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A Novel and Efficient Method for the Synthesis of Unsymmetrical Diindolylmethanes and Heterocyclic(indolyl)alkanes

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Abstract: 3-Alkylated indoles, obtained from a three-component reaction of indole, aldehyde, and *N*,*N*-dimethylbarbituric acid, undergo an elimination–addition reaction with another indole molecule or heterocyclic nucleophile giving unsymmetrical diindolylmethanes or heterocyclic(indolyl)alkanes in the absence of a catalyst.

Key words: unsymmetrical diindolylmethanes, indole, 3-alkylated indole, anticancer

3,3′-Diindolylmethane (DIM) is a major digestive product of indole-3-methanol, a potential anticancer component of cruciferous vegetables.[1] 3,3′-Diindolylmethane is a potent activator of the immune response system in vivo.[2] It activates and potentiates interferon-gamma signaling in human cells[3] and its use as supplement in human increases the 2-hydroxylation of estrogen metabolites.[4] It reduces the growth of breast cancer cells by 95%.[5] 3,3′-Diindolylmethane exhibits potent antiproliferative and antiandrogenic properties in androgen-dependent human prostate cancer cells.[6] Its various potent anticancer properties have lead to the National Cancer Institute of the United States beginning clinical trials of 3,3′-diindolylmethane as a therapeutic for numerous forms of cancer. Recently it was found that 3,3′-diindolylmethane **A** (Figure 1) worked as HIV-1 integrase inhibitor.[7] Vibrindole A, a metabolite of the marine bacterium *Vibrio parahaemolyticus* (isolated from the toxic mucus of the boxfish *Ostracion cubicus*), has been demonstrated to exhibit antibacterial activity.[8] Compound **C** has growth inhibitory activity on prostate cancer cell lines.[9] Compound **D** was reported to act as a nonsteroidal aromatase inhibitor against breast cancer.[10]

Symmetrical diindolylalkanes can readily be synthesized by Lewis or protic acid catalyzed indole–aldehyde condensation reactions,[11] but the synthesis of unsymmetrical 3,3′-diindolylmethanes have a number of drawbacks and limitations.[12] Vallee and co-workers[12a] reported the first synthesis of unsymmetrical 3,3′-diindolylmethanes, but the procedure was complex. Chakrabarty et al.[12b] reported another method for the preparation of such 3,3′-diindolylmethanes through the Michael reaction of 3-(2-nitrovinyl)indole with indoles. However, the method was limited to 2,2-bis(indol-3-yl)-1-nitroethane derivatives. Ji and co-workers[13] reported the synthesis of unsymmetrical 3,3′-diindolylmethanes from the reaction of indoles with (1*H*-indol-3-yl)(alkyl)methanols catalyzed by ammonium cerium(IV) nitrate and ultrasound. Although the yields of the products were good, the reaction took a long time to go to completion. Recently Csaky and co-workers[14] have synthesized unsymmetrical 3,3′-diindolylmethanes from gramine using an expensive catalyst, moreover, the procedure was operationally difficult.

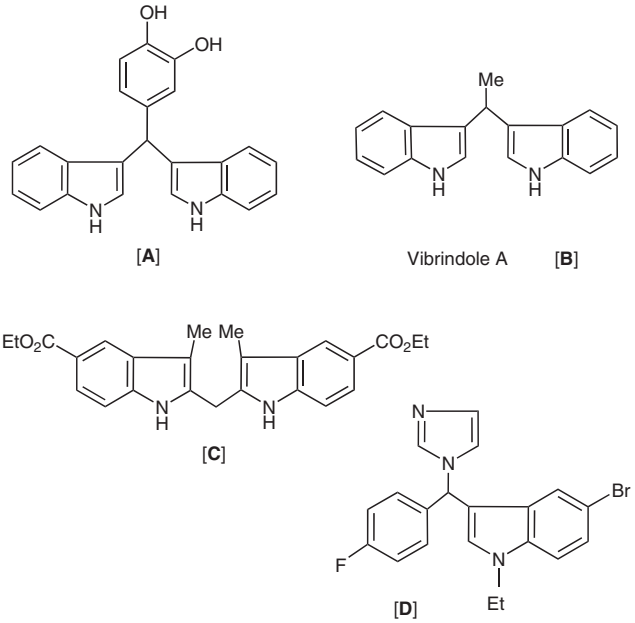

Figure 1

Recently we reported[15] the synthesis of some novel 3-alkylated indoles utilizing equimolar amounts of indole, aldehyde, and *N*,*N*-dimethylbarbituric acid in one pot under thermal and solvent-free conditions. In the reaction we also observed the formation of small amounts of diindolylmethanes for which a mechanism was proposed. That interesting observation encouraged us to explore the utility of the reaction for the preparation of unsymmetrical diindolylmethanes **3** from the reaction of 3-alkylated indoles **1** and indoles **2** (Scheme 1).

The 3-alkylated indoles **1** were prepared from the reaction of indoles, aldehydes, and *N*,*N*-dimethylbarbituric acid.[15] Then equimolar amounts of 3-alkylated indole **1a** and indole **2a** were refluxed in ethanol–water for 30 minutes to afford, after workup, diindolylmethane **3a** in excellent

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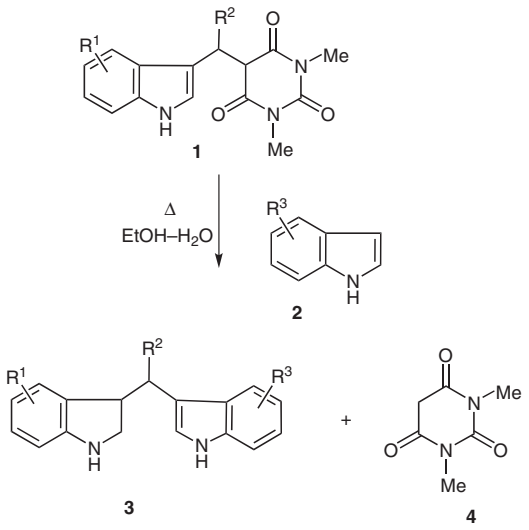


