Synthesis of New Indoyl-1,3,4-oxadiazole and Oxadiazine Derivatives. Potential Monoamine Oxidase Inhibitor Activity

Silvia Pérez [1], Berta Lasheras [2], Carmen Oset [2], Antonio Monge [1]*

Department of Organic and Pharmaceutical Chemistry, University of Navarra, 31080 Pamplona, Spain

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New indolyl-1,3,4-oxadiazole and oxadiazine derivatives were prepared as reversible monoamine oxidase inhibitors. The compound 5-(3-methylindolyl)-1,3,4-oxadiazol-2(3*H*)one was shown to be a good monoamine oxidase B inhibitor.

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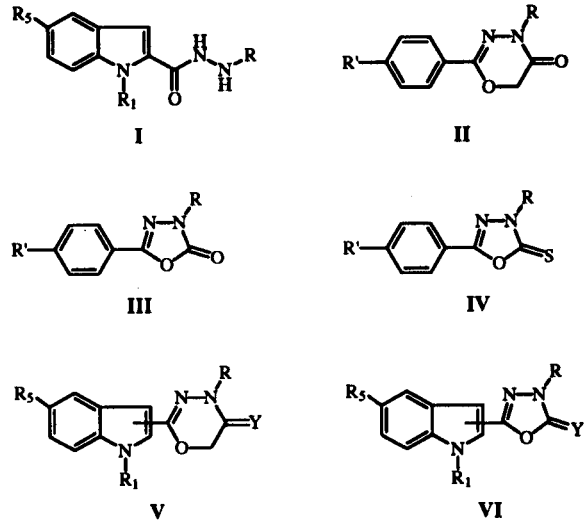
The mitochondrial enzyme monoamine oxidase (MAO, EC 1.4.3.4) is a Flavine-adenine dinucleotide-containing enzyme [1] implicated in the oxidative deamination of a variety of biogenic and exogenic monoamines. It exists as two isoforms monoamine oxidase A and monoamine oxidase B [2,3] and it has been well established that they are encoded by separate genes located on the human X chromosome [4]. Monoamine oxidase A selectively deaminates biogenic amines and is irreversibly inhibited by chlorgyline. Monoamine oxidase B preferentially deaminates β-phenylethylamine and is irreversibly inhibited by L-deprenyl. The monoamine oxidase's and their inhibitors have been recently reviewed [5-8]. A resurgence in interest has occurred in all aspects of monoamine oxidase and, especially, in monoamine oxidase inhibitors as potential therapeutic agents in depressive illnesses [9] or Parkinson's disease [10].

Previously we had prepared some indole hydrazine derivatives **I** with inhibitory monoamine oxidase A activity in our laboratory [11] (Figure 1). The toxicity of the new compounds forced us to interrupt the work. 2-Aryl-4*H*-1,3,4-oxadiazin-5(6*H*)-one derivatives **II**, 5-aryl-1,3,4-oxadiazol-2(3*H*)-one derivatives **III** and sulphur analogues **IV** have been published [12-14] as new classes of reversible monoamine oxidase inhibitors.

In a new approach of our initial work, we have focused our syntheses on the development of new indolyl oxadiazine **V** and oxadiazole **VI** derivatives as reversible monoamine oxidase inhibitors (Figure 1) (Tables I to VII).

Figure 1



As shown in Scheme 1, indolyl-1,3,4-oxadiazol-2(3*H*)-one derivatives **2** were achieved in one step by reaction of triphosgene with the appropriate monosubstituted hydrazides **1** as described in publication [11].

Indolyl-1,3,4-oxadiazole-2(3*H*)-thiones **3** were generated directly by treatment of the corresponding indole-hydrazides **1** with thiophosgene.

Table I

5-(2-indolyl)-1,3,4-oxadiazol-2-one Derivatives

Compound	R_1	R_5	X	mp (C°)	Recrystallization Solvent [a]	Yield	IR Absorption (cm^{-1}) CN	C=O	C=N	Formula
2a	H	H	H	238-239	A / B	73		1715	1640	$C_{10}H_7N_3O_2$
2b	H	CH_3O	H	245-246	A / B	54		1767	1626	$C_{11}H_9N_3O_3$
2c	H	$PhCH_2O$	H	226-227	A / B	35		1739	1635	$C_{17}H_{13}N_3O_3$
2d	H	OH	H	268-269	A / B	41		1740	1636	$C_{10}H_7N_3O_3$
2e	CH_3	H	H	237-238	A / B	52		1785	1623	$C_{11}H_9N_3O_2$
2f	CH_3	CH_3O	H	210-212	B / C	60		1770	1621	$C_{12}H_{11}N_3O_3$
2g	CH_3	$PhCH_2O$	H	213-214	A / B	65		1749	1623	$C_{18}H_{15}N_3O_3$
2h	CH_3	OH	H	240-241	A	27		1765	1625	$C_{11}H_9N_3O_3$
5e	CH_3	H	CH_2CH_2CN	164-165	A / B	75	2249	1768	1628	$C_{14}H_{12}N_4O_2$
5f	CH_3	CH_3O	CH_2CH_2CN	101-102	D	16	2251	1774	1660	$C_{15}H_{14}N_4O_3$

[a] Recrystallization solvent: A = Ethyl acetate, B = Ethanol, C = Water, D = Methanol.

Table II

5-(2-Indolyl)-1,3,4-oxadiazole-2-thione Derivatives

Compound	R_1	R_5	X	mp (C°)	Recrystallization Solvent [a]	Yield	IR Absorption (cm^{-1}) CN	C=N	C=S	Formula
3e	CH_3	H	H	192-193	E	20		1621	1163	$C_{11}H_9N_3OS$
3f	CH_3	CH_3O	H	229-230	F	34		1615	1172	$C_{12}H_{11}N_3OS$
6e	CH_3	H	CH_2CH_2CN	168-170	D	47	2249	1624	1109	$C_{14}H_{12}N_4OS$

[a] Recrystallization solvent: D = Methanol, E = DMF, F = Chloroform.

