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An expedient approach for the synthesis of dispiropyrrolidine bisoxindoles, spiropyrrolidine oxindoles and spiroindane-1,3-diones through 1,3-dipolar cycloaddition reactions

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ABSTRACT

A series of dispiropyrrolidine bisoxindoles were synthesized via a multicomponent 1,3-dipolar cycloaddition reaction of isatin, sarcosine and isatylidene malononitrile in refluxing methanol. Also a series of spiropyrrolidine oxindoles and spiroindane-1,3-diones were synthesized using 2-(1*H*-Indole-3-carbonyl)-3-phenyl-acrylonitrile and 2-(1,3-dioxo-indan-2-ylidene)-malononitrile as dipolarophiles, respectively.

Multicomponent 1,3-dipolar cycloaddition reactions play a key role in the synthesis of five-membered heterocycles.[1] 1,3-Dipolar cycloaddition of ylidic species, such as azomethine ylides with dipolarophiles, is a powerful method for the construction of biologically active five-membered heterocycles[2] especially substituted pyrrolidine rings.[3] Pyrrolidines are important heterocycles which have glucosidase inhibitory activity, potent antiviral, antibacterial, antidiabetic and anticancer activities.[4]

The heterocyclic spiro-oxindole framework is an important structural motif in relevant compounds as natural products and also act as potent nonpeptide inhibitor of the p53-MDM2 interaction.[5] Spiropyrrolidine oxindole ring systems are found in a number of alkaloids such as horsifiline, spirotryprostatine A and B and elacomine.[6] Isatin derivatives are useful precursors in the synthesis of wide number of naturally occurring oxindole alkaloids.[7]

The synthesis of spiro-oxindoles via 1,3-dipolar cycloaddition reaction of piperidone derivatives,[5b] Baylis–Hillman and Morita–Baylis–Hillman adducts of isatin has been reported.[8,9] Recently, Murugan et al. have synthesized dispiropyrrolidine oxindoles by [3+2] cycloaddition reaction of azomethine ylides.[10] To the best of our knowledge, there are only a few methods to synthesize dispiro-oxindoles using isatin derivatives as both dipoles and dipolarophiles in 1,3-dipolar cycloaddition reaction.[9,11] Herein, we report a 1,3-dipolar cycloaddition reaction involving the olefin segment of isatylidene malononitrile to synthesize dispiropyrrolidine bisoxindoles via generation of azomethine ylides from isatin and sarcosine. The generated azomethine ylides approached the dipolarophile isatylidene malononitrile regioselectively.

In our initial endeavour, we have investigated a three-component reaction of isatin **1a,** sarcosine **2** and isatylidene malononitrile **3** in various solvents like methanol, toluene and acetonitrile under reflux condition to afford functionalized dispiropyrrolidine bisoxindole **4a** with two spiro centres. The best results were obtained by refluxing the reaction mixture in methanol with high yield of the product (Scheme 1).

A mixture of isatin **1a** (1.0 mmol), sarcosine **2** (1.2 mmol) and isatylidene malononitrile **3** (1.1 mmol) in methanol was refluxed for 100 min. The reaction mixture was cooled to room temperature. The solid precipitated from the reaction was filtered and recrystallized from ethanol to furnish dispiropyrrolidine bisoxindole **4a** as a single regioisomer.

The feasibility of the reaction was further studied with various substituted isatin derivatives. Under optimized conditions, the reaction proceeded smoothly with various isatin derivatives, including those containing halogens and N-substituted isatin derivatives to provide dispiropyrrolidine bisoxindoles **4b–f** in good yields (82–85%). The results are given in Table 1.

Initially, the reaction proceeds through the generation of azomethine ylide (dipole **2a**) via the decarboxylative condensation

