Synthesis of New PMB-Substituted Indoles Containing 1,3,4-Oxadiazole and 1,2,4-Triazole Units

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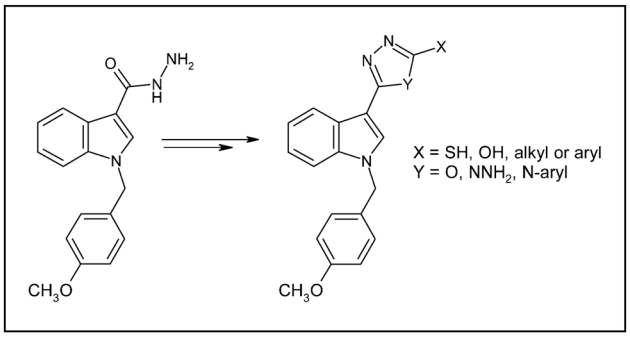

A series of new indolyl-1,3,4-oxadiazole derivatives **3–7** and **10**, indolyl-1,2,4-triazole derivatives **14** and **15** was prepared, using 1-(4-methoxybenzyl)-1*H*-indole-3-carbohydrazide (**2**) as a key intermediate. Some of the new compounds were evaluated for their antineoplastic activity.

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INTRODUCTION

The indole structure represents a highly relevant heterocyclic system, since numerous indole-containing natural and synthetic products such as reserpine, vincristine, indolmicine, mitomycine, pindolol, dolasetron mesylate, indomethacin, or sumatriptan are being used for the treatment of various illnesses. More specifically, several reports describe that indole-2-carbohydrazides and related compounds exhibit antihistaminic [1], antidepressant [2], MAO inhibitory [3,4], and antimicrobial activity [5]. In addition, it was reported that various three-substituted indoles had been used as starting materials for the synthesis of a number of alkaloids, agrochemicals, pharmaceuticals, and perfumes [6]. Moreover, it has been demonstrated that introduction of heterocyclic moieties such as isothiazoles at position 3 of the indole nucleus can enhance these biological activities [7]. On the other hand, 1,3,4-oxadiazoles are a class of heterocycles, which have attracted considerable interest in medicinal chemistry, as they are associated with a wide range of biological effects, including antimicrobial, antifungal, anti-inflammatory, and antihypertensive activity [8–12]. The widespread use of the 1,3,4-oxadiazole system as a scaffold in medicinal chemistry establishes this moiety and its derivatives as an important bioactive class of heterocycles. This is also due to their favorable metabolic profile and their ability to engage in hydrogen bonding. In particular, marketed antihypertensive agents such as tiodazosin [13] and nesapidil [14] as well as antibiotics such as furamizole [15] contain the oxadiazole nucleus. 1,3,4-Oxadiazole-containing compounds are also useful as HIV integrase inhibitors and as angiogenesis inhibitors [15,16]. Furthermore, they exhibit antibacterial, anticonvulsant, and anticancer activities, and they are used to fight infections involving AIDS [17–19]. They are also applied in agriculture as herbicides, fungicides, or insecticides [20,21]. As a closely related class of compounds, 1,2,4-triazole derivatives are known to exhibit anti-inflammatory [22,23], antiviral [24], analgesic [25], antimicrobial [26–28], anticonvulsant [29], and antidepressant activity [30]. Combination of the oxadiazole or triazole motifs with the indole nucleus may enhance these activities. In view of these previous findings and in continuation of our interest in the synthesis of new biologically active azoles and in the development of new synthetic methods [31–36], we, here, report on the synthesis and evaluation of their antitumor activity of some new indole derivatives containing 1,3,4-oxadiazole or 1,2,4-triazole substituents at C-3.

RESULTS AND DISCUSSION

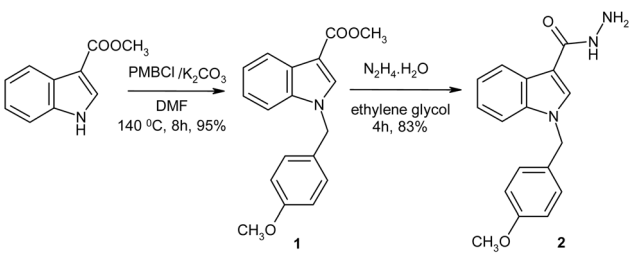
The easily accessible methyl 1-(4-methoxybenzyl)-1*H*-indole-3-carboxylate (**1**), which has not been reported hitherto, was chosen as the starting material. The 4-methoxybenzyl residue should ensure balanced lipophilicity/hydrophilicity properties of the target compounds and, on the other hand, can be easily removed from the indole scaffold, if desired. The compound was prepared by reaction of methyl 1*H*-indole-3-carboxylate with 4-methoxybenzyl chloride in dry dimethylformamide in the presence of potassium carbonate under nitrogen atmosphere. Hydrazinolysis of the ester with hydrazine hydrate in a high-boiling solvent (ethylene glycol) afforded the corresponding hydrazide (**2**) in good yield (Scheme 1), whereas when the reaction was conducted neat or in ethanol, it did not give satisfactory results. The structures of compounds **1** and **2** were confirmed by their spectral data (IR, ^{1}H NMR, ^{13}C NMR, and HRMS) together with elemental analyses. The IR spectrum of compound **1** reveals the absence of an indole NH function. Its ^{1}H NMR spectrum expectedly shows three new, characteristic signals near δ 3.82, 5.15, and 6.77/7.02 ppm, assignable to OCH_3, CH_2 and the para-substituted benzene unit, respectively. The ^{13}C NMR spectrum shows signals at δ 50.35 and 54.75 ppm for two methoxy carbons and at 59.30 ppm for the CH_2 unit. The HRMS spectrum shows the $[M]^+$ peak at *m/z* 295.1225 in agreement with the molecular formula. In the case of compound **2**, the IR spectrum is characterized by two new bands at 3350–3250 cm^{-1}, which are due to NH and NH_2 groups. Its ^{1}H NMR spectrum revealed two new characteristic signals at δ 4.41 and 9.18 ppm, assignable to NH_2 and NH, respectively. Further confirmation was achieved by the ^{13}C NMR spectrum, which shows signals at δ 48.99 and 55.09 ppm due to OCH_3 and CH_2, respectively.