Table III

3-Indolyl-1,3,4-oxadiazol-2-one Derivatives

Compound	R_1	n	mp (C°)	Recrystallization Solvent [a]	Yield	IR Absorption (cm^{-1}) C=O	C=Na	Formula
9a	H	0	204-205	B / C	79	1746	1635	$C_{10}H_7N_3O_2$
9e	CH_3	0	225-226	B	20	1766	1634	$C_{11}H_9N_3O_3$
10a	H	1	112-114	B / C	62	1744	1628	$C_{11}H_9N_3O_2$

[a] Recrystallization solvent: B = Ethanol, C = Water.

Table IV

N_2-(2-Haloacethyl)indole-2-carbohydrazides

Compound	R_1	R_5	X	mp (C°)	Recrystallization Solvent [a]	Yield	IR absorption (cm^{-1}) C=O	C=O	Formula
12a	H	H	Br	215-216	B	73	1688	1647	$C_{11}H_{10}BrN_3O_2$
12e	CH_3	H	Br	175-176	B	71	1677	1606	$C_{12}H_{12}BrN_3O_2$
12f	CH_3	OCH_3	Br	207-208	B	81	1675	1608	$C_{13}H_{14}BrN_3O_3$
11a	H	H	Cl	232-233	B	80	1688	1648	$C_{11}H_{10}ClN_3O_2$
11e	CH_3	H	Cl	199-200	B	88	1681	1606	$C_{12}H_{12}ClN_3O_2$

[a] Recrystallization solvent: B = Ethanol

Table V

N_2-(2-Cyanoethyl)-*N*-methylindole-2-carbohydrazides

Compound	R_5	mp (C°)	Recrystallization Solvent [a]	Yield	IR Absorption (cm^{-1}) CN	C=O	C-O	Formula
4e	H	134-135	A/G	47	2246	1641		$C_{13}H_{14}N_4O$
4f	CH_3O	115-116	A/G	57	2248	1656	1142	$C_{14}H_{16}N_4O_2$

[a] Recrystallization solvent: A = Ethyl acetate, G = Petroleum ether.

Table VI

2-Indolyl-4*H*-1,3,4-oxadiazin-5(*6H*)-one Derivatives

Compound	R_1	R_5	mp (C°)	Recrystallization Solvent [a]	Yield	IR Absorption (cm^{-1}) C=O	C=N	C-O	Formula
13a	H	H	230-231	B	21	1674	1645	1227	$C_{11}H_9N_3O_2$
13e	CH_3	H	230-231	A/B	14	1723	1632	1226	$C_{12}H_{11}N_3O_2$
13f	CH_3	CH_3O	258-259	A/B	16	1724	1630	1215	$C_{13}H_{13}N_3O_3$

[a] Recrystallization solvent: A = Ethyl acetate, B = Ethanol

The monosubstituted indole-2-cyanoethylhydrazides **4**, were obtained initially by Michael addition of acrylonitrile on the corresponding indolehydrazides **1**, and then used as starting material in the syntheses of indolyl-1,3,4-oxadiazole-3-(2-cyanoethyl)-2-one **5** and 2-thione **6** derivatives, with triphosgene and thiophosgene respectively.

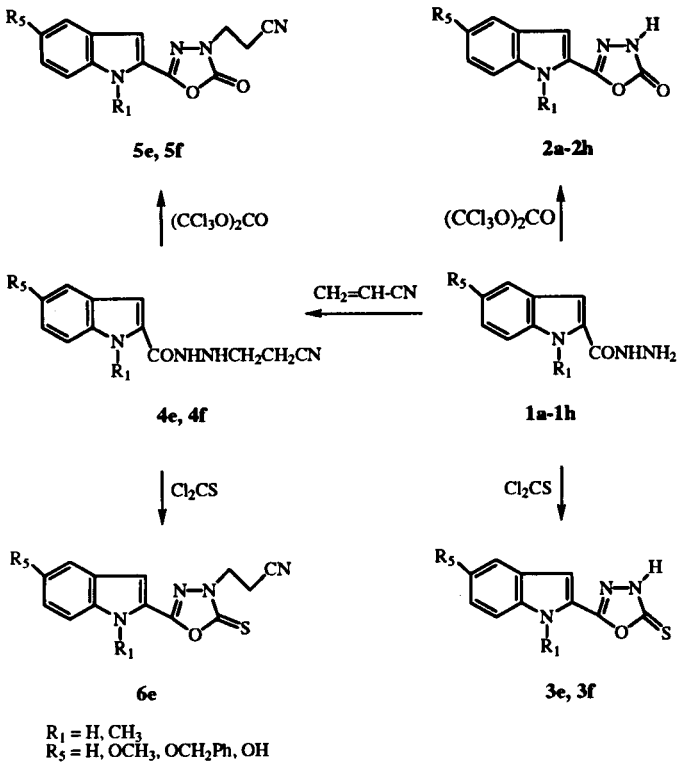
Table VII

N_2-(2-propyl)-indole-2-carbohydrazides

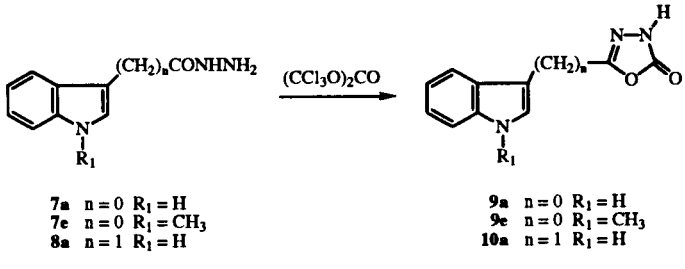
Compound	R_1	R	mp (C°)	Recrystallization Solvent [a]	Yield	IR Absorption (cm^{-1}) OH	C=O	C=O	Formula
14a	H	Br	210-211	B	80		1700	1602	$C_{12}H_{12}BrN_3O_2$
14e	CH_3	Br	207-208	B	78		1695	1643	$C_{13}H_{14}BrN_3O_2$
16a	H	OH	217-218	A/B	63	3379	1658	1638	$C_{12}H_{13}BrN_3O_3$
16e	CH_3	OH	178-179	A/B	75	3378	1677	1649	$C_{13}H_{15}N_3O_3$

[a] Recrystallization solvent: A = Ethyl acetate, B = Ethanol.

