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Research Article

SYNTHESIS OF SOME NEW OXINDOLE DERIVATIVES AS POTENTIAL ANTIPSYCHOTIC AND ANTICONVULSANT AGENTS

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ABSTRACT

New 1-substituted oxindoles were synthesized and screened for their antipsychotic and anticonvulsant activities. It is concluded from the results that compounds **4c** and **4e** were found to be very promising as far as efficacy and safety as antipsychotic and anticonvulsant agents.

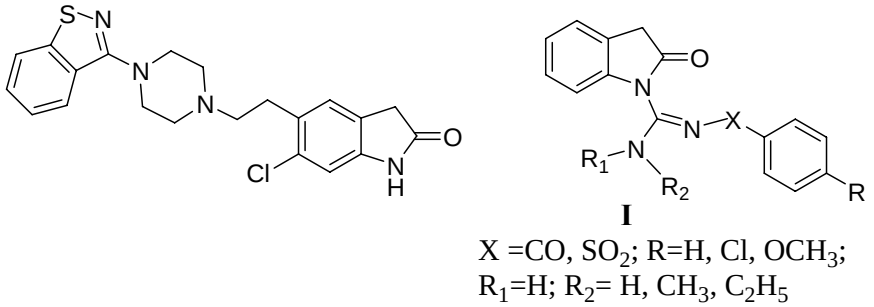
Keywords: Oxindole, Antipsychotic activity, Anticonvulsant activity, Acute toxicity.

INTRODUCTION

Psychosis is the major CNS disorder which causes the serious distortion of capacity to recognize reality[1]. All clinically effective antipsychotic (except Clozapine Like) have potent post – dopaminergic D_2 receptor blocking action. Blockade of dopamine action is responsible for extrapyrimidal symptoms (EPS) that often associated with antipsychotic drugs[1].

Moreover, epilepsy is very often associated with CNS psychiatric disorders; therefore, a drug of both antipsychotic as well as antiepileptic activity will be more beneficial[2]. Considerable interest has been focused on the oxindole derivatives, which have been reported to possess antihypoxic, anticonvulsant, anti-inflammatory and anxiolytic activities[3-7]. Furthermore, the discovery of Ziprasidone (Fig.1) led the exploration of oxindole.

Ziprasidone is a novel effective atypical antipsychotic agent having an oxindole scaffold and has been recently approved by Food and Drug Administration (FDA) for the treatment of schizophrenia[8]. As with other atypical antipsychotics, the precise mechanism of action of the new drug is not known. Ziprasidone was, however, known to be a potent serotonin and dopamine antagonist[9-14]. Based on this finding and in a scope of a research program aimed to the development of new oxindole derivatives to treat neurological disorders, the authors describe the synthesis of some new 1-substituted oxindole derivatives of the general formula **I** and evaluate them for their antipsychotic and anticonvulsant activities.



I

X =CO, SO_2; R=H, Cl, OCH_3;
R_1=H; R_2= H, CH_3, C_2H_5

Fig. 1: Ziprasidone

MATERIALS AND METHODS

Chemistry

Melting points are uncorrected and determined in one end open capillary tubes using Gallen Kamp melting point apparatus MFB-595-010M (Gallen Kamp, London, England). Microanalysis was carried at Micro analytical Unit, Faculty of Science, Cairo University. IR spectra were determined using KBr discs (cm^{-1}) on Shimadzu Infrared Spectrometer IR-435 (Shimadzu, Kyoto, Japan), Perkin-Elmer FT-IR 1650 (Perkin-Elmer, Waltham, Massachusetts 02451, USA) and Mattson Genesis II FTIRTM Spectrometer (Mattson, Madison, WI, USA). ^{1}HNMR (DMSO-d_6, D_2O) δ *ppm* spectra were determined using Joel NMR Varian Gemini 200 MHz Spectrometer (Joel, Tokyo, Japan) and Varian Mercury VX-300 MHz NMR Spectrometer (Varian, Oxford, England). TLC was carried out using Art. DC-Plastikfolien, Kieselgel 60 F254 sheets (Merck, Darmstadt, Germany), the developing solvents were ethyl acetate-petroleum ether (1:1) and the spots were visualized at 366, 254 nm by UV Vilber Lourmat 77202 (Vilber, Marne La Vallee, France).

Oxoindoline-1-carboximidamide (3)

A magnetically stirred mixture of compound **1** (4.9 g, 20 mmol), **2** (2.09 g, 23.0 mmol) and pyridine (10 ml) was stirred at 110ºC for 1 hr. After one night standing at room temperature, diethylether was added and the precipitate was collected by filtration and washed three times with Et_2O to afford a white solid (5.0g). The obtained solid was dissolved in methanol (20 ml) and a 2N sodium hydroxide solution (12 ml) and water (20 ml) were successively added. The formed precipitate was collected by filtration and re-crystallized from ethanol, yield 65%, m.p. 125-127 ºC. IRυ_{max} (cm^{-1}) 3367, 3269 (NH_2), 3167 (NH), 3099 (CH aromatic), 2981–2939 (CH aliphatic), 1689 (C=O), 1589 (NH). ^{1}HNMR ($CDCl_3$-300 MHz): δ 3.5 (s, 2H, CH_2CO), 7.26–6.98 (m, 4H, aromatic H), 9.47 (3, 3H, NH_2, NH, exch.). Anal. Calcd. for $C_9H_9N_3O$ (175); C, 61.70; H, 5.18; N, 23.99, Found: C, 61.55, H, 5.21.