Treatment of the acid hydrazide **2** with carbon disulfide in boiling pyridine led to the formation of the corresponding oxadiazolethione **3** in 86% yield. Whereas reaction of **2** with 1,1′-carbonyldiimidazole (CDI) in tetrahydrofuran (THF) at 70°C did not afford the expected 5-[1-(4-methoxybenzyl)-1*H*-indol-3-yl]-1,3,4-oxadiazol-2(3*H*)-one (**4**), an unexpected debenzylation occurred and the oxadiazolone **5** [37] was obtained in 80% yield. However, when the reaction was carried out in boiling dioxane, the N-substituted analogue **4** was obtained in 69% yield (Scheme 2). The formation of oxadiazolethione derivative **3** was clearly evidenced by appearance of a characteristic absorption band at 1170 cm^{-1} (C═S) and disappearance of the absorption bands belonging to the $NHNH_2$ group. The IR spectrum of compound **4** showed a characteristic absorption band at 1758 cm^{-1} (C═O) which revealed that the C═O is adjacent to oxygen in the five-membered ring. The observed debenzylation during the formation of compound **5** was evidenced by disappearance of the characteristic signals at δ 3.69, 5.42 and 6.87/7.23 ppm (OCH_3, CH_2 and phenyl protons, respectively). Further confirmation for the structure of compound **5** was obtained by HRMS which showed the $[M+K]^+$ ion at *m/z* 240.0162.

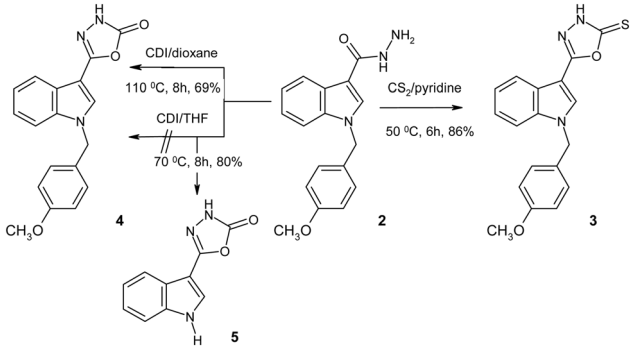
On the other hand, condensation of carbohydrazide **2** with trimethyl orthoformate gave the corresponding 2-[1-(4-methoxybenzyl)-1*H*-indol-3-yl]-1,3,4-oxadiazole (**6**), whereas its reaction with trimethyl orthoacetate afforded a mixture of 2-[1-(4-methoxybenzyl)-1*H*-indol-3-yl]-5-methyl-1,3,4-oxadiazole (**7**) and methyl *N*-{[1-(4-methoxybenzyl)-1*H*-indol-3-yl]carbonyl}ethanehydrazonoate (**8**) in 62 and 25% yield, respectively (Scheme 3). The IR spectrum of compound **6** is characterized by the disappearance of the absorption bands at 3350–3250 cm^{-1} (NH and NH_2 of the starting material **2**). The ^{1}H NMR spectrum of compound **7** shows a new singlet at δ 1.98 ppm due to the CH_3 group, whereas the ^{1}H NMR spectrum of compound **8** shows characteristic signals at δ 1.23, 3.40, and 10.11 ppm, corresponding to CH_3, OCH_3, and NH, respectively.

However, reaction of carbohydrazide **2** with acid chlorides such as benzoyl chloride, phenylacetyl chloride and 2,4,6-trimethylbenzoyl chloride in refluxing dry dioxane did not lead to cyclized products but afforded the corresponding substituted carbohydrazide derivatives **9a–c**. The latter compounds then could be cyclized into the oxadiazole derivatives **10a–c** by heating with phosphorus oxychloride at 100°C for 1–2 h (Scheme 4). As expected, the IR spectra of the cyclized products **10a–c** did not show the characteristic bands of the precursors **9a–c** at 3200 and 1680 cm^{-1} (NH and C═O).

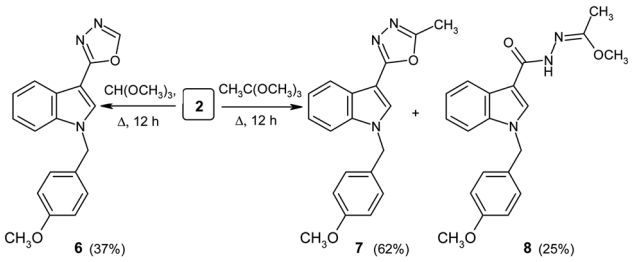
Scheme 1



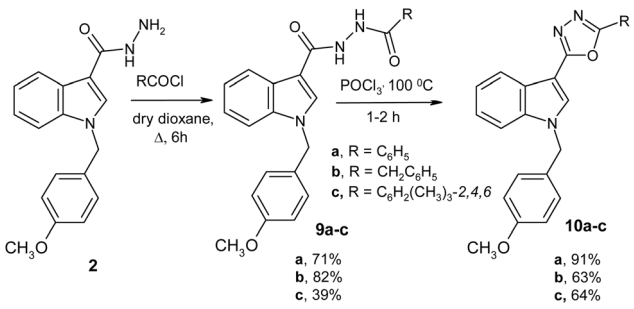
Scheme 2



Scheme 3



Scheme 5



Moreover, reaction of compound **2** with isothiocyanates in refluxing ethanol afforded the substituted thiosemicarbazide derivatives **11–13**, which were transformed into the corresponding 1,2,4-triazole-3-thione derivatives **14a–c** by intramolecular cyclization in boiling ethanolic potassium hydroxide solution. The formation of the thiosemicarbazides **11–13** was confirmed by their IR spectra, showing characteristic absorption bands at 3400 and 3300 cm^{-1} (three NH groups) and 1170 cm^{-1} (C═S) in addition to ^{1}H NMR and ^{13}C NMR spectra and elemental analyses (cf. Experimental). The disappearance of the most prominent NH bands is in agreement with the formation of the cyclized products **14a–c** (Scheme 5).