Scheme 1

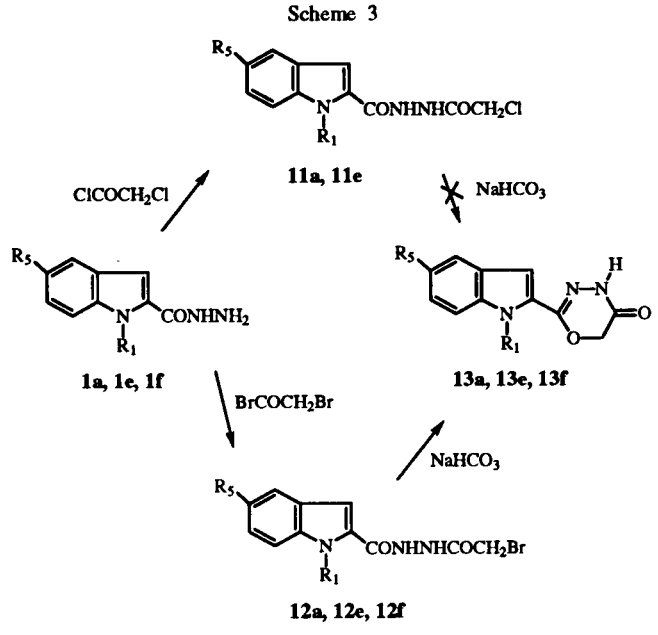


Scheme 2

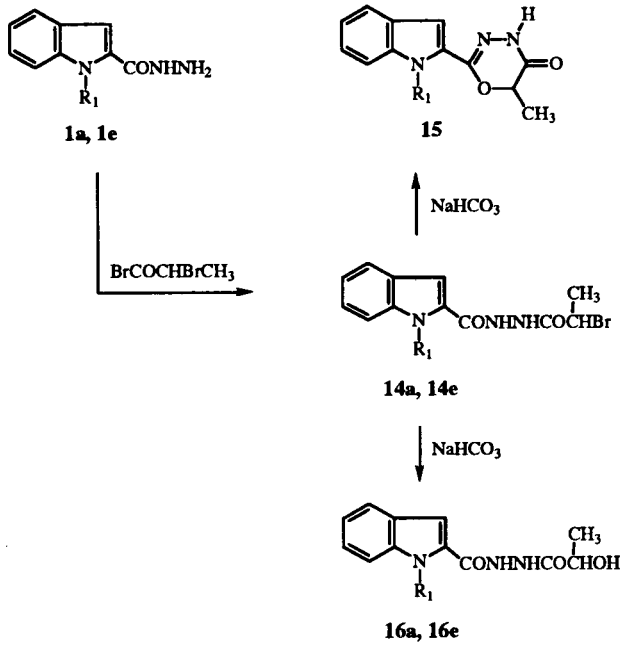


As shown in Scheme 2, 3-indolyl-1,3,4-oxadiazol-2(3*H*)-one derivatives **9a** and **9e**, were prepared in one step by reaction of triphosgene with the appropriate monosustituted

Scheme 3



Scheme 4



hydrazide **7**, as described in [11]. The compound 5-(3-methylindolyl)-1,3,4-oxadiazol-2-(3*H*)-one **10a**, was prepared following the some procedure, using commercial Aldrich indole-3-acetylcarbohydrazide **8a** as the starting material.

As shown in Scheme 3, 2-indolyl-4*H*-1,3,4-oxadiazin-5(6*H*)-one derivatives **13** were synthesised by cyclization of suitable N_2-(2-bromoacethyl)indole-2-carbohydrazides **12** upon treatment with sodium bicarbonate in dry dimethylformamide. These hydrazides **12** were prepared by reaction of indolehydrazides **1** with α-bromoacyl bromide. The syntheses of compounds **13** by cyclization from the suitable N_2-(2-chloro-acetyl)indole-2-carbohydrazides **11** was unsuccessful.

The syntheses of 2-indolyl-4*H*-1,3,4-oxadiazin-5(6-methyl)-one derivatives **15**, Scheme 4 was unsuccessful. Treatment of indolehydrazides **1** with 2-bromopropanoyl bromide gave the N_2-(2-bromopropanoyl)indole-2-carbohydrazides **14**. Subsequent treatment with sodium bicarbonate in dry dimethylformamide gave the N_2-(2-hydroxypropanoyl)indole-2-carbohydrazides **16**.

The activity of the compounds prepared in this work as monoamine oxidase inhibitors was screened by the method previously described [15]. The most active compound was the 5-(3-methylindolyl)-1,3,4-oxadiazole-2(3*H*)one **10a**.

EXPERIMENTAL

Melting points were determined using a Mettler FP82 + FP80 apparatus and are uncorrected. Elemental analyses were obtained from vacuum-dried samples (over phosphorus pentoxide at 3-4 mm Hg, 24 hours at 80-100°). Elemental analyses were performed on a Carlo-Erba Strumentazione 1106 Analyzer. Infrared spectra were recorded on a Perkin-Elmer 681 apparatus using potassium bromide tablets; the frequencies are expressed in cm^{-1}. The ^1H nmr spectra were obtained on a Bruker AC-200E (200 MHz) instrument, with tetramethylsilane as the internal reference, at a concentration of about 0.1 g/ml and with dimethyl sulfoxide-d_6 as the solvent; the chemical shifts are reported in ppm with tetramethylsilane in δ units as the standard and coupling constants (J) are given in Hertz (Hz). The mass spectra were recorded on a Hewlett-Packard 5988-A instrument at 70 eV. Thin layer chromatography (tlc) was carried out on silica gel 60 Merck (HF, 254-266, Merck or DSF-5, Cammaga) with dichloromethane/methanol (9:1) and the plates were scanned under ultraviolet light at 254 and 366 nm.

