Digest Journal of Nanomaterials and Biostructures Vol. 5, No 4, August 2010, p. 739 – 747

SYNTHESIS, PHARMACOLOGICAL EVALUATION AND QSAR STUDY OF 6-[3-(4-SUBSTITUTED PHENYLPIPERAZIN-1-YL)PROPOXY]BENZO[*D*][1,3] OXATHIOL-2-ONES AS POTENTIAL ANTIPSYCHOTICS

RADHA CHARAN DASH, SHARAD H. BHOSALE*, KAKASAHEB R. MAHADIK

Department of Pharmaceutical Chemistry, Bharati Vidyapeeth Deemed University, Poona College of Pharmacy, Pune-411038, India. Tel: +91-9011032735

In a search towards new and efficient agents to treat mental disorders such as schizophrenia 6-[3-(4-substitutedphenylpiperazin-1-l)propoxy]benzo[*d*][1,3]oxathiol-2-ones were designed, synthesized and evaluated *in vivo* for their ability to inhibit apomorphine induced climbing behaviour and inhibition of 5-HTP induced head twitches representing antidopaminergic and antiserotonergic action respectively in albino mice. The pharmacological screening revealed that the compounds 6-(3-(4-(2,3-dichlorophenyl)piperazin-1-l)propoxy)benzo[*d*][1,3]oxathiol-2-one **3l** and 6-(3-(4-(2,3-dimethylphenyl)piperazin-1-yl)propoxy)benzo[*d*] [1,3]oxathiol-2-one **3n** showed better antipsychotic potential with lower potency of catalepsy induction. To understand the structural activity relationship QSAR model was generated for antipsychotic activity. The resulting study produced highly predictive model that comprised various descriptors like dip^2/V, WPSA. These descriptors highlight the important characteristic of antipsychotic potential of title compounds in relation to affinity towards target through electrostatic and steric interaction.

(Received July 12, 2010; accepted August 31, 2010)

Keywords: Antipsychotic; 6-(3-(4-substitutedphenylpiperazin-1-l)propoxy)benzo[*d*] [1,3]oxathiol-2-one, Climbing behavior, Head twitches, catalepsy, QSAR.

1. Introduction

Schizophrenia describes a mental disorder characterised by impairments in the perception or expression of reality, most commonly manifested as auditory hallucinations and paranoid or bizarre delusions, and significant social or occupational dysfunction [1]. The symptoms related to schizophrenia are characterized by the presence of “positive symptoms" (or “productive”) which include mostly auditory hallucinations, delusions, disorganised thoughts and "negative symptoms" (or “deficit”) include alogia, inability to experience pleasure and social withdrawal [2]. Various classical or typical antipsychotics like chlorpromazine, fluphenazine, and haloperidol block the postsynaptic dopaminergic transmission in the mesolimbic and prefontal cortex regions of the brain which is thought to be responsible for alleviating positive symptoms [3]. Blocking of dopaminergic transmission in midbrain is involved in extrapyramidal side effect (EPS) [4], tardive dyskinesia and hyperprolactinemia [5]. The second generation or atypical antipsychotics such as clozapine, risperidone, olanzapine, and ziprasidone block both dopaminergic as well as serotonergic transmission and alleviate both positive and negative symptoms of the disorder [6]. The blocking of serotonergic transmission has inhibitory influence on dopaminergic neurons at the level of the midbrain (substantia nigra and ventral tegumental area), the terminal regions of the nigrostriatal and mesocortical dopaminergic pathways [7]; on the contrary it gives positive influence on dopaminergic tone in the medial prefrontal cortex [8].

* Corresponding author: dr_shbhosale@rediffmail.com / drbhosalesh@gmail.com.

Although, several classes of atypical antipsychotics are currently being used, their clinical limitations and adverse effects such as weight gain, blood dyscrasias, hyperglycemia, agranulocytosis etc. are forcing development of efficient and safe drugs for treatment of psychosis [9,10,11].