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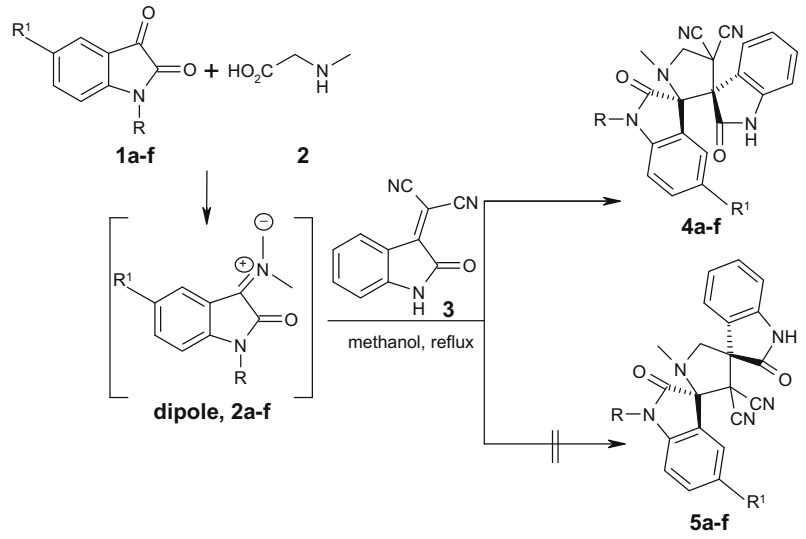


Scheme 1. Synthesis of dispiropyrrolidine oxindoles **4a**–**f**.

Table 1
Synthesis of dispiropyrrolidine bisoxindoles **4a**–**f**

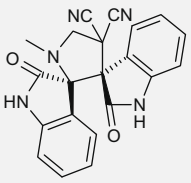
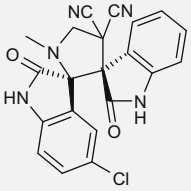
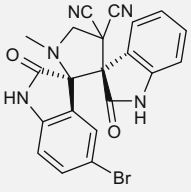
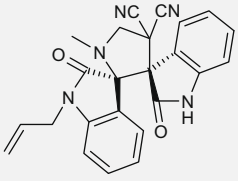
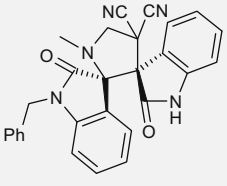
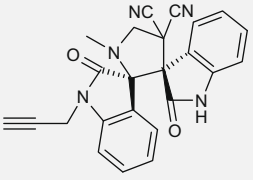
Entry	Isatin **1**	R	R^1	Product[a] (**4**)	Time (min)	Yield[b] (%)
1	**1a**	H	H	 **4a**	100	85
2	**1b**	H	Cl	 **4b**	80	83
3	**1c**	H	Br	 **4c**	80	82
4	**1d**	Allyl	H	 **4d**	80	84
5	**1e**	Benzyl	H	 **4e**	100	83

Table 1 (*continued*)

Entry	Isatin **1**	R	R^1	Product[a] (**4**)	Time (min)	Yield[b] (%)
6	**1f**	Propargyl	H	 **4f**	120	85

[a] The products were characterized by NMR, IR, mass and elemental analysis.
[b] Isolated yield.

of isatin **1a** with sarcosine **2**. The possible mode of approach of azomethine ylide (dipole **2a**) is shown in Figure 1. The regioselectivity in the product formation can be explained by considering secondary interaction of the orbitals of carbonyl group of dipolarophile **3**[12] with those of the ylide **2a** as shown in Figure 1. Accordingly, the observed regioisomer **4a** via path **A** is more favourable due to the secondary orbital interaction (**SOI**) which is not possible in path **B**. Hence, only one regioisomer **4a** was formed as evidenced by single crystal analysis.[13]

The structures of cycloadducts **4a**–**f** were confirmed by spectroscopic studies and elemental analysis. The ^{1}H NMR spectrum of compound **4a** exhibited characteristic singlets at δ 2.03 for –NCH_3 protons and δ 10.75, 11.08 for –NH protons of two oxindole rings which proved the incorporation of two oxindole rings in the structure. The amide carbonyl carbon atoms of two oxindole rings show peaks at δ 172.9 and 175.9 ppm in ^{13}C NMR spectrum. These observed chemical shift values are in accordance with the structure of the compound **4a**. Moreover, the presence of a molecular ion peak at *m/z* 370 (M^++H^+) in the mass spectrum of **4a** confirmed the structure of the cycloadduct **4a**. The relative stereochemistry of the product **4a** was established through single-crystal X-ray analysis[13–15] (Fig. 2).