General method for preparation of compounds 4a-e

To a magnetically stirred mixture of **3** (0.5 g, 2.85 mmol) and the appropriate acid chloride (3.14 mmol) in acetonitrile (10 ml) were

added N,N-dimethyl–4–amino pyridine (0.02 g, 0.18 mmol) and triethylamine (1 ml). The resulting solution was stirred at room temperature for 30 min. After addition of 2N sodium hydroxide (20 ml) and extraction with ethylacetate (100 ml), the ethylacetate layer was concentrated in vacuum. The resulting crude residue was re-crystallized from methanol to afford a crystalline product.

N-(4- Chlorophenylsulfonyl)-2-oxoindoline-1-carboximidamide (4a)

Yellowish white crystals, m.p. 168–169ºC, yield 70%. IRυ$_{max}$ (cm^{-1}): 3421, 3424 (NH_2), 3093 (CH aromatic), 1697 (C=O), 1330 (SO_2), 1157 (SO_2). ^{1}HNMR (DMSO-d_6, 300 MHz): δ 3.4 (s, 2H, CH_2CO), 8.0–7.7 (m, 8H, aromatic H), 10.4 (broad, 2H, NH_2 exch. D_2O). Anal. Calcd. for $C_{15}H_{12}ClN_3O_3S$ (349.5), C, 51.51; H, 3.46, N, 12.01, Found: C, 51.35, H, 3.25, N, 12.00.

2-Oxo-N-tosylindoline-1-carboximidamide (4b)

Yellow crystals, m.p. >300ºC. IRυ$_{max}$ (cm^{-1}): 3182, 3143 (NH_2), 1693 (C=O), 1330 (SO_2), 1103 (SO_2). ^{1}HNMR (DMSO-d_6 300 MHz): 3.4 (s, 5H, CH_3 and CH_2CO), 7.3-6.8 (m, 8H, aromatic H), 10.8 (s, 2H, NH_3, exch. D_2O). Anal.Calcd. for $C_{16}H_{15}N_3O_3S$ (329.38), C, 58.35, H, 4.55, N, 12.76, Found: C, 58.12, H, 4.25, N, 12.55.

N- (Amino (2-oxoindolin-1-yl)methylene)benzamide (4c)

Pink crystals, m.p. 195-197 ºC, yield 85%. IRυ$_{max}$ (cm^{-1}): 3429, 3421 (NH_2), 1685 (C=O), 1658 (C=O). ^{1}HNMR (DMSO–d_6 300 MHz), δ 3.4 (s, 2H, CH_2CO), 7.3-6.9 (m, 9H, aromatic H), 10.7 (s, 2H, NH_2, exch. D_2O), Anal. Calcd. for $C_{16}H_3N_3O_2$ (279.29), C, 68.81, H, 4.96, N, 15.05, Found: C, 68.62, H,4.62, N, 14.95.

N-(Amino(2-oxindolin-1-yl)methylene)-4- chlorobenzamide (4d)

Pinkish white crystals, m.p. > 300ºC, yield 50%. IRυ$_{max}$ (cm^{-1}): 3429, 3321 (NH_2), 1685 (C=O), 1658 (C=O), 759 (C-Cl). ^{1}HNMR (DMSO–d_6 300 MHz), δ 3.4 (s, 2H, CH_2CO), 7.9 - 7.3(m, 8H, aromatic H), 10.3(s, 2H, NH_2 exch. D_2O). Anal.Calcd. for $C_{16}H_{12}ClN_3O_2$ (313.74), C, 61.25, H, 3.86, N, 11.30, Found: C, 61.40, H, 3.50, N, 13.70.

N-(Amino(2-oxindolin -1- yl)methylene) -4- methoxy benzamide (4e)

Yellow Crystals, m.p. 174-175 ºC yield 80%. IRυ$_{max}$ (cm^{-1}): 3428, 3320 (NH_2), 1685 (C=O), 1658 (C=O). ^{1}HNMR (DMSO-d_6 300 MHz), 3.3(s, 2H, CH_2CO), 3.8 (s, 3H, OCH_3), 8.01–6.9 (m, 8H, aromatic H), 10.4 (s, 2H, NH_2 exch. D_2O), Anal. Calcd. for $C_{17}H_{15}N_3O_3$ (309.32): C, 66.01, H, 4.89, N, 13.58, Found: C, 66.40, H, 4.30, N, 13.30.

General method for preparation of compounds 5a-b

To a magnetically stirred solution of the appropriate p-substituted phenyl sulfonamide (40 mmol) and triethylamine (1 mmol) in anhydrous acetonitrile (40 ml) was slowly added ethyl chloroformate (60 mmol), and the resulting solution was stirred at room temperature for 6 hr and evaporated *in vacuum*. The residue was dissolved in ethylacetate and aqueous sodium bicarbonate, was added. The water layer was separated and acidified with a mixture of ice and concentrated HCl to give an oily precipitate which slowly crystallized upon standing. The crystals were collected by filtration, washed with water, dried to give the target compound which was crystallized from ethanol.