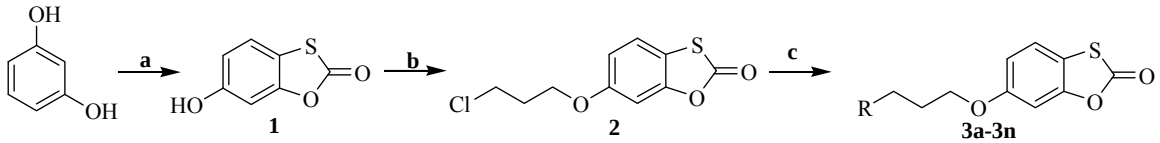
Previously we have investigated a series of 6-(3-substitutedpropoxyl)benzo [*d*][1,3]oxathiol-2-ones as centrally acting antipsychotics [12]. However, these compounds induced mild to severe catalepsy. In order to reduce catalepsy induction, here the design was based on coupling structural moieties benzo[d]oxathiol-2-one and aryl piperazines (in place of amines and phenols) via an alkyl linker in order to balance dopaminergic and serotonergic neurotransmission. Rationale for selecting arylpiperazines was their reported anti-serotonergic activity with decreased induction of EPS [13,14]. This dual pharmacological profile along with catalepsy studies should lead, in principle to a rapid and pronounced treatment of schizophrenia.

2. Experimental section

Chemistry

The melting points were determined by open capillary method on Veego VMP-D digital melting point apparatus and are uncorrected. The IR spectra of synthesised compounds were recorded on Jasco FT-IR 4100 in potassium bromide. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on NMR Varian Mercury plus 300 MHz using tetramethyl silane (TMS) in $CDCl_3$as internal standard for ^{1}H-NMR. Electron spray ionization mass spectra were recorded on Varian 410 prostar binary LC with 500MS IT PDA detector. Elemental analyses indicated by the symbols of the elements were within ±0.4% of the theoretical values. The completion of reaction was monitored by thin layer chromatography performed on precoated silica gel F_{254} plates.

All the target compounds were converted to water soluble hydrochloride salts for evaluation of pharmacological activity. The various derivatives synthesised are illustrated in **Table 1**.



Scheme 1 Synthetic protocol of title compounds a. KSCN, $CuSO_4$, H_2O; 10% HCl; b. bromochloropropane, K_2CO_3; c. K_2CO_3, CH_3CN, aryl piperazines

6-hydroxybenzo[*d*][1,3]oxathiol-2-one 1

6-hydroxybenzo[*d*][1,3]oxathiol-2one **1** was prepared as described in literature [15]. Solution of potassium thiocyanate (0.41mol) in water (25 mL) was added while stirring to a solution of resorcinol (0.1 mol) and crystallized copper sulfate (0.15 mol) in water (125 mL) at room temperature. The black cupric thiocyanate formed became colorless after a short time, which indicated that the introduction of thiocyanogen is terminated. The cupric thiocyanate was removed by filtering with suction and then washed with water and the filtrate was mixed with 2N sodium carbonate solution (25 mL), to yield the imino-thiocarbonate of resorcinol as colorless crystals. A 10% solution of the imino-thiocarbonate of resorcinol in 10% hydrochloric acid was heated for 15 minutes on the steam bath. The thiocarbonate free from nitrogen separated on cooling as fine crystals. The residue was recrystallized from methanol to furnish **1**.

Yield: 89%. mp: 158^{0}C. Molecular formula: $C_7H_4O_3S$ (168). % Elemental Analysis : Calcd. C, 49.99; H, 2.40; O, 28.54; S, 19.07. Found C, 49.78; H, 2.36; O, 28.59; S, 19.27. IR ν_{max} (cm^{-1}) (KBr): 3410, 3016, 1700, 1215, 1030. ^{1}H-NMR (δ ppm; $CDCl_3$)**:** 6.8 (s, 1H, C_7-H), 6.73 (d, 2H, C_4-H and C_5-H), 5.21 (s, 1H, OH).

6-(3-chloropropoxyl)benzo[*d*][1,3]oxathiol-2-one 2

A mixture of **1** (0.017 mol), 1-bromo-3-chloropropane (0.025 mol) and anhydrous K_2CO_3 (0.025 mol) in acetonitrile was refluxed for 24 h. The solvent was removed under vacuum. The residue was dissolved in methylene dichloride and the organic layer was washed with water and later with

5% NaOH solution. Further it was washed with water and dried overnight on anhydrous sodium sulfate. Methylene dichloride was removed under vacuum to afford residue. The residue was recrystallized from ethanol to furnish **2**.

