, 136.7, 133.6, 130.7, 128.8, 128.7, 127.0, 125.9, 125.7, 125.3, 125.2, 123.5, 119.9, 105.6, 30.9, 11.9, 11.8; Anal. calcd for $C_{31}H_{26}N_4O_2$: C, 76.52; H, 5.39; N, 11.51; found: C, 76.57; H, 5.33; N, 11.48%.

bis(5-Hydroxy-3-methyl-1-phenyl-pyrazolyl)-(4-biphenyl)methane (**6l**): Orangish white crystals; IR (KBr) ($\bar{\upsilon}_{max}$, cm^{-1}): 3444, 3026, 2922, 1599, 1580, 1499, 1405, 1294, 818, 751, 692; ^{1}H NMR (300.13 MHz) δ (ppm): 14.05 (s, 1H, OH), 12.48 (s, 1H, OH), 7.74 (d, J=7.8 Hz, 4H, aromatic CH), 7.55–7.62 (m, 4H, aromatic CH), 7.46–7.34 (m, 9H, aromatic CH), 7.23 (t, J=7.2 Hz, 2H, aromatic CH), 5.01 (s, 1H, CH), 2.35 (s, 6H, $2CH_3$); ^{13}C NMR (76.46 MHz) δ (ppm): 146.3, 141.5, 140.0, 137.9, 137.4, 137.3, 128.9, 128.8, 127.8, 127.1, 126.5, 125.5, 120.5, 104.9, 104.6, 32.8, 11.6; Anal. calcd for $C_{33}H_{28}N_4O_2$: C, 77.32; H, 5.51; N, 10.93; found: C, 77.38; H, 5.43; N, 10.84%.

bis(5-Hydroxy-3-methyl-1-phenyl-pyrazolyl)-(3-indolyl)methane (**6m**): Yellow crystals; m.p. 242–244 °C; IR (KBr) ($\bar{\upsilon}_{max}$, cm^{-1}): 3470, 3042, 2920, 1618, 1540, 1488, 1405, 1370, 1136, 830, 786, 755, 689; ^{1}H NMR (400.13 MHz) δ (ppm): 12.65 (s, 2H, OH), 9.85 (s, 1H, NH), 8.13–8.11 (m, 2H, aromatic CH), 8.06 (s, 1H, aromatic CH), 8.05–8.01 (m, 2H, aromatic CH), 7.60–7.58 (m, 1H, aromatic CH), 7.44–7.40 (m, 4H, aromatic CH), 7.32–7.29 (m, 4H, aromatic CH), 7.17–7.13 (m, 1H, aromatic CH), 7.15–7.25 (m, 2H, aromatic CH), 3.49 (s, 1H, CH), 2.39 (s, 6H, $2CH_3$); ^{13}C NMR (100.62 MHz) δ (ppm): 162.7, 150.8, 138.9, 138.2, 136.9, 136.4, 128.6, 128.1, 123.8, 123.4, 122.0, 118.5, 118.0, 112.8, 112.2, 18.5, 12.9; Anal. calcd for $C_{29}H_{25}N_5O_2$: C, 73.25; H, 5.30; N, 14.73; found: C, 73.31; H, 5.23; N, 14.66%.

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