Finally, hydrazinolysis of oxadiazolethione derivative **3** with hydrazine hydrate in boiling ethanol led to the formation of the *N*-amino-substituted 1,2,4-triazole **15** by a ring opening and ring closure sequence. The structure of compound **15** was confirmed by IR which showed new, characteristic absorption bands at 3400, 3280, and 3180 cm^{-1} (NH_2 and NH). Furthermore, the ^{1}H NMR spectrum exhibits a new signal at δ 5.84 ppm assignable to NH_2 (Scheme 6).

PHARMACLOGICAL EVALUATION

The new compounds were tested *in vitro* for antitumor activity, using the Alamar Blue assay [38] on a panel of five human tumor cell lines. It turned out that only the ester **1** showed significant cell-growth inhibitory activity (>50%) at a fixed concentration of 3.16 μg/mL (Table 1). Subsequent determination of EC_{50} concentrations from dose-response curves gave valid values for four cell lines (in the case of NCI H-460, EC_{50} was above the highest test concentration). Further evaluation of all new compounds in other biological assays is intended.

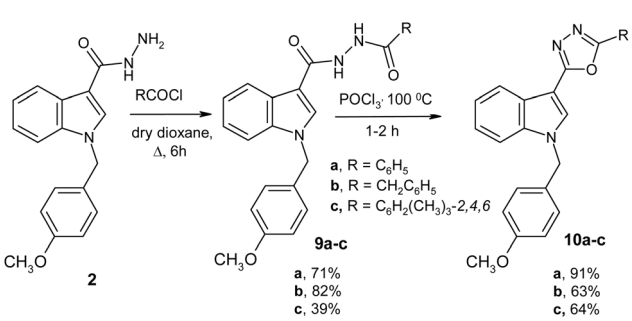
CONCLUSIONS

In conclusion, we have made available a series of hitherto unknown 1-PMB-substituted indole derivatives containing 1,3,4-oxadiazole and 1,2,4-triazole units with potential biological activity. All of these new compounds were fully characterized by IR, ^{1}H NMR, ^{13}C NMR, and HRMS in addition to elemental analysis.

EXPERIMENTAL

All reactions were carried out under an atmosphere of nitrogen in flame-dried or oven-dried glassware with magnetic stirring. Air-sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus through rubber septa. THF, diethyl ether and toluene were distilled from sodium-benzophenone ketyl. Dichloromethane was distilled from phosphorus pentoxide. Triethylamine and other nitrogen-containing bases were distilled from calcium hydride under nitrogen atmosphere before use. Methanol was distilled from sodium. Reactions were monitored by thin layer chromatography with 0.25 mm E. Merck precoated silica gel plates (60 F_{254}). Visualization was accomplished with either UV light or by immersion in solutions of *p*-anisaldehyde or phosphomolybdic acid, followed

Scheme 4



Scheme 6

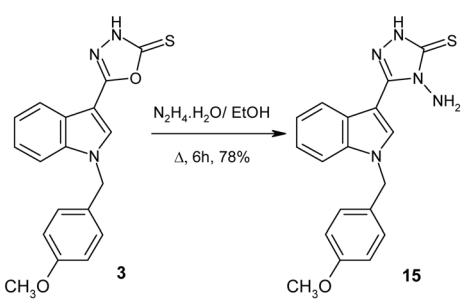


Table 1

In-vitro antitumor activity (percentage cell-growth inhibition at fixed concentration and EC_{50} values) for compound **1**.

Cell line		Percentage inhibition at 3.16 (μg/mL)	EC50 (μg/mL)
Code	Description		
KB/HELA	Cervical carcinoma	87	0.559
SK OV-3	Ovarial carcinoma	59	0.724
SF-268	CNS cancer	56	0.490
NCI H-460	Non-small-cell lung cancer	75	–
RKOp27	Colon adenocarcinoma	68	0.373

by heating on a hot plate for ~15 sec. Purification of reaction products was carried out by flash chromatography using EM Reagents silica gel 60 (230–400 mesh). Melting points were determined using a Thomas Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained using a Varian Gemini-300 (300 MHz for ^{1}H and 75 MHz for ^{13}C), or a Varian Inova-500 (500 MHz for ^{1}H and 125 MHz for ^{13}C) spectrometer. Chemical shifts are reported relative to chloroform (δ 7.26) for ^{1}H NMR and chloroform (δ 77.2) for ^{13}C NMR. Data are reported as: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constants in Hz. Ambiguous assignments were resolved on the basis of standard one-dimensional proton decoupling experiments. Elemental analyses were performed by the Organic Chemistry Research Center at Sogang University, using a Carlo Erba EA 1180 elemental analyzer. High-resolution mass spectra were recorded on a 4.7 Tesla IonSpec ESI-FTMS or a Micromass LCT ESI-TOF mass spectrometer. The progress of the reactions was monitored by high performance liquid chromatography (HPLC).

Methyl 1-(4-methoxybenzyl)-1*H*-indole-3-carboxylate (1). To a stirred solution of methyl 1*H*-indole-3-carboxylate (1.75 g, 10 mmol) and potassium carbonate (4.14 g, 30 mmol) in dry dimethylformamide (10 mL), 4-methoxybenzyl chloride (1.72 g, 11 mmol) was added. The reaction mixture was heated at 140°C for 8 h. The progress of the reaction was monitored by HPLC. The solvent was removed under reduced pressure, and the residue was triturated with water, then the product was extracted with dichloromethane (3 × 50 mL). The combined extracts were washed with water (3 × 50 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the buff semisolid product obtained was purified using *n*-hexane to afford **1** as buff solid.