On the basis of the above-mentioned results, we have extended our protocol to other two dipolarophiles such as 2-(1,3-dioxo-indan-2-ylidene)-malononitrile **6** and 2-(1*H*-Indole-3-carbonyl)-3-phenyl-acrylonitrile **8** under optimized conditions. The dipolarophiles **6** and **8** react with azomethine ylides (dipole **2a–f**) generated

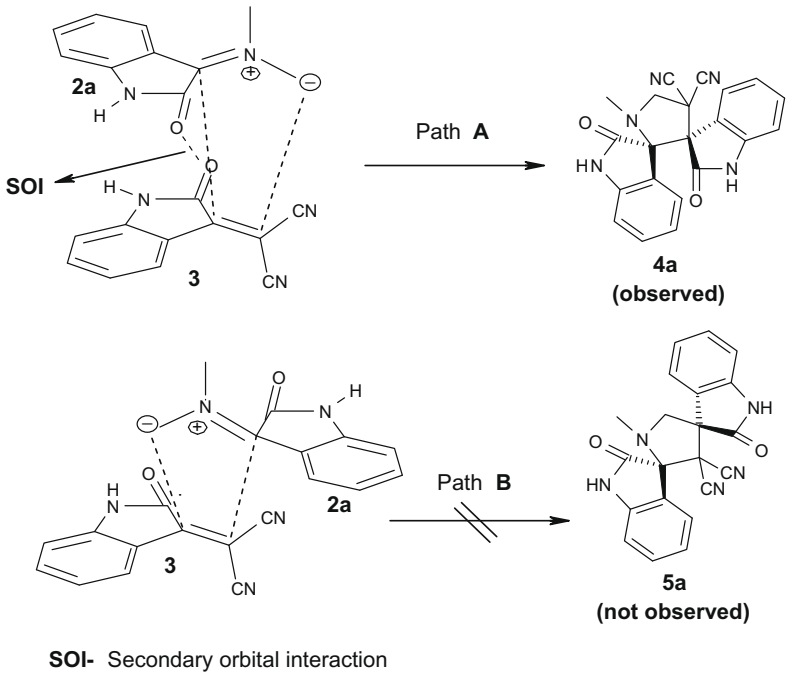


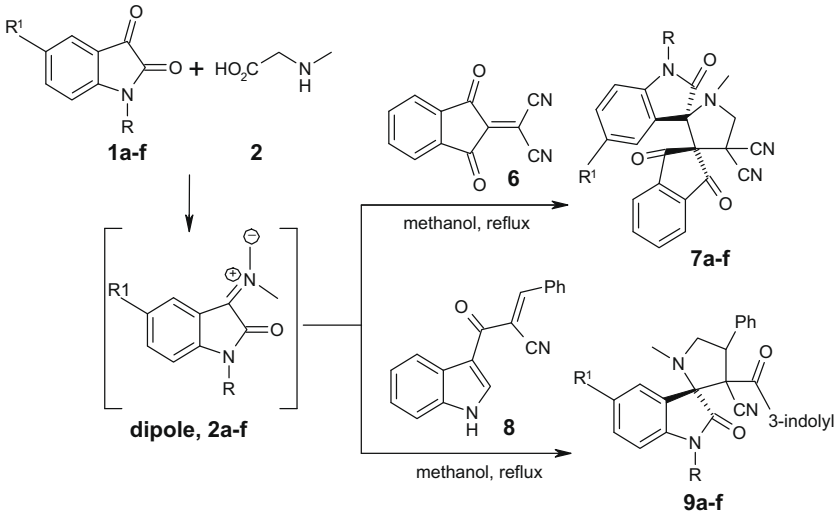
Figure 1. Mode of approach of azomethine ylide **2a**.

in situ from isatin **1a–f** and sarcosine **2** in methanol to yield spiroindane-1,3-diones **7a–f** and spiropyrrolidine oxindoles **9a–f**, respectively, as single products with good yields (75–87%) as evidenced by TLC and spectral analysis (Scheme 2). The results are summarized in Tables 2 and 3.

The products **7a–f** and **9a–f** were characterized on the basis of their elemental analysis as well as IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis.