Scheme 1

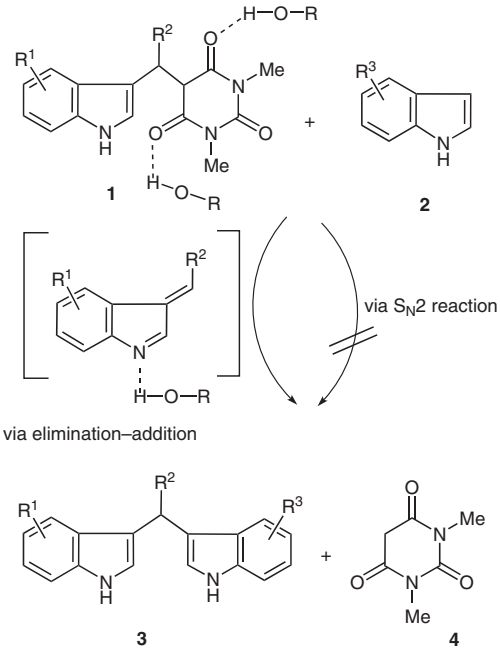
yield. The *N*,*N*-dimethylbarbituric acid (**4**) eliminated during the reaction was isolated and identified. With suitable conditions established for the reaction, compounds **3b–o** were synthesized by utilizing various 3-alkylated indoles **1a–i** with indoles **2a–f** and characterized (Table 1).

The reactions were then studied in various other solvents (e.g., MeOH, MeCN, toluene, $CHCl_3$ etc.) and also in the absence of solvent, however, the reactions proceeded smoothly only in methanol. A few drops of water to the reaction mixture accelerated the reaction considerably with improved yields of the products.

We also studied the effect of substituents in the phenyl (R^2), indole (R^1), and barbituric acid moiety. It was found that an electron-donating group on the phenyl ring accelerated the reactions. 5-Bromo-1*H*-indole and 1-methyl-1*H*-indole had least reactivity. When 3-alkylated indoles **1** bearing barbituric acid (instead of *N*,*N*-dimethylbarbituric acid) were used, the products were obtained easily with a shorter reaction time. However, it is very difficult to prepare substrates, the 3-alkylated indoles bearing barbituric acid, due to their very low solubility.

A plausible mechanism for the reaction is outlined in Scheme 2. The mechanism is an elimination–addition mechanism. First the barbituric acid moiety eliminates from the **1** and then the indole molecule (nucleophile) attacks the C=C–C=N system of the intermediate 3-alkylidene-3*H*-indolium giving the desired diindolylmethane. The rate enhancement of the reaction in protic solvents is due to the coordination of the solvent to the nitrogen atom of the intermediate, which makes it more electrophilic towards the nucleophile. The protic solvent also helps in the elimination process of barbituric acid making it a good leaving group by loose coordination with the carbonyl oxygen.

Longer reaction times were required for 2-alkylated indole **1h** (Table 1, entries 13 and 14) as in this cases the nitrogen in the intermediate could interact only via a



Scheme 2

nonbenzenoid canonical form whereas in case of 3-alkylated indoles the intermediate retained the aromaticity of the benzene ring. When unsubstituted (indol-3-ylmethyl)barbituric acid derivative **1j** was used (Table 1, entry 16), the reaction did not occur, as the barbituric acid moiety could not be eliminated even after an extended period of reflux. This can reasonably be explained by the fact that unlike aromatic aldehydes and aliphatic aldehydes containing an α-hydrogen, the intermediate is not stabilized by either resonance or hyperconjugation. This fact strongly supports our proposed mechanism. Thus the reactivity is in the order of R^2 = aromatic > aliphatic > hydrogen.

Compounds like **3a** and **3b** were also synthesized easily by the reverse process that is from the reaction of **1d**,**e** (where the indole moiety contains a methyl group at the 2- or 5-position) with indole (acting as a nucleophile). However, the preparation of compounds **1** of this type is very difficult because the elimination–addition process is so fast that it gives symmetrical diindolylmethanes (in case of 5- or 2-methylindole) as the major compound.

In order to broaden the scope of this reaction, the reactivity of **1a** with other heterocyclic nucleophiles **5a–e** were also studied and this gave a series of heterocyclic(indolyl)alkane derivatives **6a–e** in satisfactory yields (Table 2). The structures of the compounds were determined from spectroscopic data and elemental analysis. Thus, the reaction of **1a** and **5a** in refluxing ethanol–water gave **6a** in 85% yield in 30 minutes. The ^{1}H NMR spectrum of compound **6a** shows the chemical shift for the methyl protons attached to the pyrazolone ring at δ = 2.36 and for the NH proton of the indole moiety at δ = 9.55. The mass spectrum (HRMS) shows molecular ion peak at 380.1654 $[M + H]^+$.