N_2-(Cyanoacetyl)-*N*-methyl-5-methoxyindole-2-carbohydrazides **4e**, **4f**.

General Procedure.

Freshly distilled acrylonitrile (5 mmoles) was added to a suspension of the corresponding indole carbohydrazide **1e**, **1f** (4 mmoles) in ethanol (15 ml). The stirred mixture was refluxed for 24 hours. After removal of the solvent *in vacuo*, a solid was obtained with ethyl acetate/petroleum ether. The resulting residue was recrystallized from the appropriate solvent.

Indolyl-1,3,4-oxadiazol-2(3*H*)-one Derivatives **2a-2h**, **5e**, **5f**, **9a**, **9e**,**10a**.

General Procedure.

A suspension of the corresponding indole carbohydrazide **1a-1h**, **4e**, **4f**, **7a**, **7e**, **8a** (1.7 mmoles) in dry dioxane (15 ml) was added dropwise at 0° to a equimolecular quantity of triphosgene. Stirring was continued at room temperature for 24 hours. The solid obtained after evaporation to dryness was recrystallized from the appropriate solvent.

Indolyl-1,3,4-oxadiazole-2(3*H*)-thione Derivatives **3e**, **3f**, **6e**.

General Procedure.

A suspension of the corresponding indolecarbohydrazide **1e**, **1f**, **4e** (2.6 mmoles) in dry dioxane (15 ml) was added dropwise at 0° to a equimolecular quantity of thiophosgene. Stirring was continued at room temperature for 24 hours. The solid obtained after evaporation to dryness was recrystallized from the appropriate solvent.

N_2-(2-Haloacethyl)indole-2-carbohydrazides **11a**, **11e**, **12a**, **12e**, **12f**.

General Procedure.

A solution of 2-chloroacyl chloride or 2-bromoacyl bromide (12 mmoles) was added dropwise to a solution of the corresponding indole carbohidrazide **1a**, **1e**, **1f** (5 mmoles) in dry dioxane (30 ml). The mixture was stirred at room temperature for 6 hours. After removal of the solvent, a solid was obtained with ethyl ether. The resulting residue was recrystallized from the appropriate solvent.

2-Indolyl-4*H*-1,3,4-oxadiazin-5(6*H*)-one Derivatives **13a**, **13e**, **13f**.

General Procedure.

Anhydrous sodium bicarbonate (6.76 mmoles) was added to a solution of the corresponding N_2-(2-bromopropanoyl)indole-2-carbohidrazide **12a**, **12e**, **12f**, (1.69 mmoles) in dry dimethylformamide (30 ml). The resulting suspension was stirred at 60° for 24 hours. After filtration and removal of the solvent, the resulting residue was recrystallized from the appropriate solvent.

N_2-(2-Bromopropanoyl)indole-2-carbohidrazides **14a**, **14e**.

General Procedure.

A solution of 2-bromoproanoyl bromide (7 mmoles) was added dropwise to a solution of the corresponding indole carbohydrazide **1a**, **1e**, (3 mmoles) in dry dioxane (30 ml). The mixture was stirred at room temperature for 7 hours. After removal of the solvent, a solid was obtained with ethyl ether. The resulting residue was recrystallized from the appropriate solvent.

N_2-(Hydroxypropanoyl)indole-2-carbohydrazides **16a**, **16e**

General Procedure.

Anhydrous sodium bicarbonate (6.44 mmoles) was added to a solution of the corresponding N_2-(2-bromopropanoyl)-indole-2-carbohidrazide **14a**, **14e**, (1.61 mmoles) in dry dimethylformamide (30 ml). The resulting suspension was stirred at 60° for 24 hours. After filtration and removal of the solvent, the resulting residue was recrystallized from the appropriate solvent.

5-(2-Indolyl)-1,3,4-oxadiazol-2(3*H*)-one (**2a**).

This compound had ir (potassium bromide): 3349 (NH), 1715 (C=O), 1640 (C=N), 1193 (C-O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 7.03-7.12 (m, 2H, H_3+H_5), 7.24 (t, 1H, H_6, J = 7.5 Hz), 7.45

(d, 1H, H_7, J = 8.1 Hz), 7.65 (d, 1H, H_4, J = 7.9 Hz), 12.02 (bs, 1H, NH indole), 12.10-12.95 (bs, 1H, NH oxadiazole); ms: m/z 201 (M^+, 84), 144 (100), 117 (13).

Anal. Calcd. for $C_{10}H_7N_3O_2$: C, 59.70; H, 3.48; N, 20.89. Found: C, 59.64; H, 3.54; N, 20.52.

5-[2-(5-Methoxyindolyl)]-1,3,4-oxadiazol-2(3*H*)-one (**2b**).

This compound had ir (potassium bromide): 3280 (NH), 1767 (C=O), 1626 (C=N), 1220 (C-O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.77 (s, 3H, OCH_3), 6.87-6.92 (m, 2H, H_3+H_5 or H_4+H_6), 7.11 (s, 1H, H_4 or H_3), 7.33 (d, 1H, H_7, J = 8.8 Hz), 11.85 (s, 1H, NH indole), 12.57 (s, 1H, NH oxadiazole); ms: m/z 231 (M^+, 100), 216 (7), 174 (79).

Anal. Calcd. for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.89; N, 18.18. Found: C, 57.19; H, 3.89; N, 17.95.

5-[2-(5-Benzyloxyindolyl)]-1,3,4-oxadiazol-2(3*H*)-one (**2c**).

This compound had ir (potassium bromide): 3378 (NH), 1739 (C=O), 1635 (C=N), 1216 (C-O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 5.10 (s, 2H, CH_2-O), 6.91-7.48 (m, 9H, 5H benzene+4H indole), 11.81 (s, 1H, NH indole), 12.20-12.75 (bs, 1H, NH oxadiazole); ms: m/z 307 (M^+, 21), 250 (2), 216 (14), 91 (100).