The IR spectrum of **7d** showed peak at 1722 cm^{-1} due to the oxindole ring carbonyl group. The ^{1}H NMR spectrum of compound **7d** exhibited a characteristic singlet at δ 1.86 (–NCH_3 protons) and two doublets at δ 3.55 and 3.95 (–NCH_2 protons). The peaks at δ 173.3, 196.7 and 197.6 ppm in ^{13}C NMR spectrum indicated the presence of amide carbonyl group of oxindole ring and two keto carbonyl groups of indandione, respectively. The mass spectrum displayed the (M^++H^+) peak at *m/z* 423.0.[16,17]

The IR spectrum of **9a** showed peak at 1704 cm^{-1} due to the oxindole ring carbonyl group. In the ^{1}H NMR spectrum of **9a**, the benzylic proton showed a triplet at δ 5.40, which clearly proved the regiochemistry of the cycloaddition reaction. The doublet at δ 3.65 (–NCH_2 protons) in ^{1}H NMR spectrum of **9a** further confirmed the structure of the product **9a.** The signals at δ 10.40 and 11.86 in ^{1}H NMR spectrum correspond to –NH protons. The signals at δ 174.9 and 180.6 ppm in the ^{13}C NMR spectrum confirm the presence of amide carbonyl group of oxindole ring and keto carbonyl group, respectively. The mass spectrum displayed the (M^++H^+) peak at *m/z* 447.2. The stereochemistry of cycloadducts **7a–f** and **9a–f** was assigned by analogy of compound **4a**.[18,19]



Scheme 2. Synthesis of spiroindane-1,3-diones **7a–f** and spiropyrrolidine oxindoles **9a–f**.

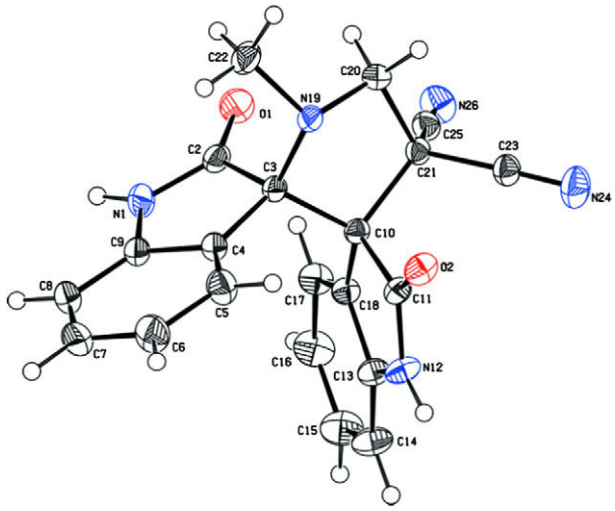


Figure 2. ORTEP diagram of compound **4a**.

Table 2
Synthesis of spiroindane-1,3-diones **7a–f**

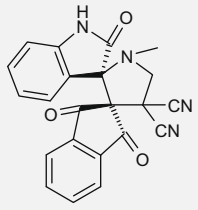
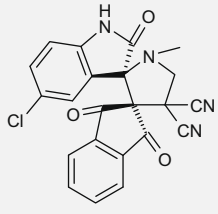
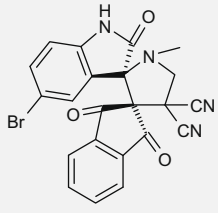
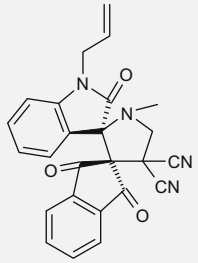
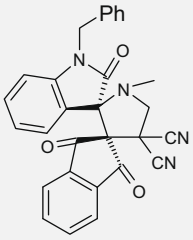
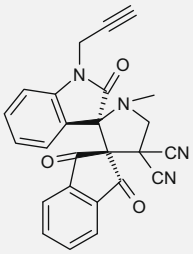
Entry	Isatin **1**	R	R^1	Product[a] (**7**)	Time (min)	Yield[b] (%)
1	**1a**	H	H	 **7a**	120	82
2	**1b**	H	Cl	 **7b**	120	78
3	**1c**	H	Br	 **7c**	130	83
4	**1d**	Allyl	H	 **7d**	120	76

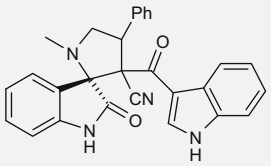
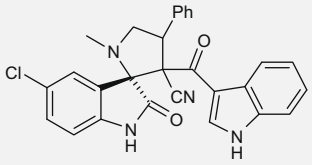
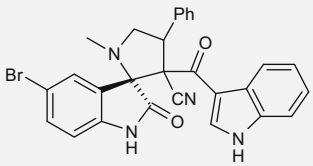
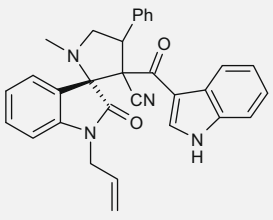
Table 2 (*continued*)

Entry	Isatin **1**	R	R^1	Product[a] (**7**)	Time (min)	Yield[b] (%)
5	**1e**	Benzyl	H	 **7e**	120	78
6	**1f**	Propargyl	H	 **7f**	130	75

[a] The products were characterized by NMR, IR, mass and elemental analysis.
[b] Isolated yield.