N-[4-Methylphenyl] sulfonyl carbamic acid ethyl ester (5a)

White crystals, m.p. 115-117 ºC, yield 55%. IRυ$_{max}$ (cm^{-1}): 3226 (NH), 1762 (C=O), 1346 (SO_2), 1161 (SO_2). ^{1}HNMR (CDCl$_3$–300 MHz): δ 1.12 (t, 3H, $CH_2\underline{CH_3}$), 2.3 (s, 3H, CH_3), 4.0 (q, 2H, $\underline{CH_2}CH_3$), 7.8-7.3 (m, 4H, aromatic H), 11.8 (broad, 1H, NH exch. D_2O).

N-(4-chlorophenyl) sulfonyl carbamic acid ethyl ester (5b)

White crystals, m.p. 90-92 ºC, yield 60%. IRυ$_{max}$ (cm^{-1}): 3224 (NH), 1755 (C=O), 1354 (SO_2), 1105 (SO_2). ^{1}HNMR (CDCl$_3$-300 MHz): δ 1.12 (t, 3H, $CH_2\underline{CH_3}$), 4.0 (q, 2H, $\underline{CH_2}CH_3$), 7.9-7.4 (m, 4H, aromatic H), 11.8 (broad, 1H, NH exch. D_2O).

General method for preparation of compounds 6a-b

To a solution of the appropriate substituted sulfonyl carbamic acid ethyl ester derivative **5a-b** (20 mmol) in toluene (20 ml), compound **1** (20 mmol) was added and the resulting mixture was refluxed for 4 hr. After cooling of the reaction mixture to room temperature, whereby crystals were formed, collected and re-crystallized from ethanol.

Oxo-*N*-tosylindoline-1-carboxamide (6a)

Yellowish white crystals, m.p. 116-118, 90 % yield. IRυ$_{max}$ (cm^{-1}): 3178 (NH), 1701 (C=O), 1681 (C=O), 1330 (SO_2), 1157 (SO_2). ^{1}HNMR (DMSO-d_6-300 MHz): δ 2.4 (s, 3H, CH_3), 3.5 (s, 2H, CH_2CO), 7.7-6.7 (m, 8H, aromatic H), 10.4 (broad, 1H, NH exch. D_2O). Anal. Calcd. for $C_{16}H_{14}N_2O_4S$ (330.64): C, 58.17; H, 4.27; N, 8.48, Found: C, 58.40; H, 4.51; N, 8.61.

N- (4-Chlorophenylsulfonyl) -2- oxoindoline -1- carboxamide (6b)

Yellow crystals, m.p. 138-140 ºC, 81 % yield, IRυ$_{max}$ (cm^{-1}): 3205 (NH), 1693(C=O), 1618.3(CO), 1354.8(SO_2), 1091.7(SO_2), 752.2(Cl), ^{1}HNMR (DMSO-d_6-300MHz), 3.4(s, 2H, CH_2CO) 7.8-7.4 (m, 8H, aromatic H), 10.4 (broad, ^{1}H, NH exch. D_2O); Anal. Calcd. for $C_{15}H_{11}CLN_2O_4S$ (350.78): C,51.36; H,3.16; N,7.99, Found: C, 51.5; H,3.41; N,8.1.

General method for preparation for compounds 7a-b

A mixture of the appropriate carboxamide derivative **6a-b** (7.5 mmol) and PCl_5 (58.14 mmol) in chlorobenzene (20 ml) was refluxed for 1 hr. After through concentration in vacuum a residue was left and used directly in the next step for the preparation of the corresponding target molecules **8a-b** which was crystallized from ethanol-acetone.

2–Oxo-*N*-tosylindoline-1-carbimidoyl chloride (7a)

Brown crystals, m.p. 191-193 ºC, 70% yield, IRυ$_{max}$ (cm^{-1}): 1631 (CO), 1353 (SO_2), 1091 (SO_2), 744 (C-Cl).

N- (4-Chlorophenylsulfonyl) -1-carbimidoyl chloride (7b)

Brown crystals, m.p. 250-253 ºC, 75% yield. IRυ$_{max}$ (cm^{-1}): 1612 (CO), 1311 (SO_2), 1087 (SO_2), 752 (C-Cl).

General method for preparation of compounds 8a-d

The formed chloro derivative **7** was suspended in dichloromethane (20 ml) and reacted with cold methyl (ethyl) amine (3 ml). After stirring the reaction mixture at room temperature for 1 hr, the mixture was concentrated in vacuum. The residue was crystallized from ethanol-chloroform.

N-Methyl-2-oxo-N′-tosylindoline-carboximidamide (8a)

Yellow crystals, m.p. 262-265 ºC, 65% yield, IRυ$_{max}$ (cm^{-1}): 3421 (NH), 1627 (C=O), 1319 (SO_2), 1122 (SO_2). ^{1}HNMR (DMSO-d_6 300MHz): δ 2.30 (d, *J*= 4Hz, 3H, CH_3), 2.95 (s, 5H, $C\underline{H_2}CO$ and CH_3), 7.5-7.1 (m, 8H, aromatic H), 8.70 (broad, 1H, NH exch. D_2O). Anal. Calcd. for $C_{17}H_{17}N_3O_3S$ (343.41): C, 59.47; H, 4.99; N, 12.24; Found: C, 59.41; H, 4.60; N, 12.51.