Yield: 2.80 g (95%); mp 40–42°C; IR (KBr): 2950 (CH aliph.), 1710 (C=O), 1620 cm^{-1} (C=N); ^{1}H NMR (500 MHz, deuteriochloroform): δ = 3.69 (s, 3H, $COOCH_3$), 3.82 (s, 3H, OCH_3), 5.15 (s, 2H, benzyl CH_2), 6.77 (d, 2H, ArH, J = 8.70 Hz), 7.02 (d, 2H, ArH, J = 8.70 Hz), 7.21 (m, 2H, H-5,6), 7.74 (s, 1H, H-7), 7.92 (s, 1H, H-2), 8.13 (m, 1H, H-4); ^{13}C NMR (125 MHz, deuteriochloroform): δ = 50.35 (OMe), 54.75 (OMe), 59.30 (CH_2), 106.60 (C), 110.03 (C), 113.81 (C), 121.41 (C), 122.35 (C), 126.40 (C), 127.48 (C), 128.25 (C), 131.52 (C), 132.14 (C), 133.17 (C), 134.00 (C), 136.20 (C), 158.96 (C), 164.82 (CO); HRMS (ESI): *m/z* calcd for $C_{18}H_{17}NO_3$ $[M]^+$: 295.1208, found: 295.1225. *Anal*. Calcd. for $C_{18}H_{17}NO_3$ (295.34): C, 73.20; H, 5.80; N, 4.74. Found: C, 73.13; H, 5.68; N, 4.62.

1-(4-Methoxybenzyl)-1*H*-indole-3-carbohydrazide (2). A mixture of **1** (2.95 g, 10 mmol) and hydrazine hydrate (5 mL, 100 mmol) in ethylene glycol (10 mL) was heated under reflux for 4 h. After cooling, the solvent was removed under reduced pressure, the residue formed was triturated with water, and the product obtained was filtered off, air-dried, and recrystallized from ethanol to afford **2** as buff crystals.

Yield: 2.45 g (83%); mp 178–180°C; IR (KBr): 3350–3250 (bs, $NHNH_2$), 1650 (C=O), 1610 cm^{-1} (C=N); ^{1}H NMR (500 MHz, dimethyl sulfoxide d_6): δ = 3.71 (s, 3H, OCH_3), 4.41 (s, 2H, NH_2), 5.36 (s, 2H, benzyl CH_2), 6.89 (d, 2H, ArH, J = 8.70 Hz), 7.18 (m, 2H, H-5,6), 7.22 (d, 2H, ArH, J = 8.70 Hz, shows positive NOE on irradiation at 5.36 ppm), 7.54 (d, 1H, H-7, J = 7.20 Hz, shows positive NOE on irradiation at 5.36 ppm), 8.07 (s, 1H, H-2, shows positive NOE on irradiation at 5.36 ppm), 8.14 (d, 1H, H-4, J = 7.20 Hz,), 9.18 (s, 1H, NH), ^{13}C NMR (75 MHz, dimethyl sulfoxide d_6): δ = 48.99 (OMe), 55.09 (CH_2), 108.59, 109.90, 110.69, 114.04, 120.65, 121.20, 122.03, 126.68, 128.82, 129.23, 130.44, 135.52, 135.89, 158.76, 164.81 (CO); *Anal*. Calcd. for $C_{17}H_{17}N_3O_2$ (295.34): C, 69.14; H, 5.80; N, 14.23. Found: C, 69.10; H, 5.87; N, 14.39.

5-[1-(4-Methoxybenzyl)-1*H*-indol-3-yl]-1,3,4-oxadiazole-2(3*H*)-thione (3). A mixture of carbohydrazide **2** (295 mg, 1 mmol) and carbon disulfide (2 mL, 26 mmol) in dry pyridine (10 mL) was heated at 50°C for 6 h. After cooling, the excess of carbon disulfide and the solvent was removed under reduced pressure. The residue obtained was treated with water and the precipitate formed was filtered off and recrystallized from ethanol to give **3** as white crystals.

Yield: 289 mg (86%); mp 160–162°C; IR (KBr): 3100 (NH), 1620 (C=N), 1170 cm^{-1} (C=S); ^{1}H NMR (500 MHz, dimethyl sulfoxide d_6): δ = 3.69 (s, 3H, OCH_3), 5.44 (s, 2H, benzyl CH_2), 6.87 (d, 2H, ArH, J = 8.70 Hz), 7.28 (m, 4H, H-5,6 and ArH), 7.64 (d, 1H, H-7, J = 7.20 Hz), 7.90 (d, 1H, H-4, J = 7.80 Hz), 8.39 (s, 1H, H-2), 8.71 (s, 1H, NH). *Anal*. Calcd. for $C_{18}H_{15}N_3O_2S$ (337.40): C, 64.08; H, 4.48; N, 12.45; S, 9.50. Found: 64.14; H, 4.59; N, 12.60; S, 9.66.

5-[1-(4-Methoxybenzyl)-1*H*-indol-3-yl]-1,3,4-oxadiazol-2(3*H*)-one (4). A suspension of carbohydrazide **2** (295 mg, 1 mmol) and CDI (178 mg, 1.1 mmol) in dioxane (10 mL) was heated at 110°C for 8 h. The solvent was removed under reduced pressure. The solid product obtained was washed with water, filtered off, and recrystallized from ethanol to afford **4** as white crystals.

Yield: 222 mg (69%); mp 345–347°C; IR (KBr): 3280 (NH), 1758 (C=O), 1615 cm^{-1} (C=N); ^{1}H NMR (500 MHz, dimethyl sulfoxide d_6): δ = 3.69 (s, 3H, OCH_3), 5.42 (s, 2H, benzyl CH_2), 6.87 (d, 2H, ArH, J = 8.70 Hz), 7.23 (m, 4H, H-5,6 and ArH), 7.80 (d, 1H, H-7, J = 7.80 Hz), 7.91 (d, 1H, H-4, J = 8.10 Hz), 8.19 (s, 1H, H-2), 12.24 (s, 1H, NH); ^{13}C NMR (75 MHz, dimethyl sulfoxide d_6): δ = 49.07, 55.06, 94.53, 111.41, 114.03, 120.38, 121.38, 122.95, 124.12, 128.93, 129.07, 130.48, 136.13, 152.18, 154.24, 158.80. *Anal*. Calcd. for $C_{18}H_{15}N_3O_3$ (321.34): C, 67.28; H, 4.71; N, 13.08. Found: C, 67.22; H, 4.66; N, 13.02.