Table 1 Synthesis of Unsymmetrical Diindolylmethanes **3**

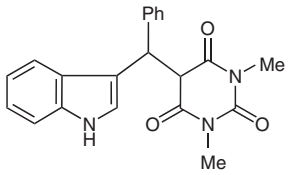
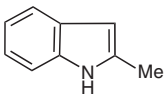
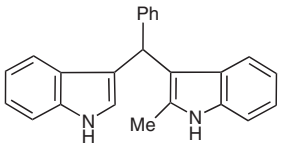
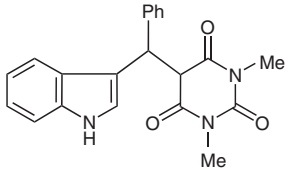
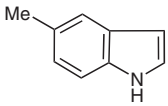
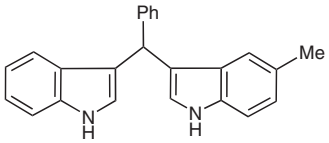
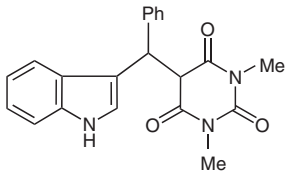
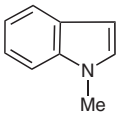
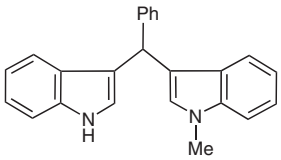
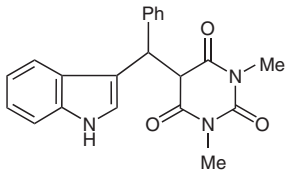
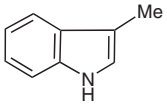
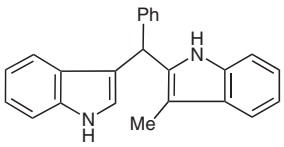
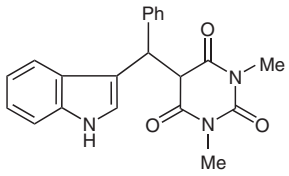
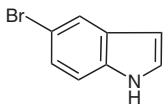
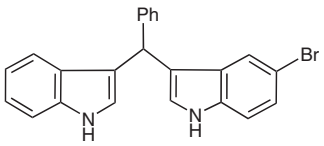
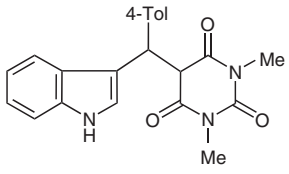
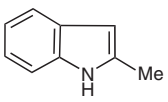
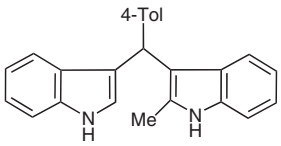
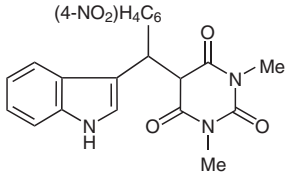
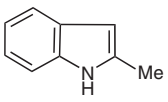
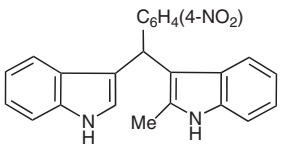
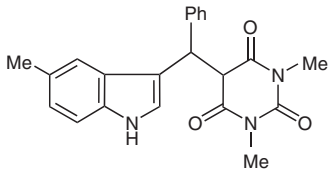
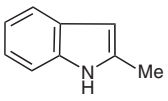
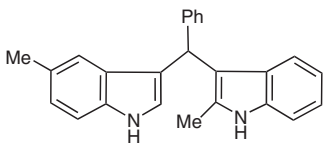
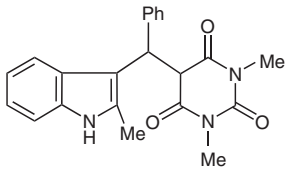
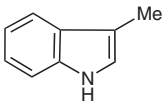
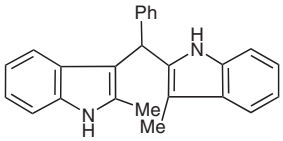
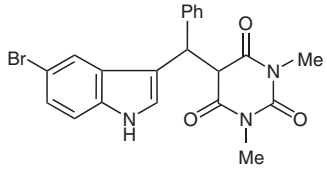
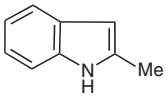
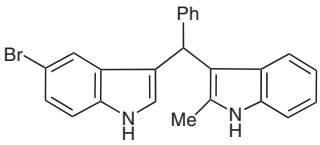
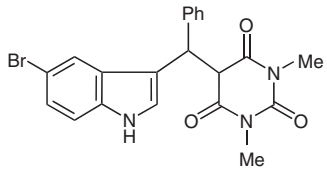
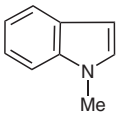
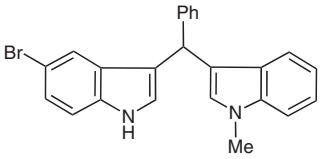
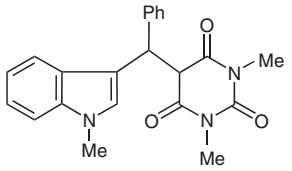
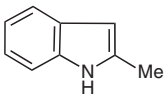
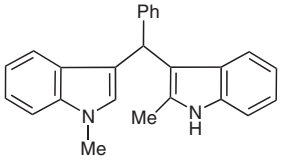
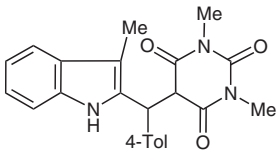
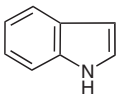
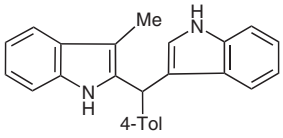
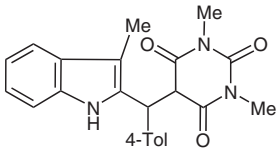
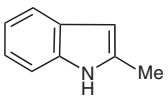
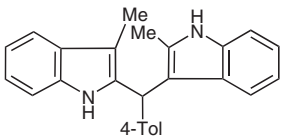
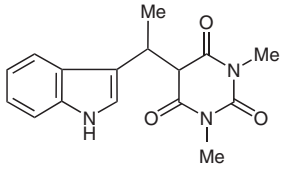
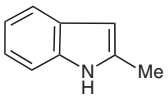
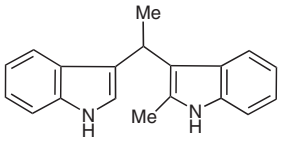
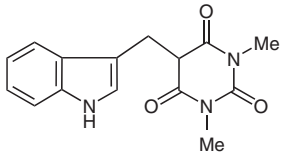
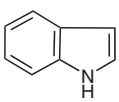
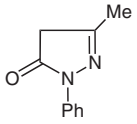
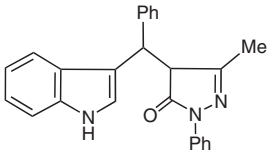
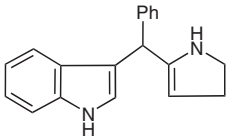
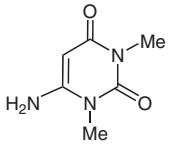
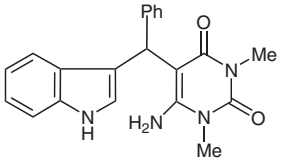
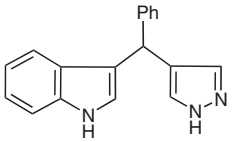
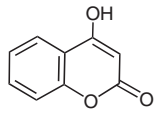
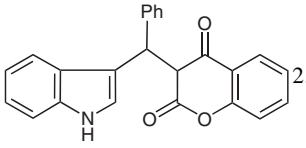
Entry	**1**	**2**	Product[a] **3**	Time (min)	Yield[b] (%)
1	 **1a**	 **2a**	 **3a**	30	82
2	 **1a**	 **2b**	 **3b**	30	82
3	 **1a**	 **2c**	 **3c**	55	61
4	 **1a**	 **2d**	 **3d**	85	72
5	 **1a**	 **2e**	 **3e**	55	62
6	 **1b**	 **2a**	 **3f**	30	75
7	 **1c**	 **2a**	 **3g**	30	63
8	 **1d**	 **2a**	 **3h**	30	88