N-Ethyl-2-oxo-N′-tosylindoline-1-carboximidamide (8b)

Yellow crystals, m.p. 270-272 ºC, 60% yield, IRυ$_{max}$ (cm^{-1}): 3394 (NH), 1631 (C=O), 1323 (SO_2), 1072 (SO_2). ^{1}HNMR (DMSO-d_6 300 MHz): δ 1.23 (t, 3H, $CH_2\underline{CH_3}$), 2.91 (s, 2H, CH_2CO), 3.3 (m, 2H, $\underline{CH_2}CH_3$), 7.7-7.2 (m, 8H, aromatic H), 8.7 (broad, 1H, NH exch. D_2O). Anal.Calcd. for $C_{18}H_{19}N_3O_3S$ (357.43): C, 60.49; H, 5.36; N, 11.76; Found: C, 60.62; H, 5.11; N, 12.12.

N′–(4-Chlorophenylsulfonyl)-N-methyl-2-oxoindoline-1-carboximidamide (8c)

Pink crystals, m.p. 212-124 ºC, 65% yield, IRυ$_{max}$ (cm^{-1}): 3390 (NH), 1620 (C=O), 1388 (SO_2), 1091 (SO_2), 752 (C-Cl), ^{1}HNMR (DMSO-d_6 300Hz): δ 2.94 (d, *J*= 4Hz, 3H, CH_3), 3.4(s, 2H, CH_2CO), 7.2-8.2 (m, 8H, aromatic H), 9.0 (broad, NH, exch. D_2O). Anal.Calcd. for $C_{16}H_{14}ClN_3O_3S$ (363.82): C, 52.82; H, 3.88; N, 11.55, Found: C, 52.5; H, 3.5; N, 11.7.

(4-Chlorophenylsulfonyl)-N-ethyl-2-oxoindoline-1-carboximidamide (8d)

Yellowish crystals, m.p. 245-247 ºC, 65% yield, IRυ$_{max}$ (cm^{-1}): 3417 (NH), 1662 (C=O), 1388 (SO_2), 1091 (SO_2), 756 (C-Cl). ^{1}HNMR (DMSO-d_6 300Hz): δ 1.24 (t, 3H, $CH_2\underline{CH_3}$), 3.3 (s, 2H, CH_2CO), 3.5 (m, 2H, $\underline{CH_2}CH_3$), 7.9-7.2 (m, 8H, aromatic H), 9.0 (broad, NH exch. D_2O). Anal. Calcd. for $C_{17}H_{16}ClN_3O_3S$ (377.85): C, 54.04; H, 4.27; N, 11.12, Found: C, 54.35; H, 4.6; N, 11.5.

General method for preparation of 4-substituted benzoylisothiocynates 9a-c

Compounds **9a-c** were prepared according to the reported procedure[15] from the appropriate 4-substituted benzoyl chloride and ammonium thiocynate and immediately reacted with the oxindole **1**.

General method for preparation of compounds 10a-c

Compound **1** (10 mmol) was added to a magnetically stirred and cooled (0ºC) solution of **9** (10.5 mmol) in anhydrous acetonitrile (10 ml), and the resulting mixture was stirred at room temperature for 1 hr. The formed precipitate (ammonium chloride) was removed by filtration and thoroughly washed with acetonitrile. The filtrate was collected and further purified by crystallization from methanol.

N-(2-Oxoindoline-1-carbonthioyl) benzamide (10a)

Yellowish white crystals, m.p. 97-99 ºC, 75% yield. ^{1}HNMR (DMSO-d_6 200 MHz): δ 3.3 (s, 2H, CH_2CO), 7.2-6.7 (m, 9H, aromatic H), 10.3 (broad, 1H, NH exch. D_2O). Anal.Calcd. for $C_{16}H_{12}N_2O_2S$ (296.35): C, 64.85; H, 4.08; N, 9.45; Found C, 64.41; H, 4.23; N, 9.62.

4-Chloro-N-(2-oxoindoline-1-carbonothioyl) benzamide (10b)

Pink crystals, m.p. 138-140ºC, 75% yield, ^{1}HNMR (DMSO-d_6 200MH$_z$)**:** δ 3.3 (s, 2H, CH_2CO), 7.7-7.1 (m, 8H, aromatic H), 10.4 (broad, 1H, NH exch. D_2O). Anal. Calcd. for $C_{16}H_{11}ClN_2O_2S$ (330.79): C, 58.10; H, 3.35; N, 8.47. Found: C, 58.3; H, 3.6; N, 8.7.

4-Methoxy-N-(2-oxindoline-1-carbonothioyl) benzamide (10c)

Yellow crystals, m.p. 187-188ºC, 60% yield, IRυ$_{max}$ (cm^{-1}): 3142 (NH), 2951 (CH aromatic), 1712 (C=O), 1701 (C=O), 1267 (C=S), ^{1}HNMR (DMSO-d_6-200MHz): δ 3.3 (s, 2H, CH_2CO), 3.8 (m, 3H, OCH_3), 7.8-6.7 (m, 8H, aromatic H), 10.3 (broad, 1H, NH exch. D_2O). Anal. Calcd. for $C_{17}H_{14}N_2O_3S$ (326.37)**:** C, 62.56; H, 4.32; N,8.58. Found**:** C, 62.4; H, 4.5; N, 8.9.

General method for preparation of compounds 11a-f

To a stirred suspension of compound **10** (4.0 mmol) in acetonitrile (20 ml) was added excess cold methylamine or ethylamine (3 mmol) to give a clear green colures solution. A solution of $HgCl_2$ (4.4 mmol) in acetonitrile (20 ml) was slowly added and the resulting dark suspension was stirred for 3 hrs, the precipitate was removed by filtration. The filtrate was successively concentrated in vacuum, dissolved in ethylacetate, washed with 2N sodium hydroxide, dried over sodium sulfate, filtered and concentrated in vacuum. The residue was recrystallized from ethanol/chloroform.