5-(1*H*-Indol-3-yl)-1,3,4-oxadiazol-2(3*H*)-one (5). A suspension of carbohydrazide **2** (295 mg, 1 mmol) and CDI (178 mg, 1.1 mmol) in THF (10 mL) was heated at 70°C for 8 h. Then, the solvent was removed under reduced pressure. The solid residue was triturated with water, filtered off, and recrystallized from ethanol to yield **5** as white crystals.

Yield: 160 mg (80%); mp 203–205°C (lit. [38] mp 204–205°C); ^{1}H NMR (500 MHz, dimethyl sulfoxide d_6): δ = 6.74 (s, 1H, NH), 7.19 (m, 2H, H-5,6), 7.80 (d, 1H, H-7, J = 8.40 Hz), 8.10 (d, 1H, H-4, J = 7.80 Hz), 8.27 (s, 1H, H-2), 9.29 (s, 1H, NH); IR (KBr): 3230 (NH), 1755 (C=O), 1615 cm^{-1} (C=N); HRMS (ESI): *m/z* calcd. for $C_{10}H_7N_3O_2K$ $[M+K]^+$: 240.0175. Found: 240.0162.

General procedure for the preparation of 2-[1-(4-methoxybenzyl)-1*H*-indol-3-yl]-1,3,4-oxadiazole derivatives (6–8). A suspension of carbohydrazide **2** (295 mg, 1 mmol) and trimethyl orthoformate or trimethyl orthoacetate (5 mL), respectively, was heated under reflux for 12 h. Then, the reagent was removed under reduced pressure. The residue was triturated with ethanol, filtered off, and recrystallized from ethanol.

2-[1-(4-Methoxybenzyl)-1H-indol-3-yl]-1,3,4-oxadiazole (6). This compound was obtained as white crystals. Yield 112 mg (37%); mp 144–146°C; IR (KBr): 3070 (CH arom.), 1620 cm^{-1} (C=N); ^{1}H NMR (300 MHz, dimethyl sulfoxide d_6): δ = 3.71 (s, 3H, OCH_3), 5.37 (s, 2H, benzyl CH_2), 6.89 (d unresolved, 2H, ArH), 7.16 (m, 4H, H-5,6 and ArH), 7.54 (m, 1H, H-7), 8.11 (d unresolved, 1H, H-4), 8.13 (s, 1H, oxadiazole H), 8.41 (s, 1H, H-2). *Anal*. Calcd. for $C_{18}H_{15}N_3O_2$ (305.34): C, 70.81; H, 4.95; N, 13.76. Found: C, 70.73; H, 4.84; N, 13.60.

2-[1-(4-Methoxybenzyl)-1H-indol-3-yl]-5-methyl-1,3,4-oxadiazole (7). This compound was obtained as white crystals. Yield: 197 mg (62%); mp 228–230°C; IR (KBr): 3050 (CH arom.), 1620 cm^{-1} (C=N); ^{1}H NMR (500 MHz, dimethyl sulfoxide d_6): δ =1.98 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 5.38 (s, 2H, benzyl CH_2), 6.82 (m, 2H, ArH), 7.22 (m, 4H, H-5,6 and ArH), 7.84 (d, 1H, H-7, *J* = 6.60 Hz,), 8.11 (s, 1H, H-4), 8.37 (s, 1H, H-2). *Anal*. Calcd. for $C_{19}H_{17}N_3O_2$ (319.37): C, 71.46; H, 5.37; N, 13.16. Found: C, 71.35; H, 5.23; N, 13.05.

Methyl N-{[1-(4-methoxybenzyl)-1H-indol-3-yl]carbonyl} ethanehydrazonoate (8). This compound was obtained from the filtrate of the reaction as white crystals. Yield: 88 mg (25%); mp 136–138°C; IR (KBr): 3200 (NH), 2950 (CH aliph.), 1650 (C=O), 1620 cm^{-1} (C=N); ^{1}H NMR (500 MHz, dimethyl sulfoxide d_6): δ = 1.23 (s, 3H, CH_3); 3.40 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 5.39 (s, 2H, benzyl-CH_2), 6.92 (m, 2H, ArH), 7.35 (m, 4H, H-5,6 and ArH), 7.87 (d, 1H, H-7, *J* = 6.70 Hz), 8.18 (s, 1H, H-4), 8.34 (s, 1H, H-2), 10.11 (s, 1H, NH). *Anal*. Calcd. for $C_{20}H_{21}N_3O_3$ (351.41): C, 68.36; H, 6.02; N, 11.96. Found: C, 68.27; H, 5.89; N, 11.86.

General procedure for the preparation of *N*-substituted-1-(4-methoxybenzyl)-1*H*-indole-3-carbohydrazides (9a–c). A mixture of carbohydrazide **2** (295 mg, 1 mmol) and the appropriate acid chloride (1 mmol) in dry dioxane (10 mL) was heated under reflux for 6–8 h. The reagent was removed under reduced pressure, and the residue was recrystallized from the proper solvent.

N′-Benzoyl-1-(4-methoxybenzyl)-1H-indole-3-carbohydrazide (9a). This compound was obtained as white crystals. Yield: 282 mg (71%); mp 180–182°C (EtOH); IR (KBr): 3200 (NH), 3050 (CH arom.), 1650 cm^{-1} (C=O); ^{1}H NMR (500 MHz, dimethyl sulfoxide d_6): δ = 3.72 (s, 3H, OCH_3), 5.42 (s, 2H, benzyl CH_2), 6.92 (d, 2H, benzoyl H, *J* = 8.40 Hz,), 7.25 (m, 4H, H-5,6 and benzoyl H), 7.52 (m, 4H, H-7 and ArH), 7.92 (m, 2H, ArH), 8.14 (d, 1H, H-4, *J* = 7.50 Hz), 8.22 (s, 1H, H-2), 9.99 (s, 1H, NH), 10.36 (s, 1H, NH). *Anal*. Calcd. for $C_{24}H_{21}N_3O_3$ (399.45): C, 72.16; H, 5.30; N, 10.52. Found: C, 72.07; H, 5.21; N, 10.30.