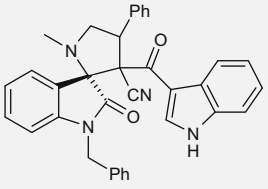
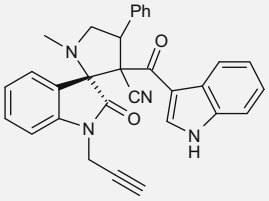
This method offers several advantages such as high yield, simple experimental and isolation procedures making it an

Table 3
Synthesis of spiropyrrolidine oxindoles **9a–f**

Entry	Isatin **1**	R	R^1	Product[a] (**9**)	Time (min)	Yield[b] (%)
1	**1a**	H	H	 **9a**	60	87
2	**1b**	H	Cl	 **9b**	60	85
3	**1c**	H	Br	 **9c**	60	82
4	**1d**	Allyl	H	 **9d**	60	80

(*continued on next page*)

Table 3 (*continued*)

Entry	Isatin **1** R	R[1]	Product[a] (**9**)	Time (min)	Yield[b] (%)
5	**1e** Benzyl	H	 **9e**	80	80
6	**1f** Propargyl	H	 **9f**	100	78

[a] The products were characterized by NMR, IR, mass and elemental analysis.
[b] Isolated yield.

efficient route to the synthesis of dispiropyrrolidine bisoxindoles, spiropyrrolidine oxindoles and spiroindane-1,3-diones that are important compounds in organic and medicinal chemistry.

In summary, we have demonstrated multicomponent 1,3-dipolar cycloaddition reactions which give an array of dispiropyrrolidine bisoxindoles and spiropyrrolidine oxindoles using isatylidene malononitrile and 2-(1*H*-Indole-3-carbonyl)-3-phenyl-acrylonitrile, respectively, and spiroindane-1,3-diones using 2-(1,3-dioxo-indan-2-ylidene)-malononitrile. The products were isolated by recrystallization without involving further purification process like column chromatography.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.079.