Yield: 63%. mp: 72-74˚C. Molecular formula: $C_{10}H_9ClO_3S$ (244). % Elemental Analysis : Calcd. C, 49.08; H, 3.71; Cl, 14.49; O, 19.62; S, 13.10. Found C, 49.28; H, 3.59; Cl, 14.41; O, 19.43; S, 13.23. IR ν_{max} (cm^{-1})(KBr):3040, 2979, 1734, 1471, 1150, 1035. ^{1}H-NMR (δ ppm; $CDCl_3$): 6.8 (s, 1H, C_7-H), 6.73 (d, 2H, C_4-H and C_5-H), 4.15 (t, 2H, -OCH_2.), 3.80 (t, 2H, -CH_2Cl), 2.24 (m, 2H, -CH_2-).

2.2.3 General method for synthesis of compounds 3a-3n

A mixture of **2** (0.005 mol), arylpiperazine (0.005 mol) and anhydrous K_2CO_3 (0.005 mol) was added to the reaction flask and refluxed in acetonitrile for 6-10h. The reaction mixture was filtered and the filtrate was concentrated under vacuum. The residue was dissolved in methylene dichloride. The organic layer was then washed with water and dried overnight on anhydrous sodium sulphate. Methylene dichloride was removed under vacuum to afford residue. The residue was then recrystallized from methanol to yield the desired compound **3a-3n**.

2.2.3.1 6-(3-(4-phenylpiperazin-1-yl)propoxy)benzo[*d*][1,3]oxathiol-2-one 3a

Yield: 65%. mp: 111-113 ˚C. Molecular formula: $C_{20}H_{22}N_2O_3S$ (370). % Elemental Analysis: Calcd. C, 64.84; H, 5.99; N, 7.56; O, 12.95; S, 8.66; Found C, 64.59; H, 6.13; N, 7.67; O, 13.07; S, 8.54. IR ν_{max} (cm^{-1})(KBr):3019, 2930, 1722, 1424, 1163, 1027. ^{1}H-NMR (δ ppm; $CDCl_3$): 7.52-6.76 (m, 8H, ArH), 4.13 (t, 2H, -OCH_2-), 3.27 (t, 4H, -CH_2-N-CH_2-), 2.69 (t, 6H, -CH_2-N(CH_2-)CH_2-), 2.19 (m, 2H, -CH_2-).^{13}C-NMR (δ; $CDCl_3$): 171.11, 151.68, 149.34, 147.46, 131.09, 130.72, 129.13, 118.38, 115.41, 111.31, 110.48, 67.62, 54.53, 52.49, 48.22, 28.19. MS (ESI):*m/z* 371.3 (M+ H^+).

6-(3-(4-o-tolylpiperazin-1-yl)propoxy)benzo[*d*][1,3]oxathiol-2-one 3b

Yield: 56%. mp:133-135 ˚C. Molecular formula: $C_{21}H_{24}N_2O_3S$ (384). % Elemental Analysis : Calcd. C, 65.60; H, 6.29; N, 7.29; O, 12.48; S, 8.34. Found C, 65.48; H 6.37; N, 7.22; O, 12.61; S, 8.32. IR ν_{max} (cm^{-1})(KBr):3024, 2941, 1734, 1418, 1173, 1033. ^{1}H-NMR (δ ppm; $CDCl_3$): 7.56-6.74 (m, 7H, ArH), 4.11 (t, 2H, -OCH_2-), 3.24 (t, 4H, -CH_2-N-CH_2-), 2.75 (t, 6H, -CH_2-N(CH_2-)CH_2-), 2.33 (s, 3H, CH_3), 2.17 (m, 2H, -CH_2-).^{13}C-NMR(δ; $CDCl_3$): 171.09, 151.35, 149.31, 146.55, 130.84, 130.61, 129.21, 126.73, 117.41, 114.98, 111.24, 111.01, 109.29, 67.52, 54.81, 51.56, 48.42, 28.15, 14.27. MS (ESI):*m/z* 385.21 (M+ H^+).