N′-(2-Phenylacetyl)-1-(4-methoxybenzyl)-1H-indole-3-carbohydrazide (9b). This compound was obtained as white crystals. Yield: 340 mg (82%) (EtOH/EtOAc, 1:2); mp 186–188°C; IR (KBr): 3200 (bs, NH), 3030 (CH arom.), 1660 cm^{-1} (C=O); ^{1}H NMR (500 MHz, deuteriochloroform): δ = 3.65 (s, 2H, $COCH_2$); 3.71 (s, 3H, OCH_3), 4.99 (s, 2H, benzyl CH_2), 6.73 (d, 2H, ArH, *J* = 8.40 Hz), 6.97 (d, 2H, Ar, *J* = 8.40 Hz), 7.28 (m, 9H, H-4,5,6,7 and ArH), 7.77 (s, 1H, H-2), 8.14 (s, 1H, NH), 9.33 (s, 1H, NH). *Anal*. Calcd. for $C_{25}H_{23}N_3O_3$ (413.48): C, 72.62; H, 5.61; N, 10.16. Found: C, 72.51; H, 5.49; N, 10.04.

N′-(2,4,6-Trimethylbenzoyl)-1-(4-methoxybenzyl)-1H-indole-3-carbohydrazide (9c). This compound was obtained as white crystals. Yield: 170 mg (39%) (EtOH); mp 256–258°C; IR (KBr): 3200 (NH), 3030 (CH arom.), 1680 cm^{-1} (C=O); ^{1}H NMR (500 MHz, dimethyl sulfoxide d_6): δ = 2.24 (s, 3H, CH_3); 2.34 (s, 6H, CH_3), 3.72 (s, 3H, OCH_3), 5.41 (s, 2H, benzyl CH_2), 6.88 (m, 2H, mesityl H), 6.91 (d, 2H, ArH, *J* = 8.70 Hz,), 7.19 (m, 2H, H-5,6), 7.26 (d, 2H, ArH, *J* = 8.70 Hz), 7.60 (d, 1H, H-7, *J* = 7.80 Hz), 8.16 (d, 1H, H-4, *J* = 7.80 Hz), 8.22 (s, 1H, H-2), 9.95 (s, 1H, NH), 9.90 (s, 1H, NH). *Anal*. Calcd. for $C_{27}H_{27}N_3O_3$ (455.56): C, 73.45; H, 6.16; N, 9.52. Found: C, 73.32; H, 6.04; N, 9.43.

General procedure for the preparation of 2-[1-(4-methoxybenzyl)-1*H*-indol-3-yl]-5-substituted-1,3,4-oxadiazoles (10a–c). A suspension of **9a–c** (1 mmol) in phosphoryl chloride (5 mL, 33 mmol) was heated at 100°C for 1–2 h. The excess of phosphoryl chloride was eliminated under reduced pressure, and the residue was triturated with ethyl acetate, filtered off, and recrystallized from the appropriate solvent.

2-[1-(4-Methoxybenzyl)-1H-indol-3-yl]-5-phenyl-1,3,4-oxadiazole (10a). This compound was obtained as buff crystals. Yield: 374 mg (91%); mp 126–128°C (EtOH); IR (KBr): 3050 (CH arom.), 1620 cm^{-1} (C=N); ^{1}H NMR (500 MHz, deuteriochloroform): δ = 3.79 (s, 3H, OCH_3), 5.34 (s, 2H, benzyl CH_2), 6.88 (d, 2H, ArH, *J* = 8.70 Hz), 7.16 (d, 2H, ArH, *J* = 8.70 Hz), 7.42 (m, 8H, H-5,6,7 and ArH), 8.14 (m, 1H, H-2), 8.35 (s, 1H, H-4). *Anal*. Calcd. for $C_{24}H_{19}N_3O_2$ (381.44): C, 75.57; H, 5.02; N, 11.02. Found: C, 75.41; H, 5.12; N, 11.13.

2-[1-(4-Methoxybenzyl)-1H-indol-3-yl]-5-benzyl-1,3,4-oxadiazole (10b). This compound was obtained as white crystals. Yield: 250 mg (63%) (EtOAc); mp 112–114°C; IR (KBr): 3030 (CH arom.), 1620 cm^{-1} (C=N); ^{1}H NMR (500 MHz, deuteriochloroform): δ = 3.77 (s, 3H, OCH_3), 4.26 (s, 2H, benzyl CH_2), 5.27 (s, 2H, benzyl CH_2), 6.83 (d, 2H, ArH, *J* = 8.70 Hz), 7.10 (d, 2H, ArH, *J* = 8.70 Hz), 7.30 (m, 8H, H-5,6,7 and ArH), 7.74 (s, 1H, H-2), 8.21 (s, 1H, H-4). *Anal*. Calcd. for $C_{25}H_{21}N_3O_2$ (395.47): C, 75.93; H, 5.35; N, 10.63. Found: C, 75.78; H, 5.22; N, 10.57.

2-[1-(4-Methoxybenzyl)-1H-indol-3-yl]-5-mesityl-1,3,4-oxadiazole (10c). This compound was obtained as buff crystals. Yield: 269 mg (64%) (EtOH); mp 188–190°C; IR (KBr): 3050 (CH arom.), 1615 cm^{-1} (C=N); ^{1}H NMR (500 MHz, dimethyl sulfoxide d_6): δ = 2.27 (s, 3H, CH_3), 2.50 (s, 6H, CH_3), 3.70 (s, 3H, OCH_3), 5.45 (s, 2H, benzyl CH_2), 6.86 (d, 2H, ArH, *J* = 8.70 Hz), 7.09 (d, 2H, ArH, *J* = 8.70 Hz), 7.29 (m, 5H, H-5,6,7 and mesityl H), 8.13 (m, 1H, H-2), 8.45 (s, 1H, H-4). *Anal*. Calcd. for $C_{27}H_{25}N_3O_2$ (423.52): C, 76.57; H, 5.95; N, 9.92. Found: C, 76.39; H, 5.82; N, 9.80.