N-[(Methylamino)(2-oxindolin-1-yl) methylene] benzamide (11a)

Yellow crystals, m.p. 88-90ºC, 60% yield, IRυ$_{max}$ (cm^{-1}): 3214 (NH), 1705 (C=O), 1620 (C=O). ^{1}HNMR (DMSO-d_6 200MH$_z$)**:** δ 2.8 (d, *J*= 4H$_z$, 3H, $\underline{CH_3}$NH), 3.4 (s, 2H, CH_2CO), 8.7-6.8 (m, 9H, Aromatic H), 10.4 (broad, 1H, NH exch. D_2O). Anal. Calcd. for $C_{17}H_{15}N_3O_2$ (293.32): C, 69.61; H, 5.15; N, 14.33. Found: C, 69.4; H, 5.5; N, 14.6.

N-[(Ethylamino)(2-oxindolin-1-yl) methylene] benzamide (11b)

Yellow crystals, m.p. 140-142ºC, 55% yield, IRυ$_{max}$ (cm^{-1}): 3294 (NH), 1725 (C=O), 1693 (C=O), ^{1}HNMR (DMSO-d_6-200MH$_z$): δ 1.3 (t,3H, $CH_2\underline{CH_3}$), 3.3 (s,2H, CH_2CO), 4.3 (q,2H, $\underline{CH_2}CH_3$), 8.5-7.2 (m, 9H, Aromatic H), 10.4 (broad, 1H, NH, exch. D_2O). Anal. Calcd. for $C_{18}H_{17}N_3O_2$ (307.35): C, 70.34; H, 5.58; N,13.67. Found: C, 70.5; H, 5.8; N, 13.9.

4-Chloro-N-[(methylamino)(2-oxindolin-1-yl) methylene] benzamide (11c)

Yellowish white crystals, m.p. 142-144ºC, 55% yield, ^{1}HNMR (DMSO-d_6-200MH$_z$): δ 2.7 (d, *J*= 4H$_z$, 3H, $\underline{CH_3}$NH), 3.3 (s,2H, CH_2CO), 8.0-7.5 (m, 8H, Aromatic H), 10.4 (broad,1H, NH exch.). Anal. Calcd. for $C_{17}H_{14}ClN_3O_2$ (327.77): C, 62.30; H, 4.31; N, 12.82. Found**:** C, 62.1; H, 4.2; N, 12.5.

4-Chloro-N-[(ethylamino)(2-oxindolin-1-yl) methylene] benzamide (11d)

Yellow crystals, m.p. 146-148ºC, 60% yield, **1**HNMR (DMSO-d_6-200MH$_z$): δ 1.2 (t, 3H, $CH_2\underline{CH_3}$), 3.3 (s, 2H, CH_2CO), 4.4 (m, 2H, $\underline{CH_2}CH_3$), 10.3 (broad, 1H, NH, exch.). Anal. Calcd. for $C_{18}H_{16}ClN_3O_2$ (341.79): C, 63.25; H, 4.72; N, 12.29. Found: C, 63.5; H, 5.1; N, 12.5.

4-Methyloxy-N-[(methylamino)(2-oxindolin-1-yl) methylene] benzamide (11e)

Yellow crystals, m.p. 82-84ºC, 55% yield, **1**HNMR (DMSO-d_6-200MH$_z$): δ 2.8 (d, *J* = 4Hz, 3H, CH_3), 3.3 (s, 2H, CH_2CO), 3.9 (s, 3H, OCH_3). Anal. Calcd. for $C_{18}H_{17}N_3O_3$ (323.35)**:** C, 66.86; H, 5.3; N, 13.0. Found: C, 66.9; H, 5.4; N, 13.2.

4-Methyloxy-N-[(ethylamino)2-oxindolin-1-yl) methylene] benzamide (11f)

Yellow crystals, m.p. 90-92ºC, 60% yield, IRυ$_{max}$ (cm^{-1}): 3421 (NH), 1724 (C=O), 1620 (C=O), ^{1}HNMR (DMSO-d_6-200MH$_z$): δ 1.3 (t, 3H, $CH_2\underline{CH_3}$), 3.4 (s, 2H, CH_2CO), 4.1(s, 3H, OCH_3), 4.4 (m, 2H, $\underline{CH_2}CH_3$). Anal. Calcd. for $C_{19}H_{19}N_3O_3$ (337.37): C, 67.64; H, 5.68; N, 12.45. Found: C, 67.9; H, 5.9; N, 12.6.

Pharmacological screening

Antipsychotic activity

All compounds have been evaluated for their evaluated for their antipsychotic activity according to the following methods:

Foot Shock induced aggression

The animals were divided into five groups of 12 mice (six pairs of male mice) per group. The vehicles are (DMSO; 0.5 ml / kg, i.p.), haloperidol (1 mg/ kg, i.p.) used as a standard and the compounds under investigation (40 mg/kg) were administered i.p., 30 minutes prior to the experiment. Foot shock-induced aggression (FSIA) behaviour was induced in pairs of mice by administering a train of impulses through an electronic stimulator to a grid floor for three minutes. Aggressive behaviour was measured in pairs of mice using two parameters number of fights and latency to fight[16].