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14. *Typical experimental procedure for* **4a**: A mixture of isatin **1a** (1.0 mmol), sarcosine **2** (1.2 mmol) and isatylidene malononitrile **3** (1.1 mmol) in methanol was refluxed for 100 min and cooled to room temperature. The solid formed in the reaction mixture was filtered, dried and recrystallized from ethanol to obtain the pure product in good yield (85%).
15. *Spectral data of compound* **4a** (Table 1, entry 1): White solid; mp 236–238 °C; R_f 0.25 (50% EtOAc/petroleum ether); IR (KBr): 3422, 1724, 1625, 1469, 757, 652 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.03 (s, 3H), 4.15 (ABq, 2H, J = 8.7 Hz), 6.59 (d, 1H, J = 7.6 Hz, -Ar-*H*), 6.72 (d, 1H, J = 7.65 Hz, -Ar-*H*), 6.93 (t, 1H, J = 7.65, -Ar-*H*), 7.02 (t, 1H, J = 7.65 Hz, -Ar-*H*), 7.14 (t, 1H, J = 7.65 Hz, -Ar-*H*), 7.23–7.25 (m, 2H, -Ar-*H*), 7.56 (d, 1H, J = 7.65 Hz, -Ar-*H*), 10.75 (br s, 1H, –N*H*, D_2O exchangeable), 11.08 (br s, 1H, -N*H*, D_2O exchangeable); ^{13}C NMR (125 MHz, DMSO-d_6): 34.4, 61.1, 62.9, 76.9, 110.6, 110.7, 115.3, 116.1, 120.1, 122.1, 122.6, 123.0, 126.6, 127.5, 131.4, 131.7, 143.5, 143.8, 172.9, 175.9; MS (ESI LCQ-MS): m/z 370 [M^++H^+]. Anal. Calcd for $C_{21}H_{15}N_5O_2$: C, 68.28; H, 4.09; N, 18.96. Found: C, 68.32; H, 4.02; N, 18.90.
16. *Typical experimental procedure for* **7d**: A mixture of isatin **1a** (1.0 mmol), sarcosine **2** (1.2 mmol) and 2-(1,3-dioxo-indan-2-ylidene)-malononitrile **6** (1.1 mmol) in methanol was stirred for 120 min. The solid formed in the reaction mixture was filtered, dried and recrystallized from ethanol to obtain the pure product in good yield (76%).
17. *Spectral data of compound* **7d** (Table 1, entry 1): Yellow solid; mp 238–240 °C; R_f 0.25 (50% EtOAc/petroleum ether); IR (KBr): 3366, 1722, 1618, 1469, 1327, 1262, 761 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 1.86 (s, 3H), 3.55 (d, 1H, J = 9.9 Hz), 3.95 (d, 1H, J = 9.2 Hz), 4.13–4.26 (m, 2H), 5.10 (d, 1H, J = 11.45 Hz), 5.20 (d, 1H, J = 16.1 Hz), 5.70–5.75 (m, 1H), 6.81 (d, 1H, J = 8.4 Hz, -Ar-*H*), 6.94 (t, 1H, J = 7.65 Hz, -Ar-*H*), 7.23 (t, 1H, J = 7.65, -Ar-*H*), 7.33–7.36 (m, 1H, -Ar-*H*), 7.46 (d, 1H, J = 7.6 Hz, -Ar-*H*), 7.60 (t, 1H, J = 7.65 Hz, -Ar-*H*), 7.65 (d, 1H, J = 7.65 Hz, -Ar-*H*), 7.78–7.83 (m, 1H, -Ar-*H*); ^{13}C NMR (125 MHz, DMSO-d_6): 33.6, 41.8, 53.4, 57.5, 74.0, 74.2, 89.3, 109.7, 117.8, 122.5, 123.4, 124.1, 125.1, 128.4, 130.5, 131.6, 132.5, 133.5, 137.7, 145.5, 152.5, 166.4, 173.3, 196.7, 197.6; MS (ESI LCQ-MS): m/z 423.0 [M^++H^+]. Anal. Calcd for $C_{25}H_{18}N_4O_3$: C, 71.08; H, 4.29; N, 13.26. Found: C, 71.02; H, 4.22; N, 13.28.
18. *Typical experimental procedure for* **9a**: A mixture of isatin **1** (1.0 mmol), sarcosine **2** (1.2 mmol) and 2-(1*H*-Indole-3-carbonyl)-3-phenyl-acrylonitrile **8** (1.1 mmol) in methanol was refluxed. The reaction mixture was allowed to reflux for 60 min and was cooled to room temperature. The solid formed in the reaction mixture was filtered, dried and recrystallized from ethanol to obtain the pure product in good yield (87%).
19. *Spectral data of compound* **9a** (Table 3, entry 1): White solid; mp 234–236 °C; R_f 0.25 (50% EtOAc/petroleum ether); IR (KBr): 3397, 3278, 1704, 1620, 1442, 747 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.12 (s, 3H), 3.65 (d, 2H, J = 8.4 Hz), 5.40 (t, 1H, J = 8.4 Hz), 6.58 (d, 1H, J = 7.65 Hz, -Ar-*H*), 6.76 (s, 1H, -Ar-*H*), 7.16–7.22 (m, 3H, -Ar-*H*), 7.26 (t, 1H, J = 6.9 Hz, -Ar-*H*), 7.31–7.34 (m, 4H, -Ar-*H*), 7.49 (d, 2H, J = 6.9 Hz, -Ar-*H*), 7.81 (d, 1H, J = 7.65 Hz, -Ar-*H*), 8.11–8.14 (m, 1H, -Ar-*H*), 10.40 (br s, 1H, –N*H*, D_2O exchangeable), 11.86 (br s, 1H, –N*H*, D_2O exchangeable); ^{13}C NMR (125 MHz, DMSO-d_6): 35.6, 45.18, 56.6, 66.5, 77.1, 110.6, 112.8, 112.9, 119.8, 122.2, 122.5, 123.2, 124.1, 125, 125.9, 126.7, 128.2, 128.8, 130.0, 131.4, 134.6, 135.9, 138.0, 144.2, 162.7, 174.9, 180.6; MS (ESI LCQ-MS): m/z 447.2 [M^++H^+]. Anal. Calcd for $C_{28}H_{22}N_4O_2$: C, 75.32; H, 4.97; N, 12.55. Found: C, 75.41; H, 4.92; N, 12.48.