***N*^{1}-[1-(4-Methoxybenzyl)-1*H*-indol-3-ylcarbonyl]-*N*^{4}-benzylthiosemicarbazide (11).** A suspension of **2** (295 mg, 1 mmol) and benzyl isothiocyanate (149 mg, 1 mmol) in ethanol (10 mL) was heated under reflux for 7 h. The solvent was concentrated and the solid product thus formed was filtered off and recrystallized from ethanol to afford **11** as white crystals.

Yield: 366 mg (85%); mp 218–220°C; IR (KBr): 3400, 3300 (NH), 2950 (CH aliph.), 1660 (C=O), 1170 cm^{-1} (C=S); ^{1}H NMR (500 MHz, dimethyl sulfoxide d_6): δ = 3.70 (s, 3H, OCH_3), 4.73 (d, 2H, CH_2NH, *J* = 7.00 Hz), 5.37 (s, 2H, benzyl CH_2), 6.88 (d, 2H, ArH, *J* = 8.70 Hz), 7.22 (m, 9H, H-5,6 and ArH), 7.57 (d, 1H, H-7, *J* = 7.20 Hz), 8.14 (m 2H, H-2,4), 8.59 (s, 1H, NH), 9.35 (s, 1H, NH), 9.87 (s, 1H, NH); ^{13}C NMR (125 MHz, dimethyl sulfoxide d_6): δ = 46.74, 49.74, 55.17, 107.71, 110.86, 114.12, 121.16, 122.39, 126.62, 126.97,

127.19, 128.06, 129.00, 129.08, 131.95, 134.70, 135.97, 139.59, 158.85, 163.10, 184.20. *Anal*. Calcd. for $C_{25}H_{24}N_4O_2S$ (444.55): C, 67.54; H, 5.44; N, 12.60; S, 7.21. Found: C, 67.61; H, 5.39; N, 12.67; S, 7.28.

***N*^{1}-[1-(4-Methoxybenzyl)-1*H*-indol-3-ylcarbonyl]-*N*^{4}-cyclohexylthiosemicarbazide (12).** A solution of **2** (295 mg, 1 mmol) and cyclohexyl isothiocyanate (141 mg, 1 mmol) in ethanol (10 mL) was heated under reflux for 7 h. The solvent was removed under reduced pressure, the residue was triturated with ethyl acetate, and the precipitate formed was collected and recrystallized from ethanol to afford **12** as white crystals.

Yield: 408 mg (93%); mp 152–154°C; IR (KBr): 3400, 3300 (NH), 2930 (CH aliph.), 1660 (C=O), 1180 cm^{-1} (C=S); ^{1}H NMR (500 MHz, dimethyl sulfoxide d_6): δ = 1.26 (m, 5H, cyclohexane H), 1.67 (m, 6H, cyclohexane H), 3.71 (s, 3H, OCH_3), 5.39 (s, 2H, benzyl CH_2), 6.89 (d, 2H, ArH, *J* = 8.70 Hz), 7.18 (m, 2H, H-5,6), 7.24 (d, 2H, ArH, *J* = 8.70 Hz), 7.59 (m 2H, H-4,7), 8.16 (m, 2H, NH and H-2), 9.16 (s, 1H, NH), 9.74 (s, 1H, NH); ^{13}C NMR (75 MHz, dimethyl sulfoxide d_6): δ = 18.59, 24.94, 34.91, 54.14, 55.89, 59.60, 110.82, 112.40, 114.06, 118.70, 120.40, 121.09, 122.40, 126.93, 128.99, 130.00, 135.92, 158.84, 164.60, 183.70. *Anal*. Calcd. for $C_{24}H_{28}N_4O_2S$ (436.57): C, 66.03; H, 6.46; N, 12.83; S, 7.34. Found: C, 65.98; H, 6.41; N, 12.90; S, 7.30.

***N*^{1}-[1-(4-Methoxybenzyl)-1*H*-indol-3-ylcarbonyl]-*N*^{4}-4-methoxyphenylthiosemicarbazide (13).** A mixture of **2** (295 mg, 1 mmol) and 4-methoxyphenyl isothiocyanate (165 mg, 1 mmol) in ethanol (10 mL) was heated under reflux for 7 h. The solvent was removed under reduced pressure, and the solid product thus formed was filtered off and recrystallized from ethanol to afford **13** as white crystals.

Yield: 400 mg (87%); mp 190–192°C; IR (KBr): 3300–3100 (NH), 2950 (CH aliph.), 1660 (C=O), 1180 cm^{-1} (C=S); ^{1}H NMR (500 MHz,, dimethyl sulfoxide d_6): δ = 3.73 and 3.70 (2s, 6H, OCH_3); 5.13 (s, 2H, benzyl CH_2), 6.77 (m, 4H, ArH), 7.04 (d, 2H, ArH, *J* = 8.10 Hz), 7.25 (m, 6H, H-4,5,6,7 and ArH), 7.84 (s, 1H, H-2), 8.15 (s, 1H, NH), 8.64 (s, 1H, NH), 9.50 (s, 1H, NH); ^{13}C NMR (75 MHz, dimethyl sulfoxide d_6): δ = 29.88, 50.43, 55.43, 55.53, 107.51, 110.89, 114.51, 121.00, 122.51, 123.32, 125.87, 126.96, 127.73, 128.80, 130.03, 132.76, 136.84, 158.28, 159.59, 164.00, 175.80. *Anal*. Calcd. for $C_{25}H_{24}N_4O_3S$ (460.56): C, 65.20; H, 5.25; N, 12.17; S, 6.96. Found: C, 65.11; H, 5.09; N, 12.03; S, 6.88.