Table 1 Synthesis of Unsymmetrical Diindolylmethanes **3** (continued)

Entry	**1**	**2**	Product[a] **3**	Time (min)	Yield[b] (%)
9	 **1e**	 **2d**	 **3i**	75	70
10	 **1f**	 **2a**	 **3j**	50	67
11	 **1f**	 **2c**	 **3k**	65	55
12	 **1g**	 **2a**	 **3l**	80	48
13	 **1h**	 **2f**	 **3m**	90	58
14	 **1h**	 **2a**	 **3n**	90	66
15	 **1i**	 **2a**	 **3o**	60	75
16	 **1j**	 **2f**	–	–	–

[a] All reactions were performed on a 1 mmol scale.
[b] Isolated yields.

Table 2 Synthesis of (Heterocyclic)(indolyl)alkanes from [(Indol-3-yl)(phenyl)methyl]barbituric Acid Derivative **1a** and Various Nucleophiles

Entry	Nucleophile **5**	Product[a] **6**	Time (h)	Yield[b] (%)
1	 **5a**	 **6a**	0.5	85[c]
2	 **5b**	 **6b**	1	45
3	 **5c**	 **6c**	1.5	50
4	 **5d**	 **6d**	1	40
5	 **5e**	 **6e**	2.5	48[c]

[a] All reactions were performed on a 1 mmol scale.
[b] Isolated yields.
[c] In both cases we obtained a single isomer.

In conclusion, we have reported a very simple, novel, and efficient method for the synthesis of unsymmetrical diindolylmethanes and some (heterocyclic)(indolyl)alkanes in moderate to excellent yields. It is interesting to note that no catalyst is required in the entire course of the reaction. The effect of solvents in the reaction was studied and protic solvents were found most suitable for the reaction. Moreover, all the reactions proceed smoothly in aqueous ethanol and do not require anhydrous conditions. The eliminated *N*,*N*-dimethylbarbituric acid, is an inexpensive, nontoxic compound and can be recycled. The presented method for the preparation of this important class of diindolylmethanes, which is much superior to the existing methods, is a valuable addition to the chemistry of indoles.

All chemicals including solvent used for reactions without drying. All reagents and solvents were of reagent grade. All IR spectra were recorded on Perkin Elmer system-2000 FTIR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance-DPX 300 MHz and 75 MHz FT NMR in $CDCl_3$ using TMS as an internal standard. LR-MS were recorded in Bruker Daltonics ESQUIRE 3000 LC ESI ion trap mass spectrometer and HRMS were obtained with a MALDI-TOF instrument. Elemental analyses were performed on Perkin Elmer-2400 spectrometer. Analytical TLC and column chromatography were performed using E. Merck aluminum-backed silica gel plates coated with silica gel G and E. Merck silica gel (100–200 mesh); petroleum ether = PE. Melting points (uncorrected) were determined on a Buchi B-540 apparatus.

Indole, aldehydes, and substituted barbituric acids were purchased from Aldrich Chemical Co. and other commercially available reagents were used without further purification.

Diindolylmethanes 3; General Procedure

Equimolar amounts of 3-alkylated indole **1** (1 mmol) and indole **2** (1 mmol) were added to a round-bottomed flask containing EtOH–H_2O (9:1, 6 mL) and refluxed for the time indicated in Table 1. The solvent was then removed under reduced pressure and the desired product **3** separated by column chromatography (15% EtOAc–PE); in some instances crystalline product appeared and filtration only gave the pure product.

3-[(1*H*-Indol-3-yl)(phenyl)methyl]-2-methyl-1*H*-indole (3a)

White shining crystals; yield: 275 mg (82%); mp 221–222 °C; R_f = 0.75 (15% EtOAc–PE).

IR (KBr): 3413 (NH stretch), 3394 (NH stretch), 3054 (w), 2928 (w), 1459 (s), 1353 (m), 744 (s), 700 cm^{-1} (m).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.24 (s, 3 H), 5.91 (s, 1 H), 6.68 (s, 1 H), 6.83–6.85 (d, *J* = 7.38 Hz, 1 H), 6.91–7.02 (m, 2 H), 7.11–7.17 (q, *J* = 7.35 Hz, 3 H), 7.22–7.27 (m, 5 H), 7.63 (s, 1 H), 7.83 (s, 1 H), 9.39 (s, 1 H, NH), 9.48 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.11, 44.91, 112.44, 115.62, 116.22, 122.48, 123.25, 123.98, 124.53, 124.70, 126.01, 126.25, 127.33, 129.12, 131.65, 133.47, 133.61, 133.83, 134.55, 139.95, 140.72, 141.66.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{20}N_2$: 337.1628; found: 337.1613.