6-(3-(4-m-tolylpiperazin-1-yl)propoxy)benzo[*d*][1,3]oxathiol-2-one 3c

Yield: 59%. mp:147-149 ˚C. Molecular formula: $C_{21}H_{24}N_2O_3S$ (384). % Elemental Analysis : Calcd. C, 65.60; H, 6.29; N, 7.29; O, 12.48; S, 8.34. Found C, 65.73; H, 6.14; N, 7.38; O, 12.31; S, 8.44.IR ν_{max} (cm^{-1})(KBr):3029, 2939, 1731, 1419, 1177, 1022. ^{1}H-NMR (δ ppm; $CDCl_3$): 7.54-6.70 (m, 7H, ArH), 4.10 (t, 2H, -OCH_2-), 3.33 (t, 4H, -CH_2-N-CH_2-), 2.74 (t, 6H, -CH_2-N(CH_2-)CH_2-), 2.37 (s, 3H, CH_3), 2.15 (m, 2H, -CH_2-).

6-(3-(4-p-tolylpiperazin-1-yl)propoxy)benzo[*d*][1,3]oxathiol-2-one 3d

Yield: 59%. mp:150-152 ˚C. Molecular formula: $C_{21}H_{24}N_2O_3S$ (384). % Elemental Analysis : Calcd. C, 65.60; H, 6.29; N, 7.29; O, 12.48; S, 8.34. Found C, 65.34; H, 6.49; N, 7.41; O, 12.25; S, 8.51.IR ν_{max} (cm^{-1})(KBr):3035, 2941, 1730, 1417, 1174, 1030. ^{1}H-NMR (δ ppm; $CDCl_3$): 7.54-6.73 (m, 7H, ArH), 4.13 (t, 2H, -OCH_2-), 3.29 (t, 4H, -CH_2-N-CH_2-), 2.78 (t, 6H, -CH_2-N(CH_2-)CH_2-), 2.39 (s, 3H, CH_3), 2.16 (m, 2H, -CH_2-).

6-(3-(4-(2-chlorophenyl)piperazin-1-yl)propoxy)benzo[*d*][1,3]oxathiol-2-one 3e

Yield: 63%. mp:148-150 ˚C. Molecular formula: $C_{20}H_{21}ClN_2O_3S$ (405). % Elemental Analysis : C, 59.33; H, 5.23; Cl, 8.76; N, 6.92; O, 11.85; S, 7.92. Found C, 59.22; H, 5.10; Cl, 8.99; N, 6.96; O, 11.80; S, 7.93; IR ν_{max} (cm^{-1})(KBr):3019, 2930, 1724, 1424, 1163, 1027. ^{1}H-NMR (δ ppm; $CDCl_3$): 7.51-6.72 (m, 7H, ArH), 4.14 (t, 2H, -OCH_2-), 3.27 (t, 4H, -CH_2-N-CH_2-), 2.60 (t, 6H, -CH_2-N(CH_2-)CH_2-), 2.15 (m, 2H, -CH_2-). ^{13}C-NMR(δ; $CDCl_3$): 171.14, 151.38, 149.27, 146.51, 130.89, 130.66, 129.34, 126.76, 117.59, 115.25, 111.79, 111.24, 109.37, 67.47, 54.79, 51.61, 48.49, 28.21. MS (ESI):*m/z* 406(M+ H^+), 407.41(M+2 H^+).

6-(3-(4-(3-chlorophenyl)piperazin-1-yl)propoxy)benzo[*d*][1,3]oxathiol-2-one 3f

Yield: 66%. mp:139-141˚C. Molecular formula: $C_{20}H_{21}ClN_2O_3S$ (405). %Elemental Analysis : Calcd. C, 77.60; H, 6.78; N, 11.31; O, 4.31. Found C, 61.27; H, 6.78; N, 4.69; O, 16.48; S, 10.78. IR ν_{max} (cm^{-1})(KBr):3014, 2927, 1727, 1420, 1159, 1024. ^{1}H-NMR (δ ppm; $CDCl_3$): 7.52-6.67 (m,

7H, ArH), 4.19 (t, 2H, -OC$\underline{H}_2$-), 3.28 (t, 4H, -C$\underline{H}_2$-N-C$\underline{H}_2$-), 2.55 (t, 6H, -C$\underline{H}_2$-N(C$\underline{H}_2$-)C$\underline{H}_2$-), 2.19 (m, 2H, -C$\underline{H}_2$-).