General procedure for the preparation of 4-substituted-5-[1-(4-methoxy-benzyl)-1*H*-indol-3-yl]-2,4-dihydro-1,2,4-triazole-3-thiones (14a–c). To a suspension of **11–13** (1 mmol) in ethanol (10 mL), 4*N* aqueous potassium hydroxide (3 mL) was added. The reaction mixture was gently refluxed for 3 h, then it was concentrated, cooled, and filtered, and the filtrate was adjusted to pH 5–6 with dilute acetic acid. The white solid formed was filtered off and recrystallized from the appropriate solvent.

4-Benzyl-5-[1-(4-methoxybenzyl)-1H-indol-3-yl]-2,4-dihydro-1,2,4-triazole-3-thione (14a). This compound was obtained as white crystals. Yield: 339 mg (79%); mp 178–180°C; IR (KBr): 3100 (NH), 2950 (CH aliph.), 1180 cm^{-1} (C=S); ^{1}H NMR (500 MHz, dimethyl sulfoxide d_6): δ = 3.71 (s, 3H, OCH_3), 5.30 (s, 2H, benzyl CH_2), 5.89 (s, 2H, benzyl CH_2), 6.81 (d, 2H ArH, *J* = 8.10 Hz), 7.15 (m, 9H, H-5,6 and ArH), 7.55 (d, 1H, H-7, *J* = 7.80 Hz), 7.91 (s, 1H, NH), 7.99 (d, 1H, H-4, *J* = 7.80 Hz), 8.04 (s, 1H, H-2). *Anal*. Calcd. for $C_{25}H_{22}N_4OS$ (426.54): C, 70.40; H, 5.20; N, 13.14; S, 7.52. Found: C, 70.32; H, 5.13; N, 13.04; S, 7.39.

4-Cyclohexyl-5-[1-(4-methoxybenzyl)-1H-indol-3-yl]-2,4-dihydro-1,2,4-triazole-3-thione (14b). This compound was obtained as white crystals. Yield: 363 mg (87%); mp 208–210°C; IR (KBr): 3400–3100 (NH), 2900 and 2850 (CH aliph.), 1620 (C=N), 1180 cm^{-1} (C=S); ^{1}H NMR (500 MHz, deuteriochloroform): δ = 1.20 (m, 5H, cyclohexane H), 1.76 (m, 6H, cyclohexane H), 3.78 (s, 3H, OCH_3), 5.31 (s, 2H, benzyl CH_2), 6.85 (d, 2H, ArH, *J* = 8.40 Hz), 7.14 (d, 2H, ArH, *J* = 8.40 Hz), 7.27 (m, 2H, H-5,6), 7.41 (d, 1H, H-7, *J* = 7.50 Hz), 7.62 (d, 1H, H-4, *J* = 7.50 Hz), 7.88 (s, 1H, H-2). *Anal*. Calcd. for $C_{24}H_{26}N_4OS$ (418.55): C, 68.87; H, 6.26; N, 13.39; S, 7.66. Found: C, 68.79; H, 6.21; N, 13.29; S, 7.59.

4-(4-Methoxyphenyl)-5-[1-(4-methoxybenzyl)-1H-indol-3-yl]-2,4-dihydro-1,2,4-triazole-3-thione (14c). This compound was obtained as fluffy crystals. Yield: 254 mg (58%); mp 272–74°C; IR (KBr): 3400–3100 (NH), 2900 (CH aliph.), 1620 (C=N), 1180 cm^{-1} (C=S); ^{1}H NMR (500 MHz, dimethyl sulfoxide d_6): δ = 3.73 (s, 3H, OCH_3); 3.84 (s, 3H, OCH_3), 5.16 (s, 2H, benzyl CH_2), 6.82 (d, 2H, ArH, *J* = 8.10 Hz), 6.99 (d, 2H, ArH, *J* = 8.10 Hz,), 7.04 (m, 2H, H-5,6), 7.24 (m, 4H, ArH), 7.55 (d, 1H, H-7, *J* = 7.50 Hz), 7.68 (d, 1H, H-4, *J* = 7.50 Hz), 7.91 (s, 1H, H-2), 8.10 (s, 1H, NH). *Anal*. Calcd. for $C_{25}H_{22}N_4O_2S$ (442.54): C, 67.85; H, 5.01; N, 12.66; S, 7.25. Found: C, 67.74; H, 5.12; N, 12.49; S, 7.12.

4-Amino-5-[1-(4-methoxybenzyl)-1*H*-indol-3-yl]-2,4-dihydro-1,2,4-triazole-3-thione (15). A suspension of **3** (337 mg, 1 mmol) and hydrazine hydrate (99%, 2 mL, 44 mmol) in ethanol (10 mL) was refluxed for 6 h. After cooling, the solvent was removed under reduced pressure, the residue was triturated with water, and the precipitate was collected and recrystallized from ethanol to afford **15** as white crystals.

Yield: 273 mg (78%); mp 182–184°C; IR (KBr): 3400, 3280, 3180 (NH_2 and NH), 2900 (CH aliph.), 1620 (C=N), 1180 cm^{-1} (C=S); ^{1}H NMR (500 MHz, dimethyl sulfoxide d_6): δ = 3.68 (s, 3H, OCH_3), 5.43 (s, 2H, benzyl CH_2), 5.84 (sb, 2H, NH_2), 7.20 (m, 4H, H-5,6 and ArH), 7.59 (d, 1H, H-7, *J* = 7.80 Hz), 8.12 (d, 1H, H-4, *J* = 7.80 Hz), 8.56 (s, 1H, H-2), 8.86 (d, 2H, ArH, *J* = 8.10 Hz,), 9.35 (s, 1H, NH); MS *m/z* (%) 351 (M^+, 42), 318 (100). *Anal*. Calcd. for $C_{18}H_{17}N_5OS$ (351.43): C, 61.52; H, 4.88; N, 19.93; S, 9.12. Found: C, 61.45; H, 4.73; N, 19.86; S, 9.04.

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