3-[(1*H*-Indol-3-yl)(phenyl)methyl]-5-methyl-1*H*-indole (3b)

Light brown powder; yield: 275 mg (82%) ; mp 98–101 °C; R_f = 0.74 (15% EtOAc–PE).

IR ($CHCl_3$): 3407 (NH stretch), 3398 (NH stretch), 3055 (w), 2928 (w), 1456 (s), 1351 (m), 744 (s), 701 cm^{-1} (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.49 (s, 3 H), 5.90 (s, 1 H), 6.66 (s, 1 H), 6.69 (s, 1 H), 6.91–7.0 (m, 3 H), 7.14–7.26 (m, 4 H), 7.35–7.43 (m, 5 H), 7.83 (s, 1 H, NH), 7.91 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.45, 44.93, 113.31, 115.88, 116.27, 122.55, 123.71, 123.98, 124.53, 124.72, 126.01, 126.31, 127.56, 129.12, 131.61, 133.47, 133.69, 133.86, 134.56, 139.95, 140.80, 141.67.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{20}N_2$: 337.1628; found: 337.1639.

3-[(1*H*-Indol-3-yl)(phenyl)methyl]-1-methyl-1*H*-indole (3c)

White powder; yield: 205 mg (61%); mp 187–188 °C; R_f = 0.81 (15% EtOAc–PE).

IR ($CHCl_3$): 3410 (NH stretch), 3055 (w), 2919 (w), 1456 (s), 1013 (m), 744 cm^{-1} (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.50 (s, 3 H), 5.77 (s, 1 H), 6.38 (s, 1 H), 6.46 (s, 1 H), 6.86–6.91 (t, *J* = 7.65 Hz, 3 H), 7.02–7.18 (m, 5 H), 7.22–7.29 (m, 4 H), 7.42 (s, 1 H), 8.25 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.20, 40.68, 109.70, 111.61, 118.64, 119.22, 119.75, 120.26, 120.48, 120.60, 122.02, 122.43, 124.22, 126.67, 127.59, 127.99, 128.80, 128.85, 129.28, 137.17, 137.95, 141.79.

MS: *m*/*z* = 335.5 $[M - H]^+$.

2-[(1*H*-Indol-3-yl)(phenyl)methyl]-3-methyl-1*H*-indole (3d)
Pink powder; yield: 242 mg (72%); mp 194–195 °C; R_f = 0.77 (15% EtOAc–PE).

IR ($CHCl_3$): 3417 (NH stretch), 3409 (NH stretch), 3055 (w), 2923 (w), 1456 (s), 744 cm^{-1} (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.24 (s, 3 H), 5.91 (s, 1 H), 6.64 (s, 1 H), 7.08–7.17 (m, 4 H), 7.21–7.33 (m, 4 H), 7.55–7.58 (d, *J* = 7.42 Hz, 3 H), 7.85 (s, 2 H), 8.09 (s, 1 H, NH), 8.18 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.59, 45.37, 112.36, 115.69, 116.22, 122.36, 123.28, 123.99, 124.59, 124.72, 126.01, 126.28, 127.32, 129.03, 131.66, 133.49, 133.55, 133.84, 134.55, 139.96, 140.71, 141.62.

MS: *m*/*z* = 337.9 $[M + H]^+$.

5-Bromo-3-[(1*H*-indol-3-yl)(phenyl)methyl]-1*H*-indole (3e)
White powder; yield: 248 mg (62%); mp 161–163 °C; R_f = 0.71 (15% EtOAc–PE).

IR ($CHCl_3$): 3410 (NH stretch), 3393 (NH stretch), 3056 (w), 2921 (w), 1456 (s), 1159 (m), 744 cm^{-1} (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.76 (s, 1 H), 6.49–6.50 (d, *J* = 3.38 Hz, 2 H), 6.95–6.99 (t, *J* = 6.90 Hz, 2 H), 7.06–7.13 (m, 3 H), 7.16–7.26 (m, 3 H), 7.44–7.47 (d, *J* = 8.51 Hz, 2 H), 7.72 (s, 2 H), 8.39 (s, 1 H, NH), 8.57 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.43, 111.63, 112.98, 113.06, 119.67, 119.74, 120.28, 122.47, 122.70, 124.08, 125.23, 125.33, 126.81, 127.32, 128.81, 129.07, 129.17, 135.65, 137.10, 143.98.

MS: *m*/*z* = 401.3 ($[M + H]^+$, ^{79}Br, 100), 403.3 ($[M + H]^+$, ^{81}Br, 98).

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{17}N_2{}^{79}Br$: 401.0576; found: 401.0558.

3-[(1*H*-Indol-3-yl)(4-methylphenyl)methyl]-2-methyl-1*H*-indole (3f)
White shining crystals; yield: 262 mg (75%); mp 198–199 °C; R_f = 0.74 (15% EtOAc–PE).

IR ($CHCl_3$): 3410 (NH stretch), 3402 (NH stretch), 3056 (w), 2927 (w), 1456 (s), 743 cm^{-1} (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.28 (s, 3 H), 2.32 (s, 3 H), 5.83 (s, 1 H), 6.62 (s, 1 H), 6.98–7.0 (d, *J* = 7.17 Hz, 2 H), 7.05–7.08 (d, *J* = 7.79 Hz, 2 H), 7.11–7.20 (m, 4 H), 7.29–7.40 (m, 4 H), 8.19 (s, 1 H, NH), 8.28 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.98, 21.22, 44.67, 114.07, 116.04, 123.27, 123.56, 124.06, 124.81, 124.89, 125.02, 126.36, 126.74, 128.61, 128.93, 132.03, 132.41, 133.20, 133.52, 133.89, 136.38, 140.40, 142.35.

MS: *m*/*z* = 351.7 $[M + H]^+$.