Anal. Calcd. for $C_{17}H_{13}N_3O_3$: C, 66.45; H, 4.23; N, 13.68. Found: C, 66.53; H, 4.57; N, 13.53.

5-[2-(5-Hydroxyindolyl)]-1,3,4-oxadiazol-2(3*H*)-one (**2d**).

This compound had ir (potassium bromide): 3339, 3215 (NH, OH), 1740 (C=O), 1636 (C=N), 1219 (C-O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 6.76-6.84 (m, 2H, H_4+H_6 or H_3+H_6), 6.92 (s, 1H, H_3 or H_4), 7.25 (d, 1H, H_7, J = 8.7 Hz), 8.95 (s, 1H, OH), 11.72 (s, 1H, NH indole), 12.58 (s, 1H, NH oxadiazole); ms: m/z 217 (M^+, 100), 160 (98), 132 (13).

Anal. Calcd. for $C_{10}H_7N_3O_3$: C, 55.29, H, 3.23; N, 19.35. Found: C, 54.95; H, 3.40; N, 19.19.

5-[2-(*N*-methylindolyl)]-1,3,4-oxadiazol-2(3*H*)-one (**2e**).

This compound had ir (potassium bromide): 3124 (NH), 2900-2750 (C-H), 1785 (C=O), 1623 (C=N), 1222 (C-O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 4.00 (s, 3H, NCH_3), 7.08-7.17 (m, 2H, H_3+H_5), 7.34 (t, 1H, H_6), 7.57 (d, 1H, H_7, J = 8.2 Hz), 7.67 (d, 1H, H_4, J = 7.8 Hz), 12.45-12.85 (bs, 1H, NH); ms: m/z 215 (M^+, 100), 158 (43), 143 (10).

Anal. Calcd. for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.21; N, 19.52. Found: C, 61.74; H, 4.31; N, 19.80.

5-[2-(5-Methyl-5-methoxyindolyl)]-1,3,4-oxadiazol-2(3*H*)-one (**2f**).

This compound had ir (potassium bromide): 3126 (NH), 2832 (C-H), 1770 (C=O), 1621 (C=N), 1212 (C-O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.77 (s, 3H, NCH_3), 3.97 (s, 3H, OCH_3), 6.95 (d, 2H, H_3+H_6 or H_4+H_6), 7.13 (s, 1H, H_4 or H_3), 7.49 (d, 1H, H_7, J = 9.0 Hz); ms: m/z 245 (M^+, 100), 230 (27), 188 (22), 160 (6).

Anal. Calcd. for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.49; N, 17.14. Found: C, 58.57; H, 4.52; N, 17.20.

5-[2-(5-Benzyloxy-*N*-methylindolyl)]-1,3,4-oxadiazol-2(3*H*)-one (**2g**).

This compound had ir (potassium bromide): 3224 (NH), 2906-2861 (C-H), 1749 (C=O), 1623 (C=N), 1199 (C-O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.98 (s, 3H, NCH_3), 5.12 (s, 2H, CH_2O), 6.97-7.53 (m, 9H, 5H benzene+4H indole); ms: m/z 321 (M^+, 46), 230 (100), 91 (71).

Anal. Calcd. for $C_{18}H_{15}N_3O_3$: C, 67.30; H, 4.67; N, 13.08. Found: C, 67.48; H, 4.93; N, 13.13.

5-[2-(5-Hydroxy-*N*-methylindolyl)]-1,3,4-oxadiazole-2(3*H*)-one (**2h**).

This compound had ir (potassium bromide): 3413 (NH, OH), 1765 (C=O), 1625 (C=N), 1191 (C-O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.93 (s, 3H, NCH_3), 6.82-6.93 (m, 3H, H_3+H_4+H_6), 7.37 (d, 1H, H_7, J = 8.8 Hz), 9.02 (s, 1H, OH), 12.64 (s, 1H, NH); ms: m/z 231 (M^+, 100), 174 (40), 146 (8).

Anal. Calcd. for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.89; N, 18.05. Found: C, 57.51; H, 4.28; N, 17.67.

5-[2-(*N*-Methylindolyl)]-1,3,4-oxadiazole-2(3*H*)-thione (**3e**).

This compound had ir (potassium bromide): 3090 (NH), 2925 (C-H), 1621 (C=N), 1163 (C=S) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 4.02 (s, 3H, NCH_3), 7.16 (t, 1H, H_5, J = 7.4 Hz), 7.24 (s, 1H, H_3), 7.36 (t, 1H, H_6, J = 7.6 Hz), 7.61 (d, 1H, H_7, J = 8.4 Hz), 7.70 (d, 1H, H_4, J = 7.9 Hz), 14.30-15.25 (bs, 1H, NH); ms: m/z 231 (M^+, 100), 171 (24), 158 (26), 143 (16).

Anal. Calcd. for $C_{11}H_9N_3OS$: C, 57.14; H, 3.89; N, 18.18. Found: C, 57.05; H, 3.99; N, 18.13.

5-[2-(5-Methyl-5-methoxyindolyl)]-1,3,4-oxadiazole-2(3*H*)-thione (**3f**).

This compound had ir (potassium bromide): 3411 (NH), 2950 (C-H), 1615 (C=N), 1209 (C-O), 1172 (C=S) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.79 (s, 3H, NCH_3), 3.98 (s, 3H, OCH_3), 6.97-7.03 (m, 3H, H_3+H_4+H_6), 7.52 (d, 1H, H_7, J = 9.0 Hz), 14.20-15.18 (bs, 1H, NH); ms: m/z 261 (M^+, 100), 188 (19).

Anal. Calcd. for $C_{12}H_{11}N_3O_2S$: C, 55.17; H, 4.21; N, 16.09. Found: C, 54.95; H, 4.18; N, 15.89.