Amphetamine-induced stereotyped behaviour in rats

This was scored every five minutes for 30 minutes. The following scores were given

stereotypy scoring- 0, absence of stereotyped behaviour; 1, intermittent sniffing; 2, constant sniffing; 3, constant sniffing with intermittent licking and/or false biting; 4, constant licking or false licking; 5, constant licking; 6, constant biting and moving around; 7, constant biting and restricted to a small area in the cage; 8, rearing.

The animals were divided into groups, each containing seven animals. They were treated with DMSO (0.5 ml/kg, i.p.) or compounds under investigation (40 mg/kg i.p.) and placed individually in the cage. D-amphetamine (2 mg/kg i.p.) was given 30 minutes after the compounds were administered. The stereotyped behaviour was recorded [17].

Phenobarbitone-induced sleeping time in mice

Phenobarbitone (50 mg/kg) was injected i.p. to mice (n= 6) pre-treated with DMSO (0.5 mg/kg, i.p.) or compounds under investigation (40 mg/kg i.p.) Haloperidol (1mg/kg, i.p.) was used as positive control. The vehicle, compounds under investigation and haloperidol were administered 30 minutes prior to the administration of phenobarbitone. Immediately after the phenobarbitone administration, each animal was placed in an

individual cage and observed. The latency to the loss of righting reflex (*induction time in min*) and the time required to recover righting reflex or awakening (sleeping time in min) were registered for each animal [18, 19].

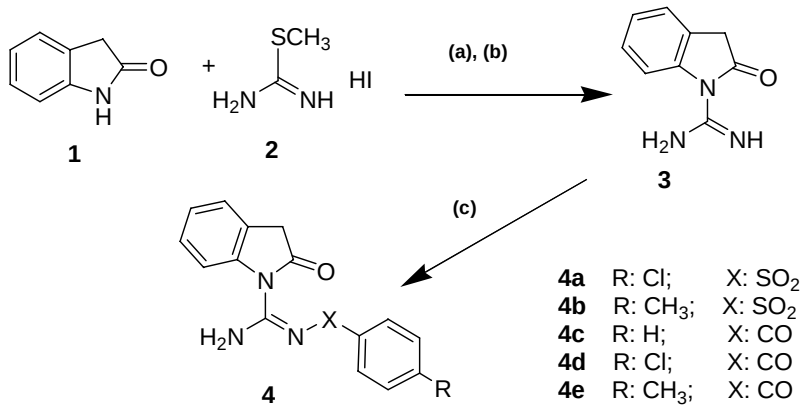
Anticonvulsant activity

The maximal electroshock (MES) seizure model

The maximal electroshock (MES) seizure test was used as described by Swinyard *et al* [20]**.** Rats were subjected to 0.02 s, 60 Hz electrical stimulus through corneal electrode 60 minutes after i.p. administration of compounds under investigation. The endpoint measured was suppression of hind limb tonic extension (HTE), which is expressed as the percentage of animals in which the response was inhibited.

Acute toxicity test

Compounds were investigated for acute toxicity study (LD_{50}) according to method of Smith[21]. Compounds were administered i.p. in doses of 50, 100, 200, 500, 1000, 1500 and 2000 mg/kg to different groups of mice, each group consisting of six animals (n = 6). The mortality rate was observed and recorded for a 24 hr period.



Scheme 1. (a) Pyridine, 110 C^{O}; (b) 2N NaOH; (c) RArXCl, CH_3CN, DMAP, Et_3N, room temp.

RESULTS AND DISCUSSION

Chemistry

Reaction of oxindole **1** with **2** gave the amidine **3**, which was reacted with various arylsulfonyl halides or arylcarbonyl halides to furnish the target molecules **4** in good yields (Scheme 1).

Moreover, for the synthesis of the target having one additional methyl or ethyl group on their carboxamidine moiety, a more convergent approach was devised; where in the NHR moiety is introduced in the last step. The synthetic strategy is based on the coupling of the oxindole **1** with sulfonylated carbamic acid ethyl esters **5** which were obtained from the corresponding arylsulfonamide and ethyl chloroformate, to furnish the products **6**. Chlorination of **6** using phosphorus pentachloride in chlorobenzene yielded the intermediate chloro derivative **7**. Compounds **8** were obtained from the reaction of **7** with methyl or ethylamine (Scheme 2).

An intriguing modification in our target molecules was the replacement of their sulfonyl group by a carbonyl group (Scheme 3). 4-(Un) substituted benzoyl isothiocyanate **9** was prepared in situe from 4-(un)substituted benzoyl chloride and ammonium isothiocyanate[15]. Nucleophilic addition of oxindole **1** to **9** yielded the adduct **10**. The target molecule **11** was achieved by the reaction of **10** with methyl or ethylamine in the presence of mercuric chloride.

Biological activity

Antipsychotic activity

It was evaluated by using three methods, the foot shock – induced aggression in mice, the amphetamine induced stereotyped behaviour in rats and Phenobarbital – induced sleeping time in mice. The first method depends on measuring the aggressive behaviour of the tested mice that was expressed in terms of numbers of fights and latency to fight[16]. The second method based on recording the stereotyped behaviour of the rats[17], while, the Phenobarbital – induced sleeping method depends on measuring the induction time and the sleeping time in minutes[18, 19], (tables 1, 2 and 3).