3-[(1*H*-Indol-3-yl)(4-nitrophenyl)methyl]-2-methyl-1*H*-indole (3g)
Yellowish crystals; yield: 240 mg (63%); mp 207–209 °C; R_f = 0.63 (15% EtOAc–PE).

IR ($CHCl_3$): 3414 (NH stretch), 3398 (NH stretch), 3056 (w), 2927 (w), 1512 (s), 1456 (s), 1355 (m), 743 cm^{-1} (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.28 (s, 3 H), 5.88 (s, 1 H), 6.69 (s, 1 H), 6.90–6.93 (d, *J* = 7.29 Hz, 2 H), 7.01–7.07 (q, *J* = 8.28 Hz, 3 H), 7.14–7.29 (m, 5 H), 7.36–7.39 (d, *J* = 8.1 Hz, 2 H), 8.06 (s, 1 H, NH), 8.09 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.78, 44.27, 115.33, 116.25, 117.63, 122.22, 124.00, 124.35, 124.45, 124.61, 126.11, 126.29, 127.29, 128.44, 128.94, 131.97, 132.86, 134.51, 136.69, 140.19, 141.54, 147.94.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{19}N_3O_2$: 382.4102; found: 382.4126.

2-Methyl-3-[(5-methyl-1*H*-indol-3-yl)(phenyl)methyl]-1*H*-indole (3h)
White solid; yield: 308 mg (88%); mp 217–218 °C; R_f = 0.74 (15% EtOAc–PE).

IR (KBr): 3410 (NH stretch), 3387 (NH stretch), 3057 (w), 2929 (w), 1456 (s), 743 cm^{-1} (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.24 (s, 3 H), 2.48 (s, 3 H), 5.91 (s, 1 H), 6.66 (s, 1 H), 6.97–7.0 (d, *J* = 7.33 Hz, 2 H), 7.08–7.13 (t, *J* = 7.91 Hz, 3 H), 7.24–7.32 (m, 4 H), 7.35–7.42 (m, 3 H), 8.11 (s, 1 H, NH), 8.24 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.37, 20.41, 42.54, 109.78, 111.13, 114.27, 116.44, 119.20, 122.49, 124.39, 124.71, 126.10, 126.44, 127.29, 128.47, 128.99, 132.12, 132.80, 134.51, 136.64, 138.11, 140.19, 141.34.

MS: *m*/*z* = 351.8 $[M + H]^+$.

2-Methyl-3-[(3-methyl-1*H*-indol-2-yl)(phenyl)methyl]-1*H*-indole (3i)
Pink powder; yield: 245 mg (70%); mp 175–177 °C; R_f = 0.78 (15% EtOAc–PE).

IR (KBr): 3416 (NH stretch), 3404 (NH stretch), 3058 (w), 2928 (w), 1456 (s), 744 cm^{-1} (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.21 (s, 3 H), 2.29 (s, 3 H), 5.89 (s, 1 H), 6.87–6.90 (d, *J* = 7.18 Hz, 2 H), 7.08–7.18 (m, 5 H), 7.26–7.29 (t, *J* = 7.44 Hz, 2 H), 7.52–7.55 (d, *J* = 7.40 Hz, 2 H), 7.96 (s, 2 H), 8.31 (s, 1 H, NH), 8.38 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.27, 13.05, 41.39, 112.31, 115.60, 116.75, 121.98, 123.11, 123.77, 124.59, 124.71, 126.42, 126.76, 127.09, 128.86, 131.04, 134.44, 134.58, 135.97, 137.11, 139.96, 141.63, 142.54.

MS: *m*/*z* = 351.4 $[M + H]^+$.

3-[(5-Bromo-1*H*-indol-3-yl)(phenyl)methyl]-2-methyl-1*H*-indole (3j)
Light orange powder; yield: 277 mg (67%); mp 188–191 °C; R_f = 0.65 (15% EtOAc–PE).

IR ($CHCl_3$): 3417 (NH stretch), 3405 (NH stretch), 3056 (w), 2927 (w), 1456 (s), 1168 (m), 743 cm^{-1} (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.27 (s, 3 H), 5.89 (s, 1 H), 6.66 (s, 1 H), 6.94–6.95 (d, *J* = 6.13 Hz, 2 H), 7.01–7.09 (m, 3 H), 7.13–7.24 (m, 4 H), 7.35–7.37 (d, *J* = 7.24 Hz, 3 H), 8.14 (s, 1 H, NH), 8.19 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.27, 42.56, 109.98, 111.23, 113.36, 116.17, 122.24, 123.28, 124.11, 124.75, 126.34, 126.81, 127.12, 127.43, 128.65, 130.43, 133.31, 134.57, 138.10, 140.03, 141.54, 142.56.

MS: *m*/*z* = 415.2 ($[M + H]^+$, ^{79}Br, 100), 417.5 ($[M + H]^+$, ^{81}Br, 98).

3-[(5-Bromo-1*H*-indol-3-yl)(phenyl)methyl]-1-methyl-1*H*-indole (3k)
Pink powder; yield: 227 mg (55%); mp 211–213 °C; R_f = 0.68 (15% EtOAc–PE).

IR ($CHCl_3$): 3413 (NH stretch), 3056 (w), 2927 (w), 1456 (s), 1165 (m), 743 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 3.50 (s, 3 H), 5.78 (s, 1 H), 6.66 (s, 1 H), 6.69 (s, 1 H), 6.99–7.02 (d, *J* = 7.22 Hz, 2 H), 7.05–7.10 (t, *J* = 7.43 Hz, 3 H), 7.13–7.21 (m, 4 H), 7.35–7.38 (d, *J* = 7.55 Hz, 3 H), 8.14 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.67, 41.86, 109.91, 111.28, 113.36, 115.98, 122.06, 123.29, 124.18, 124.55, 126.37, 126.83, 127.12, 127.47, 128.76, 130.13, 132.88, 134.51, 138.10, 140.21, 141.55, 142.32.