N_2-(2-Cyanoethyl)-*N*-methylindole-2-carbohydrazide (**4e**).

This compound had ir (potassium bromide): 3290, 3232 (NH), 2938 (C-H), 2246 (C(N), 1641 (C=O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.67 (t, 2H, CH_2CN, J = 6.3 Hz), 3.06 (c, 2H, CH_2NH), 3.98 (s, 3H, NCH_3), 5.55 (c, 1H, NH, J = 8.3 Hz), 7.07-7.14 (m, 2H, H_3+H_5), 7.28 (t, 1H, H_6, J = 7.6 Hz), 7.53 (d, 1H, H_7, J = 8.3 Hz), 7.63 (d, 1H, H_4, J = 7.8 Hz), 10.09 (d, 1H, NHCO); ms: m/z 242 (M^+, 15), 202 (1), 174 (1), 158 (100), 130 (7).

Anal. Calcd. for $C_{13}H_{14}N_4O$: C, 64.46; H, 5.78; N, 23.14. Found: C, 64.30; H, 5.87; N, 22.76.

N_2-(2-Cyanoethyl)-*N*-methyl-5-methoxyindole-2-carbohydrazide (**4f**).

This compound had ir (potassium bromide): 3232 (NH), 2937 (C-H), 2248 (C(N), 1656 (C=O), 1142 (C-O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.68 (t, 2H, CH_2CN), 3.22 (c, 2H, CH_2NH), 3.77 (s, 3H, NCH_3), 3.91 (s, 3H, OCH_3), 3.95 (s, 1H, NH), 6.90-7.09 (m, 3H, H_3+H_4+H_6), 7.43 (d, 1H, H_7, J = 8.8 Hz), 9.61 (s, 1H, NHCO); ms: m/z 272 (M^+, 14), 232 (1), 188 (100).

Anal. Calcd. for $C_{14}H_{16}N_4O_2$: C, 61.76; H, 5.88; N, 20.59. Found: C, 62.14; H, 5.95; N, 20.93.

5-[2-(*N*-Methylindolyl)]-3(2-cyanoethyl)-1,3,4-oxadiazol-2-one (**5e**).

This compound had ir (potassium bromide): 2948 (C-H), 2249 (C(N), 1768 (C=O), 1628 (C=N) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.04 (t, 2H, CH_2CN), 3.23-3.44 (bs, 2H, CH_2N), 4.03 (s, 3H,

NCH_3), 7.19 (m, 2H, H_3+H_5), 7.34 (t, 1H, H_6, J = 7.6 Hz), 7.59 (d, 1H, H_7, J = 8.3 Hz), 7.68 (d, 1H, H_4, J = 7.9 Hz); ms: m/z 268 (M^+, 56), 215 (2), 156 (100).

Anal. Calcd. for $C_{14}H_{12}N_4O_2$: C, 62.69; H, 4.48; N, 20.89. Found: C, 62.57; H, 4.63; N, 20.82.

5-[2-(5-methyl-5-methoxyindolyl)]-3-(2-cyanoethyl)-1,3,4-oxadiazol-2-one (**5f**).

This compound had ir (potassium bromide): 2942 (C-H), 2251 (C(N), 1774 (C=O), 1660 (C=N) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.68 (t, 2H, CH_2CN), 3.23 (t, 2H, CH_2N), 3.78 (s, 3H, NCH_3), 3.91 (s, 3H, OCH_3), 6.91-7.15 (m, 3H, H_3+H_4+H_6), 7.44 (d, 1H, H_7, J = 8.8 Hz); ms: m/z 298 (M^+, 75), 188 (100).

Anal. Calcd. for $C_{15}H_{14}N_4O_3$: C, 60.37; H, 4.70; N, 18.79. Found: C, 60.37; H, 4.65; N, 18.78.

5-[2-(*N*-Methylindolyl)]-3-(2-cyanoethyl)-1,3,4-oxadiazole-2-thione (**6e**).

This compound had ir (potassium bromide): 2920 (C-H), 2249 (C(N), 1624 (C=N), 1109 (C=S) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.16 (t, 2H, CH_2CN), 4.06 (s, 3H, NCH_3), 4.42 (t, 2H, CH_2N), 7.18 (t, 1H, H_5, J = 7.4 Hz), 7.32-7.42 (m, 2H, H_3+H_6), 7.63 (d, 1H, H_7, J = 8.4 Hz), 7.72 (d, 1H, H_4, J = 7.9 Hz); ms: m/z 286 (M^+, 5), 231 (10), 158 (11), 156 (100).

Anal. Calcd. for $C_{14}H_{12}N_4OS$: C, 59.15; H, 4.22; N, 19.71. Found: C, 58.97; H, 4.26; N, 19.39.

5-(3-Indolyl)-1,3,4-oxadiazol-2(3*H*)-one (**9a**).

This compound had ir (potassium bromide): 3267 (NH), 1746 (C=O), 1635 (C=N) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 7.19-7.25 (m, 2H, H_6+H_5), 7.51 (d, 1H, H_7, J = 7.3 Hz), 7.90-7.99 (m, 2H, H_4+H_2), 11.87 (s, 1H, NH indole), 12.21 (s, 1H, NH oxadiazole); ms: m/z 201 (M^+, 100), 144 (39), 117 (14).

Anal. Calcd. for $C_{10}H_7N_3O_2$: C, 59.70; H, 3.48; N, 20.89. Found: C, 60.08; H, 3.49; N, 20.53.

5-[3-(*N*-Methylindolyl)-1,3,4-oxadiazol-2(3*H*)-one (**9e**).

This compound had ir (potassium bromide): 3122 (NH), 2961-2854 (C-H), 1766 (C=O), 1634 (C=N) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.88 (s, 3H, CH_3), 7.20-7.35 (m, 2H, H_2+H_5), 7.58 (d, 1H, H_7, J = 8.0 Hz), 7.91 (t, 1H, H_6), 8.70 (d, 1H, H_4, J = 8.9 Hz), 12.26 (s, 1H, NH); ms: m/z 215 (M^+, 100).