6-(3-(4-(4-chlorophenyl)piperazin-1-yl)propoxy)benzo[*d*][1,3]oxathiol-2-one 3g

Yield: 61%. mp:143-145 ˚C. Molecular formula: $C_{20}H_{21}ClN_2O_3S$ (405). % Elemental Analysis : C, 59.33; H, 5.23; Cl, 8.76; N, 6.92; O, 11.85; S, 7.92. Found C, 59.47; H, 5.08; Cl, 8.89; N, 7.03 O, 11.52; S, 8.01.IR ν_{max} (cm^{-1})(KBr):3022, 2926, 1722, 1431, 1161, 1020. ^{1}H-NMR (δ ppm; $CDCl_3$): 7.55-6.76 (m, 7H, ArH), 4.21 (t, 2H, -OC$\underline{H}_2$-), 3.19 (t, 4H, -C$\underline{H}_2$-N-C$\underline{H}_2$-), 2.51 (t, 6H, -C$\underline{H}_2$-N(C$\underline{H}_2$-)C$\underline{H}_2$-), 2.21 (m, 2H, -C$\underline{H}_2$-).

6-(3-(4-(2-methoxyphenyl)piperazin-1-yl)propoxy)benzo[*d*][1,3]oxathiol-2-one 3h

Yield: 51%. mp:154-156 ˚C. Molecular formula: $C_{21}H_{24}N_2O_4S$ (400). % Elemental Analysis : Calcd. C, 62.98; H, 6.04; N, 6.99; O, 15.98; S, 8.01. Found C, 62.84; H, 5.91; N, 7.13; O, 15.94; S, 8.18. IR ν_{max} (cm^{-1})(KBr):3027, 2921, 1729, 1419, 1155, 1021. ^{1}H-NMR (δ ppm; $CDCl_3$): 7.55-6.76 (m, 7H, ArH), 4.15 (t, 2H, -OC$\underline{H}_2$-), 3.84 (s, 3H, -OC$\underline{H}_3$), 3.21 (t, 4H, -C$\underline{H}_2$-N-C$\underline{H}_2$-), 2.54 (t, 6H, -C$\underline{H}_2$-N(C$\underline{H}_2$-)C$\underline{H}_2$-), 2.20 (m, 2H, -C$\underline{H}_2$-). ^{13}C-NMR(δ; $CDCl_3$): 171.14, 151.38, 149.27, 146.51, 130.89, 130.66, 129.34, 126.76, 117.59, 115.25, 111.79, 111.24, 109.37, 67.47, 54.79, 51.61, 48.49, 28.21.MS (ESI):*m/z* 401.62(M^+ H^+).

6-(3-(4-(4-methoxyphenyl)piperazin-1-yl)propoxy)benzo[*d*][1,3]oxathiol-2-one 3i

Yield: 49%. mp:165-167 ˚C. Molecular formula: $C_{21}H_{24}N_2O_4S$ (400). % Elemental Analysis : Calcd. C, 62.98; H, 6.04; N, 6.99; O, 15.98; S, 8.01. Found C, 62.79; H, 6.19; N 7.10; O, 15.75; S, 8.17. IR ν_{max} (cm^{-1})(KBr):3033, 2919, 1734, 1419, 1157, 1030. ^{1}H-NMR (δ ppm; $CDCl_3$): 7.51-6.77 (m, 7H, ArH), 4.17 (t, 2H, -OC$\underline{H}_2$-), 3.88 (s, 3H, -OC$\underline{H}_3$), 3.21 (t, 4H, -C$\underline{H}_2$-N-C$\underline{H}_2$-), 2.57 (t, 6H, -C$\underline{H}_2$-N(C$\underline{H}_2$-)C$\underline{H}_2$-), 2.17 (m, 2H, -C$\underline{H}_2$-).