MS: *m*/*z* = 415.0 ($[M + H]^+$, ^{79}Br, 100), 417.0 ($[M + H]^+$, ^{81}Br, 100).

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{19}N_2{}^{81}Br$: 417.0732; found: 417.0714.

1-Methyl-3-[(2-methyl-1*H*-indol-3-yl)(phenyl)methyl]1*H*-indole (3l)

Pink powder; yield: 168 mg (48%); mp 224–226 °C; R_f = 0.78 (15% EtOAc–PE).

IR ($CHCl_3$): 3411 (NH stretch), 3056 (w), 2933 (w), 1456 (s), 1013 (m), 744 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 2.15 (s, 3 H), 3.58 (s, 3 H), 5.88 (s, 1 H), 6.50 (s, 1 H), 6.84–7.03 (m, 4 H), 7.15–7.17 (d, *J* = 6.53 Hz, 2 H), 7.20–7.24 (t, *J* = 7.38 Hz, 4 H), 7.29–7.31 (d, *J* = 7.40 Hz, 3 H), 8.18 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.13, 37.55, 44.12, 114.0, 114.99, 118.92, 122.29, 123.56, 123.87, 124.35, 124.85, 125.51, 126.32, 128.61, 130.73, 132.74, 132.95, 133.34, 133.68, 136.39, 140.05, 142.22.

MS: *m*/*z* = 373.3 $[M + Na]^+$.

2-[(1*H*-Indol-3-yl)(4-methylphenyl)methyl]-3-methyl-1*H*-indole (3m)

Straw colored powder; yield: 203 mg (58%); mp 154–156 °C; R_f = 0.62 (15% EtOAc–PE).

IR ($CHCl_3$): 3410 (NH stretch), 3388 (NH stretch), 3061 (w), 2931 (w), 1456 (s), 744 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 2.20 (s, 3 H), 2.32 (s, 3 H), 5.88 (s, 1 H), 6.55 (s, 1 H), 6.98–7.00 (d, *J* = 7.37 Hz, 2 H), 7.06–7.17 (m, 4 H), 7.20–7.24 (t, *J* = 7.34 Hz, 2 H), 7.34–7.37 (d, *J* = 8.18 Hz, 2 H), 7.54–7.56 (d, *J* = 6.98 Hz, 2 H), 7.99 (s, 1 H, NH), 8.09 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.02, 21.52, 40.40, 111.07, 111.58, 118.14, 118.68, 119.36, 120.16, 121.36, 122.75, 124.35, 127.15, 128.79, 128.88, 129.68, 130.01, 135.37, 136.31, 136.60, 137.09, 139.42.

MS: *m*/*z* = 351.5 $[M + H]^+$.

2-Methyl-3-[(3-methyl-1*H*-indol-2-yl)(4-methylphenyl)methyl]-1*H*-indole (3n)

Brown powder; yield: 240 mg (66%); mp 183–185 °C; R_f = 0.62 (15% EtOAc–PE).

IR ($CHCl_3$): 3410 (NH stretch), 3393 (NH stretch), 3058 (w), 2931 (w), 1456 (s), 744 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 2.13 (s, 3 H), 2.20 (s, 3 H), 2.30 (s, 3 H), 5.87 (s, 1 H), 6.89–6.91 (d, *J* = 7.58 Hz, 2 H), 7.04–7.12 (m, 4 H), 7.20–7.23 (d, *J* = 7.99 Hz, 2 H), 7.52–7.59 (m, 4 H), 7.69 (s, 1 H, NH), 7.94 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.18, 12.37, 21.57, 39.46, 107.97, 110.94, 111.25, 112.29, 118.72, 119.43, 119.51, 120.14, 121.53, 128.44, 128.79, 129.64, 129.91, 132.90, 135.42, 135.78, 136.35, 136.46, 139.28.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{24}N_2$: 365.1941; found: 365.1967.

3-[1-(1*H*-Indol-3-yl)ethyl]-2-methyl-1*H*-indole (3o)

Red powder; yield: 205 mg (75%); mp 143–145 °C; R_f = 0.65 (15% EtOAc–PE).

IR ($CHCl_3$): 3414 (NH stretch), 3396 (NH stretch), 3056 (w), 2965 (w), 2931 (w), 1456 (s), 744 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.84–1.86 (d, *J* = 7.13 Hz, 3 H), 2.33 (s, 3 H), 4.62–4.69 (q, *J* = 7.08 Hz, 1 H), 6.75 (s, 1 H), 6.96–7.0 (m, 2 H), 7.25–7.27 (d, *J* = 6.98 Hz, 2 H), 7.31–7.34 (d, *J* = 8.14 Hz, 2 H), 7.41–7.44 (d, *J* = 7.92 Hz, 2 H), 7.92 (s, 1 H, NH), 8.15 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.09, 25.80, 32.79, 115.17, 115.96, 120.67, 123.69, 123.99, 124.21, 124.61, 125.48, 125.96, 126.35, 126.70, 132.18, 132.94, 135.13, 140.22, 141.60.

MS: *m*/*z* = 275.3 $[M + H]^+$.

3-[(Heterocyclic)(phenyl)methyl]-1*H*-indoles 6; General Procedure

Equimolar amounts of 3-alkylated indole **1a** (1 mmol) and heterocyclic nucleophile **5** (1 mmol) were taken in a round-bottomed flask containing EtOH–H_2O (9:1, 6 mL) and refluxed for 0.5 to 2.5 h. The solid product that appeared was filtered off and purified by recrystallization (EtOH–$CHCl_3$); in the case of **6b** it was separated by column chromatography (12% EtOAc–PE).

4-[(1*H*-Indol-3-yl)(phenyl)methyl]-5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (6a)

White powder; yield: 322 mg (85%); mp 233–234 °C; R_f = 0.45 (25% EtOAc–PE).

IR (KBr): 3405 (NH stretch), 3056 (w), 2925 (w), 1621 (s), 1561 (s), 1456 (s), 771 cm^{-1} (s).