Anal. Calcd. for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.19; N, 19.53. Found: C, 61.53; H, 4.58; N, 19.16.

5-(3-Indolylmethyl)-1,3,4-oxadiazol-2(3*H*)-one (**10a**).

This compound had ir (potassium bromide): 3363, 3237 (NH), 2924 (C-H), 1744 (C=O), 1628 (C=N) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 4.01 (s, 2H, CH_2), 7.00-7.10 (m, 2H, H_6+H_5), 7.32-7.39 (m, 2H, H_2+H_7), 7.51 (d, 1H, H_4, J = 7.5 Hz), 11.05 (s, 1H, NH indole), 12.10 (s, 1H, NH oxadiazole); ms: m/z 215 (M^+, 87), 130 (100), 116 (3).

Anal. Calcd. for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.19; N, 19.54. Found: C, 61.78; H, 4.38; N, 19.55.

N_2-(2-Chloroacetyl)indole-2-carbohydrazide (**11a**).

This compound had ir (potassium bromide): 3319, 3265 (NH), 1689 (C=O), 1648 (C=O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 4.24 (s, 2H, CH_2), 7.07-7.25 (m, 3H, H_6+H_5+H_3), 7.46 (d, 1H, H_7, J = 8.0 Hz), 7.66 (d, 1H, H_4, J = 7.7 Hz), 10.42 (s, 1H, NHCO), 10.56 (s, 1H, NHCO), 11.73 (s, 1H, NH indole); ms: m/z 251 (M^+, 16), 144 (100), 116 (11).

Anal. Calcd. for $C_{11}H_{10}ClN_3O_2$: C, 52.48; H, 3.98; N, 16.70. Found: C, 52.56; H, 4.29; N, 16.56.

N_2-(2-Chloroacetyl)-*N*-methylindole-2-carbohydrazide (**11e**).

This compound had ir (potassium bromide): 3199 (NH), 1681(C=O), 1606 (C=O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.99 (s, 3H, NCH_3), 4.23 (s, 2H, CH_2), 7.09-7.35 (m, 3H, H_6+H_5+H_3), 7.56 (d, 1H, H_7, J = 8.2 Hz), 7.68 (d, 1H, H_4, J = 7.7 Hz), 10.38 (s, 1H, NHCO), 10.52 (s, 1H, NHCO); ms: m/z 265 (M^+, 12), 158 (100), 130 (8).

Anal. Calcd. for $C_{12}H_{12}ClN_3O_2$: C, 54.24; H, 4.52; N, 15.85. Found: C, 54.22; H, 4.62; N, 15.54.

N_2-(2-Bromoacetyl)-indole-2-carbohydrazide (**12a**).

This compound had ir (potassium bromide): 3316, 3266 (NH), 1688 (C=O), 1647 (C=O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 4.01 (s, 2H, CH_2), 7.02-7.24 (m, 3H, H_6+H_5+H_3), 7.46 (d, 1H, H_7, J = 7.9 Hz), 7.64 (d, 1H, H_4, J = 7.6 Hz), 10.41 (s, 1H, NHCO), 10.52 (s, 1H, NHCO), 11.65 (s, 1H, NH indole); ms: m/z 295 (M^+, 9), 215 (4), 144 (100), 116 (11).

Anal. Calcd. for $C_{11}H_{10}BrN_3O_2$: C, 44.61; H, 3.38; N, 14.19. Found: C, 44.78; H, 3.49; N, 14.13.

N_2-(2-bromoacetyl)-*N*-methylindole-2-carbohydrazide (**12e**).

This compound had ir (potassium bromide): 3203 (NH), 1677 (C=O), 1606 (C=O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.98-4.00 (bs, 5H, NCH_3+CH_2), 7.09-7.35 (m, 3H, H_6+H_5+H_3), 7.55 (d, 1H, H_7, J = 8.3 Hz), 7.67 (d, 1H, H_4, J = 7.7 Hz), 10.39 (s, 1H, NHCO), 10.49 (s, 1H, NHCO); ms: m/z 309 (M^+, 6), 158 (100), 130 (9).

Anal. Calcd. for $C_{12}H_{12}BrN_3O_2$: C, 46.47; H, 3.87; N, 13.55. Found: C, 46.51; H, 3.99; N, 13.66.

N_2-(2-bromoacyl)-*N*-methyl-5-methoxyindole-2-carbohydrazide (**12f**).

This compound had ir (potassium bromide): 3183 (NH), 1675 (C=O), 1608 (C=O), 1209 (C-O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.78 (s, 3H, NCH_3), 3.95 (s, 3H, OCH_3), 4.00 (s, 2H, CH_2), 6.96 (d, 1H, H_6, J = 9.0 Hz), 7.14 (s, 2H, H_4+H_3), 7.47 (d, 1H, H_7, J = 9.0 Hz), 10.41 (s, 1H, NHCO), 10.48 (s, 1H, NHCO); ms: m/z 339 (M^+, 6), 259 (25), 216 (5), 188 (100).

Anal. Calcd. for $C_{13}H_{14}BrN_3O_3$: C, 45.89; H, 4.12; N, 12.36. Found: C, 46.28; H, 4.29; N, 12.38.

2-(2-Indolyl)-4*H*-1,3,4-oxadiazin-5(6*H*)-one (**13a**).

This compound had ir (potassium bromide): 3381 (NH), 1674 (C=O), 1645 (C=N) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 4.79 (s, 2H, CH_2), 6.84 (s, 1H, H_3), 7.03 (t, 1H, H_5, J = 7.3 Hz), 7.17 (t, 1H, H_6, J = 7.4 Hz), 7.42 (d, 1H, H_7, J = 8.1 Hz), 7.58 (d, 1H, H_4, J = 7.8 Hz), 11.11 (s, 1H, NH indole), 11.49 (s, 1H, NH oxadiazine); ms: m/z 215 (M^+, 100), 144 (66), 142 (7), 116 (12).