The data revealed that, only the following compounds showed variable degrees of antipsychotic activity by applying the three methods in this ascending order **7b**, **8e**, **6a**, **7a**, **8a**, **8b**, **4b**, **4a**, **4d**, **4c** and **4e**.

Compound **7b** showed mild activity by applying foot shock – induced aggression in mice and the stereotyped behaviour in rats only.

Anticonvulsant activity[20]

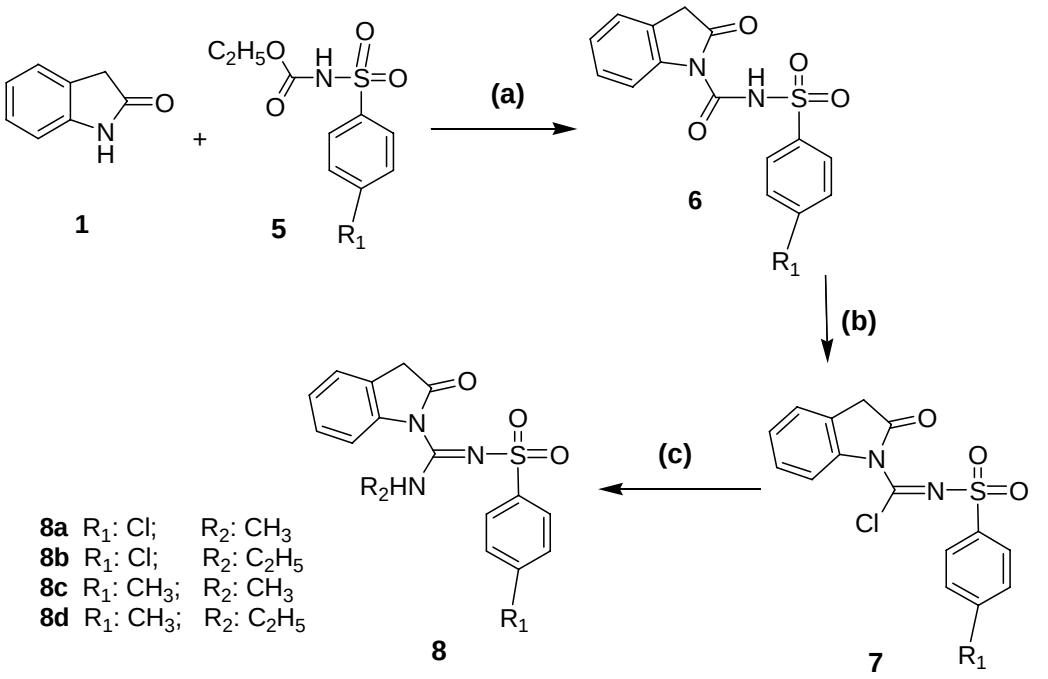
The compounds were screened for the anticonvulsant activity by the maximum electroshock seizure (MES) method using phenytoin as reference drug. The results of such a study were recorded in table 4. It was found that, among all the tested compounds, only these compounds showed anticonvulsant activity in the following ascending order, **4b**, **4a**, **4c**, **4e** as compared to the normal control and the reference drug.

Acute toxicity test

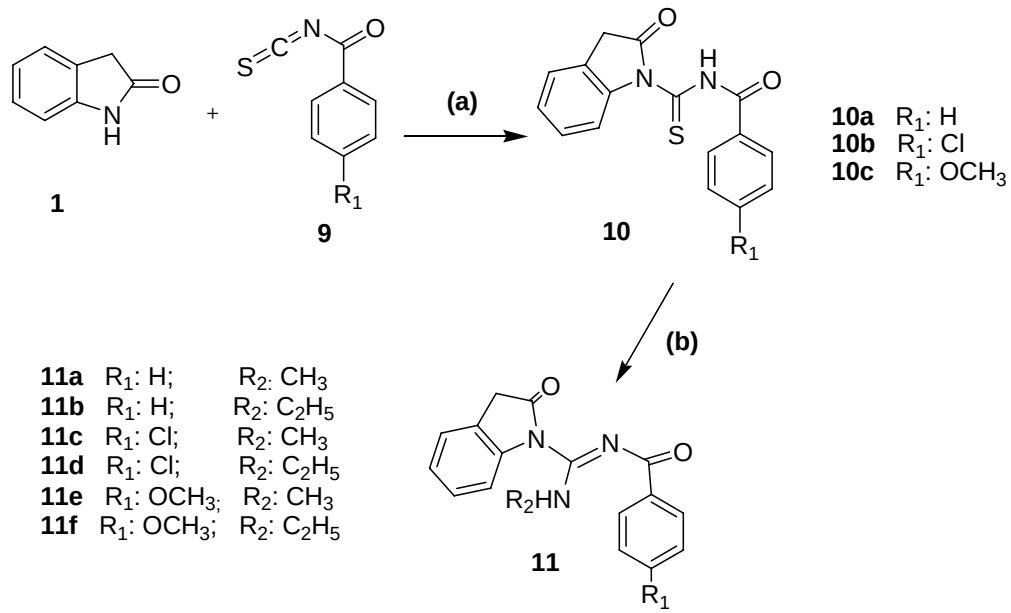
The compounds that showed antipsychotic and anticonvulsant activities were investigated for acute toxicity study (LD_{50}) according to the method of Smith[21]. It was found that, these compounds are safe at the chosen dose (40 mg/ kg).