6-(3-(4-(4-flurophenyl)piperazin-1-yl)propoxy)benzo[*d*][1,3]oxathiol-2-one 3j

Yield: 53%. mp:135-137 ˚C. Molecular formula: $C_{20}H_{21}FN_2O_3S$ (388). % Elemental Analysis : C, 61.84; H, 5.45; F, 4.89; N, 7.21; O, 12.36; S, 8.25. Found C, 61.72; H, 5.33; F, 5.03; N, 7.14; O, 12.35; S, 8.43. IR ν_{max} (cm^{-1})(KBr):3039, 2915, 1730, 1417, 1153, 1027. ^{1}H-NMR (δ ppm; $CDCl_3$): 7.51-6.77 (m, 7H, ArH), 4.11 (t, 2H, -OC$\underline{H}_2$-), 3.24 (t, 4H, -C$\underline{H}_2$-N-C$\underline{H}_2$-), 2.59 (t, 6H, -C$\underline{H}_2$-N(C$\underline{H}_2$-)C$\underline{H}_2$-), 2.19 (m, 2H, -C$\underline{H}_2$-). MS (ESI):*m/z* 389.73 (M+ H^+).

6-(3-(4-(3-trifluromethylphenyl)piperazin-1-yl)propoxy)benzo[*d*][1,3] oxathiol -2-one 3k

Yield: 55%; mp:135-136 ˚C. Molecular formula: $C_{21}H_{21}F_3N_2O_3S$ (438). % Elemental Analysis : Calcd. CC, 57.52; H, 4.83; F, 13.00; N, 6.39; O, 10.95; S, 7.31; Found C, 57.36; H, 4.93; F, 13.11; N, 6.23; O, 10.95; S, 7.42. IR ν_{max} (cm^{-1})(KBr):3027, 2917, 1736, 1419, 1158, 1021. ^{1}H-NMR (δ ppm; $CDCl_3$): 7.57-6.76 (m, 7H, ArH), 4.15 (t, 2H, -OC$\underline{H}_2$-), 3.75 (s, 3H, C$\underline{H}_3$), 3.21 (t, 4H, -C$\underline{H}_2$-N-C$\underline{H}_2$-), 2.57 (t, 6H, -C$\underline{H}_2$-N(C$\underline{H}_2$-)C$\underline{H}_2$-), 2.20 (m, 2H, -C$\underline{H}_2$-).

6-(3-(4-(2,3-dichlorophenyl)piperazin-1-yl)propoxy)benzo[*d*][1,3] oxathiol-2-one 3l

Yield: 61%. mp:149-152 ˚C. Molecular formula: $C_{20}H_{20}Cl_2N_2O_3S$ (439). % Elemental Analysis : Calcd. C, 54.67; H, 4.59; Cl, 16.14; N, 6.38; O, 10.92; S, 7.30. Found C, 54.83; H, 4.41; Cl, 16.34; N, 6.51; O, 11.25; S, 7.63. IR ν_{max} (cm^{-1})(KBr):3034, 2922, 1732, 1421, 1136, 1027. ^{1}H- NMR (δ ppm; $CDCl_3$): 7.59-6.76 (m, 6H, ArH), 4.13 (t, 2H, -OC$\underline{H}_2$-), 3.16 (t, 4H, -C$\underline{H}_2$-N-C$\underline{H}_2$-), 2.64 (t, 6H, -C$\underline{H}_2$-N(C$\underline{H}_2$-)C$\underline{H}_2$-), 2.18 (m, 2H, -C$\underline{H}_2$-). MS (ESI):*m/z* 440(M+ H+), 441.23[(M+ H^+) + 1].