Anal. Calcd. for $C_{11}H_9N_3O_2$: C, 61.40; H, 4.18; N, 19.53. Found: C, 61.56; H, 4.34; N, 19.45.

2-[2-(*N*-methylindole)]-4*H*-1,3,4-oxadiazin-5(6*H*)-one (**13e**).

This compound had ir (potassium bromide): 3205 (NH), 1723 (C=O), 1632 (C=N), 1226 (C-O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.96 (s, 3H, NCH_3), 4.79 (s, 2H, CH_2), 6.96 (s, 1H, H_3), 7.08 (t, 1H, H_5, J = 7.4 Hz), 7.28 (t, 1H, H_6, J = 7.5 Hz), 7.51 (d, 1H, H_7, J = 8.3 Hz), 7.61 (d, 1H, H_4, J = 7.8 Hz), 11.17 (s, 1H, NH); ms: m/z 229 (M^+, 100), 158 (40).

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.88; H, 4.80; N, 18.34. Found: C, 62.86; H, 5.09; N, 18.34.

2-[2-(*N*-Methyl-5-methoxyindolyl)]-4*H*-1,3,4-oxadiazin-5(6*H*)-one (**13f**).

This compound had ir (potassium bromide): 3203 (NH), 2933 (C-H), 1724 (C=O), 1630 (C=N), 1215 (C-O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.76 (s, 3H, NCH_3), 3.93 (s, 3H, OCH_3), 4.79 (s, 2H, CH_2), 6.86-6.89 (m, 2H, H_3+H_6 or H_4+H_6), 7.10 (s, 1H, H_3 or H_4), 7.43 (d, 1H, H_7, J = 8.9 Hz), 11.16 (s, 1H, NH); ms: m/z 259 (M^+, 100), 244 (30), 216 (17), 188 (14), 173 (5).

Anal. Calcd. for $C_{13}H_{13}N_3O_3$: C, 60.23; H, 5.02; N, 16.22. Found: C, 60.59; H, 5.24; N, 16.26.

N_2-(2-Bromopropanoyl)indole-2-carbohydrazide (**14a**).

This compound had ir (potassium bromide): 3317 (NH), 1700 (C=O), 1602 (C=O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.75 (d, 3H, CH_3), 4.65 (c, 1H, CH), 7.08 (t, 1H, H_5, J = 7.5 Hz), 7.18-7.23 (m, 2H, H_6+H_3), 7.45 (d, 1H, H_7, J = 8.1 Hz), 7.65 (d, 1H, H_4, J = 7.9 Hz), 10.43 (s, 1H, NHCO), 10.60 (s, 1H, NHCO), 11.71 (s, 1H, NH indole); ms: m/z 309 (M^+, 8), 229 (5), 175 (3), 144 (100).

Anal. Calcd. for $C_{12}H_{12}BrN_3O_2$: C, 46.47; H, 3.87; N, 13.55. Found: C, 46.77; H, 3.98; N, 13.38.

N_2-(2-Bromopropanoyl)-*N*-methylindole-2-carbohydrazide (**14e**).

This compound had ir (potassium bromide): 3369, 3211 (NH), 2960 (C-H), 1695 (C=O), 1643 (C=O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.75 (d, 3H, CH_3), 3.99 (s, 3H, NCH_3), 4.65 (c, 1H, CH), 7.16 (t, 1H, H_5, J = 7.3 Hz), 7.23 (s, 1H, H_3), 7.32 (t, 1H, H_6, J = 7.6 Hz), 7.57 (d, 1H, H_7, J = 8.3 Hz), 7.68 (d, 1H, H_4, J = 7.9 Hz), 10.42 (s, 1H, NHCO), 10.55 (s, 1H, NHCO); ms: m/z 323 (M^+, 7), 158 (100), 130 (6).

Anal. Calcd. for $C_{13}H_{14}BrN_3O_2$: C, 48.16; H, 4.32; N, 12.97. Found: C, 48.47; H, 4.63; N, 12.74.

N_2-(2-Hydroxypropanoyl)indole-2-carbohydrazide (**16a**).

This compound had ir (potassium bromide): 3379, 3326 (NH, OH), 2981 (C-H), 1658 (C=O), 1638 (C=O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.31 (d, 3H, CH_3), 4.15 (m, 1H, CH), 5.54 (d, 1H, OH), 7.12-7.18 (m, 2H, H_5+H_3), 7.46 (d, 1H, H_7, J = 7.1 Hz), 8.11-8.15 (m, 2H, H_4 + H_6), 9.35-9.80 (bs, 2H, NH-NH), 11.65 (s, 1H, NH indole); ms: m/z 247 (M^+, 10), 144 (100), 116 (11).

Anal. Calcd. for $C_{12}H_{13}N_3O_3$: C, 58.30; H, 5.26; N, 17.00. Found: C, 58.51; H, 5.52; N, 16.84.

N_2-(2-Hydroxypropanoyl)-*N*-methylindole-2-carbohydrazide (**16e**).

This compound had ir (potassium bromide): 3378, 3202 (NH, OH), 1677(C=O), 1649 (C=O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.29-1.32 (d, 3H, CH_3), 3.99 (s, 3H, NCH_3), 4.12-4.18 (m, 1H, CH), 5.57 (d, 1H, OH), 7.09-7.20 (m, 2H, H_5+H_3), 7.30 (t, 1H, H_6, J = 7.5 Hz), 7.56 (d, 1H, H_7, J = 8.2 Hz), 7.67 (d, 1H, H_4; J = 7.7 Hz), 9.60-9.75 (bs, 1H, NH), 10.15-10.30 (bs, 1H, NH); ms: m/z 261 (M^+, 24), 243 (12), 158 (100), 131 (5).

Anal. Calcd. for $C_{13}H_{15}N_3O_3$: C, 59.77; H, 5.75; N, 16.09. Found: C, 60.15; H, 5.91; N, 16.37.

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