Structure activity relationships

On studying the relationship between the structures of the tested compounds and the antipsychotic and the anticonvulsant activities, it was found that: Replacement of 4-methyl group (electron donating) as in compounds **7b**, **8c** and **4b** by 4-chloro (electron withdrawing) as in compounds **7a**, **8a** and **4a** gave a substantial increase in the antipsychotic activity. Moreover, the unsubstituted amidine NH_2 enhances the antipsychotic activity and showed significant potentiating for the anticonvulsant activity as found on comparing the activities of compounds **4b**, **4a**, **4d**, by **4c** and **4e** with the activities of other tested compounds.



Scheme 2. (a) Toluene, reflux; (b) PCl_5, reflux; (c) CH_3NH_2 or $C_2H_5NH_2$, CH_2Cl_2, room temp.



Scheme 3. (a) CH_3CN, $0C^o$; (b) CH_3NH_2 or $EtNH_2$, $HgCl_2$, CH_3CN, room temp.

It was also found that, the antipsychotic activity decreases by increasing the size of the substituent on the amidine NH_2 as obtained on comparing the activities of both compounds **8a** and **8b**. Furthermore, compounds containing carbonyl group as **4d** are more active than those containing sulfonyl groups as in **4a**. On the other hand, in the carbonyl containing compounds **4d**, **4c** and **4e** which exhibited promising antipsychotic and anticonvulsant, the activity order was maximal with **4e** having 4-methoxy (electron donating), then the 4- unsubstituted **4c** and the least active one is that having the 4-chloro (electron withdrawing), **4d**.

Table 1: Effect of compounds under investigation on foot shock-induced aggression

Compound (40 mg/kg, i.p.)	Latency to fight	Number of fights
DMSO (vehicle)	31.5 ± 8.07	62.66 ± 5.50
Haloperidol	286.64 ± 9.07***	7.67± 1.02***
7b	68.87 ± 9.54*	47.17±5.52 *
8c	67..22 ± 7.21 *	45.50 ± 4.67*
6b	84.17 ± 9.85***	28.33 ± 5.25***
7a	84.50 ± 11.22***	25.83± 1.31***
8a	96.01 ± 9.60***	19.17 ± 3.09***
8b	107.33 ± 7.20***	18.67 ± 2.91***
4b	113.67 ± 10.06***	13.50 ± 1.81***
4a	150.17 ±17.57***	14.83 ±2.26***
4d	161.33 ± 18.75***	11.50± 18.75***
4c	195.31 ± 5.47***	10.60 ± 1.21***
4e	215.67 ± 15.23***	9.34± 2.06***

* P< 0.05, *** P<0.001.

Table 2: Effect of compounds under investigation on D- amphetamine induced stereotyped behaviour in rats

Compound (40 mg/kg, i.p.)	Stereotyped behavior scores
DMSO + d-amphetamine	20.50 ± 1.34
7b	14.17± 0.83*
8c	13.33 ± 0.84 **
6b	12.83± 1.40***
7a	12.17± 1.01***
8a	11.83 ± 1.50***
8b	10.21 ±1.37***
4b	11.34 ± 1.13 ***
4a	8.17 ±1.08 ***
4d	6.50 ± 0.89 ***
4c	5.00± 1.07 ***
4e	4.30 ± 1.20***

* P< 0.05, P >0.01 and *** P<0.001.

Table 3: Effect of compounds under investigation on phenobarbitone induced sleeping time

Compound (40 mg/kg, i.p.)	Induction of sleeping time (min)	Sleeping time (min)
DMSO (vehicle)	44.50 ± 2.80	117.83± 4.57
Haloperidol	7.17± 1.54***	292.67± 8.34***
7b	29.17 ± 2.52***	151.67±11.11
8c	26.67 ± 1.80 ***	199.17±3.98***
6b	25.00± 2.30***	224.00 ±4.07***
7a	24.17± 1.66***	231.21± 7.65***
8a	21.00 ± 1.18***	235.11± 8.25***
8b	18.67 ± 1.45***	237.18± 9.25***
4b	15.17 ± 1.14***	256.17 ± 10.54***
4a	12.33 1.20***	268.00± 7.21***
4d	10.66 ± 1.63***	256.50± 12.49***
4c	9.50 ± 0.76***	283.33± 3.20***
4e	8.33± 1.31***	288.67± 3.44***

*** P<0.001

Table 4: Effect of compounds under investigation on the maximal electroshock (MES) seizure test

Compound no.	MES (% seizure protection)
Vehicle (DMSO)	0
Phenytoin (30 mg/kg)	90***
4b	50*
4a	70***
4d	60**
4c	80***
4e	90***

* P< 0.05, P >0.01 and *** P<0.001.

CONCLUSION

We have successfully synthesized a series of 1-substituted oxindole derivatives, and screened them for their antipsychotic and anticonvulsant activities. The pharmacological studies showed that compounds **7b**, **8c**, **6b**, **8a** and **8b** showed good antipsychotic activity, but did not exhibit any anticonvulsant response. On the other hand, compounds **4b**, **4a**, **4d**, **4c** and **4e** showed good antipsychotic and anticonvulsant activities as compared to the other tested compounds and the reference drugs. It is also found that, both compounds **4c** and **4e** exhibited the most promising antipsychotic and anticonvulsant activities as compared to other tested compounds.

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