6-(3-(4-(3,4-dichlorophenyl)piperazin-1-yl)propoxy)benzo[*d*][1,3]oxathiol-2-one 3m

Yield: 64%. mp:156-158 ˚C. Molecular formula: $C_{20}H_{20}Cl_2N_2O_3S$ (439). % Elemental Analysis : Calcd. C, 54.67; H, 4.59; Cl, 16.14; N, 6.38; O, 10.92; S, 7.30; Found C, 54.59; H, 4.67; Cl, 16.27; N, 6.31; O, 10.67; S, 7.43. IR ν_{max} (cm^{-1})(KBr): 3031, 2918, 1737, 1430, 1134, 1029. ^{1}H-NMR (δ ppm; $CDCl_3$): 7.55-6.74 (m, 6H, ArH), 4.11 (t, 2H, -OC$\underline{H}_2$-), 3.23 (t, 4H, -C$\underline{H}_2$-N-C$\underline{H}_2$-), 2.61 (t, 6H, -C$\underline{H}_2$-N(C$\underline{H}_2$-) C$\underline{H}_2$-), 2.18 (m, 2H, -C$\underline{H}_2$-).

6-(3-(4-(2,3-dimethylphenyl)piperazin-1-yl)propoxy)benzo[*d*] [1,3]oxathiol-2-one 3n

Yield: 59%. mp:126-128 ˚C.Molecular formula: $C_{22}H_{26}N_2O_3S$ (398). % Elemental Analysis : Calcd C, 66.30; H, 6.58; N, 7.03; O, 12.04; S, 8.05; Found C C, 66.30; H, 6.58; N, 7.03; O, 12.04; S, 8.05. IR ν_{max} (cm^{-1})(KBr):3025, 2921, 1731, 1429, 1140, 1018. ^{1}H-NMR (δ ppm; $CDCl_3$): 7.58-6.77 (m, 6H, ArH), 4.18 (t, 2H, -OC$\underline{H}_2$-), 3.27 (t, 4H, -C$\underline{H}_2$-N-C$\underline{H}_2$-), 2.57 (t, 6H, -C$\underline{H}_2$-N(C$\underline{H}_2$-)C$\underline{H}_2$-),2.22 (m, 2H, -C$\underline{H}_2$-), 2.19(s,, 3H, -CH_3), 2.11(s, 3H, -C$\underline{H}_3$).

Pharmacological Activity

Experimental groups

Institutional Animal Ethics Committee, Poona College of Pharmacy, approved all animal experiments and all the experiments involved in this work were performed in accordance with CPCSEA guidelines for the use and care of experimental animals. Only adult male albino mice procured from Serum Institute of India, Pune (weighing in the range of 20-25 g) were selected for the purpose of experiment. The animals were kept in suitable laboratory environment (22 ± 2 ^{0}C with 12hr light/dark cycle) and feed ad libitum with standard food pellet. Animals were divided in to three groups; control, test and standard group, each with 6 animals. All the doses were calculated in terms of mg/kg of the animals and dissolved in water for injection (WFI). Aripiprazole and clozapine were taken as standard.

Inhibition of apomorphine induced mesh climbing behavior

The relative antipsychotic potential of the compounds has been determined on the basis of this test. As apomorphine acts as agonist for dopamine receptor, after administration of apomorphine animal climbs up the walls of the cylinder. Climbing behavior was assessed in the animals by placing them individually in cylindrical wire mesh cage (height 18 cm, diameter 14 cm) 5 min. after administering apomorphine (1mg/kg, s.c.).Test or standard compound was given 30 min before administration (15mg/kg, i.p.) of apomorphine while animals in control group receive WFI and remained on the floor of the cylinder. Climbing behavior was assessed at 5-min intervals for 30 min, starting from 5 min after apomorphine administration [16].

Antagonism of 5-HTP induced Head Twitches

Antagonism of head twitches induced by L-5-hydroxytryptophan (5-HTP) in mice indicates anti-serotonergic activity. Each animal in the control group was injected with WFI. After 30 min. the animals were injected with carbidopa solution (25 mg/kg, i.p.) prepared in WFI. It was followed by administration of 5-HTP solution (100 mg/kg, i.v.) after 30 min. The numbers of head twitches were counted for a period of 5 min which was followed by an interval of 5 min. before the next count. Head twitches were counted for a period of 1 h., in same manner [17].

Haloperidol induced catalepsy

It has been noticed that catalepsy in rodent is a model predictive of EPS in human. The animals in the control group were administered with haloperidol (1mg/kg, i.p.), which was taken as a prototype of typical antipsychotic. Assessment of catalepsy was done by gently placing the forepaws of the mice over a metal bar (diameter 2 mm), kept at a height of 2.5cm from the platform, with his hind paws resting on the platform. The evaluation of haloperidol induced catalepsy was done by recording the time span for which the mice retained their forepaws on the horizontal bar during the observation periods of 5 min [18]. The animals in the test group were administered with test drug instead of haloperidol and the remaining procedure for assessment of catalepsy was same as mentioned above.