^1H NMR (300 MHz, DMSO-d_6): δ = 2.36 (s, 3 H), 3.63–3.66 (d, *J* = 8.24 Hz, 1 H), 5.62–5.64 (d, *J* = 8.19 Hz, 1 H), 6.76 (s, 1 H), 6.96–7.0 (t, *J* = 7.23 Hz, 2 H), 7.12–7.17 (t, *J* = 7.41 Hz, 3 H), 7.22–7.29 (m, 3 H), 7.34–7.40 (m, 2 H), 7.62–7.74 (m, 4 H), 9.55 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 13.46, 45.77, 54.58, 111.23, 113.65, 117.61, 118.12, 121.43, 121.59, 122.74, 124.38, 125.57, 125.93, 127.89, 131.23, 132.90, 134.27, 139.29, 141.44, 146.45, 161.76.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{21}N_3O$: 380.1686; found: 380.1654.

Anal. Calcd for $C_{25}H_{21}N_3O$: C, 79.15; H, 5.54; N, 11.08. Found: C, 79.10; H, 5.61; N, 11.17.

3-[Phenyl(1*H*-pyrrol-2-yl)methyl]-1*H*-indole (6b)

Brown semisolid; yield: 122 mg (45%); R_f = 0.68 (15% EtOAc–PE).

IR ($CHCl_3$): 3425 (NH stretch), 3405 (NH stretch), 3060 (w), 1456 (s), 744 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 5.22 (s, 1 H), 6.11–6.15 (m, 2 H), 6.63–6.68 (m, 2 H), 7.09–7.12 (d, *J* = 7.44 Hz, 3 H), 7.24–7.28 (t, *J* = 7.19 Hz, 2 H), 7.34–7.47 (m, 4 H), 7.92 (s, 1 H, NH), 8.10 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.26, 106.43, 109.0, 113.51, 115.13, 118.35, 121.47, 121.84, 124.42, 125.98, 126.46, 127.81, 128.08, 131.35, 132.91, 137.23, 141.98.

MS: *m*/*z* = 295.5 $[M + Na]^+$.

6-Amino-5-[(1*H*-indol-3-yl)(phenyl)methyl]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (6c)
Colorless crystal; yield: 180 mg (50%); mp 254–256 °C; R_f 0.60 (40% EtOAc–PE).

IR (KBr): 3411(s), 3397 (s), 3355 (m), 2951 (w), 1659 (s), 1499 (s), 1456 (s), 771 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 3.32 (s, 3 H), 3.34 (s, 3 H), 5.02 (s, 1 H), 6.34 (s, br s, 2 H, NH_2), 6.67 (s, 1 H), 6.84–6.87 (d, *J* = 7.65 Hz, 2 H), 7.04–7.09 (t, *J* = 7.43 Hz, 2 H), 7.19–7.37 (m, 5 H), 8.25 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.61, 28.73, 57.85, 78.54, 114.41, 119.05, 120.45, 122.36, 123.71, 124.26, 127.43, 128.41, 128.80, 136.54, 138.82, 140.23, 151.44, 155.91, 163.20.

MS: *m*/*z* 361.3 $[M + H]^+$.

Anal. Calcd for $C_{21}H_{20}N_4O_2$: C, 70.00; H, 5.55; N, 15.55. Found: C, 70.11; H, 5.63; N, 15.48.

3-[(1*H*-Imidazol-4-yl)(phenyl)methyl]-1*H*-indole (6d)
White solid; yield: 109 mg (40%); mp 292–294 °C; R_f = 0.30 (60% EtOAc–PE). Due to solubility problems, the ^{13}C NMR spectrum of this compound could not be taken

IR (KBr): 3442 (br s), 3413 (s), 2955 (w), 1456 (s), 743 cm^{-1} (s).

^1H NMR (300 MHz, DMSO-d_6): δ = 5.87 (s, 1 H), 6.68 (s, 1 H), 6.79 (s, 1 H), 7.02–7.07 (t, *J* = 7.29 Hz, 3 H), 7.16–7.19 (d, *J* = 7.54 Hz, 2 H), 7.33–7.41 (m, 3 H), 7.52–7.54 (d, *J* = 7.18 Hz, 2 H), 9.34 (s, 1 H, NH), 9.49 (s, 1 H, NH).

MS: *m*/*z* = 272.4 $[M - H]^+$.

Anal. Calcd for $C_{18}H_{15}N_3$: C, 79.12; H, 5.49; N, 15.38. Found: C, 79.18; H, 5.54; N, 15.46.

3-[(1*H*-Indol-3-yl)(phenyl)methyl]-2*H*-1-benzopyran-2,4(3*H*)-dione (6e)
Yellow shining crystal; yield: 176 mg (48%); mp 248–250 °C; R_f = 0.40 (50% EtOAc–PE).

IR (KBr): 3409 (NH stretch), 2931 (w), 1747 (s, OC=O), 1717 (s, C=O), 1456 (s), 1235 (s), 744 cm^{-1} (s).

^1H NMR (300 MHz, DMSO-d_6): δ = 4.14 (d, *J* = 6.14 Hz, 1 H), 5.53 (d, *J* = 6.19 Hz, 1 H), 6.66 (s, 1 H), 7.08–7.11 (d, *J* = 7.41 Hz, 2 H), 7.14–7.23 (m, 3 H), 7.29–7.34 (t, *J* = 7.14 Hz, 3 H), 7.54–7.63 (m, 5 H), 9.95 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 51.23, 58.52, 111.31, 113.62, 118.44, 121.33, 122.39, 124.21, 124.57, 126.78, 126.89, 128.41, 133.56, 137.53, 137.98, 138.34, 140.41, 141.71, 154.12, 165.79, 197.23.

MS: *m*/*z* = 368.5 $[M + H]^+$.

Anal. Calcd for $C_{24}H_{17}NO_3$: C, 78.47; H, 4.63; N, 3.81. Found: C, 78.44; H, 4.71; N, 3.89.

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