Statistical analysis

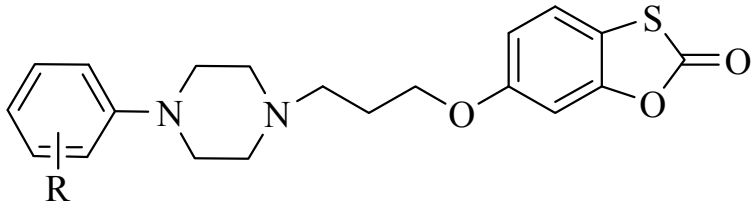
The data obtained from the above studies was analysed to one way analysis of variance (ANOVA) for determining the significant difference between the groups. The inter group significance or post hoc comparison was analysed using Dunnet's t test. P values < 0.05 were considered to be significant. All the values were expressed as percentage inhibition of respective behaviour model relative to control group and depicted in Table 1.

QSAR studies

The 14 derivatives and their corresponding antipsychotic potential was used in this QSAR study. The experimental %inhibition of climbing behavior (EIC) reflects the antipsychotic potential of the synthesized compounds. EIC was converted to Log EIC (LIC) to get the linear relationship in the QSAR equation. All the computational studies were performed using maestro, graphical user interface for Schrodinger suite 2009 [19]. The 3D structure of molecules was built using 'build' module within Schrodinger. The use of reasonably low energy conformation is a useful starting point for the statistical comparisons of flexible structure within the QSAR models because it is thought that low energy conformation is the most stable pose inside body. All the structures were minimized using MacroModel [20] by OPLS_2005 with Powell-Reeves conjugate

gradient convergence criterion of 0.05kcal/mol force field at a maximum of 3500 iteration. A 8 A^0 and 20A^0 cutoff was applied for both van der Waals interactions and electrostatic energies respectively. Physically significant descriptors and pharmaceutically relevant properties were calculated by using QikProp module [21] within Schrodinger suite. To derive QSAR model, the QikProp calculated descriptors were used as independent variables and the LIC as the dependent variables. All the statistical work was done in Strike module [22]. Cross-validated multiple linear regression (MLR) method of leave one out (LOO) was performed to generate QSAR equation. The QSAR equation for antipsychotic potential was evaluated by cross validated correlation coefficient (r^2_{cv}), standard error of estimation (s), Fisher test (F) and correlation coefficient (r^2). The LIC and predicted %inhibition of climbing behavior (PIC) are tabulated in Table 1. The correlation graph between LIC and PIC of the synthesized compounds is depicted in **Fig 1**.

Table 1. In vivo data of the compounds 3a-3n at the dose 15mg/kg in albino mice



Compd.	R	%Inhibition of climbing behavior(EIC)	%Inhibition of head twitches	%catalepsy induction	LIC	PIC
3a	H	20.464	23.367	33.319	1.311	1.334
3b	2-CH_3	32.938	27.096	36.327	1.518	1.439
3c	3-CH_3	28.635	35.180	31.862	1.457	1.442
3d	4-CH_3	25.457	31.536	33.064	1.406	1.426
3e	2-Cl	39.820	25.574	37.369	1.600	1.621
3f	3-Cl	20.338	36.283	30.246	1.308	1.221
3g	4-Cl	17.923	31.326	31.443	1.253	1.287
3h	2-OCH_3	37.844	23.431	37.932	1.578	1.623
3i	4-OCH_3	32.077	19.893	58.391	1.506	1.508
3j	4-F	12.023	25.061	27.648	1.080	1.115
3k	3-CF_3	15.603	43.351	30.343	1.193	1.206
3l	2,3-diCl	36.678	37.679	23.687	1.564	1.538
3m	3,4-diCl	12.480	38.098	23.735	1.096	1.115
3n	2,3-diCH_3	32.870	31.835	28.348	1.517	1.513
Aripiprazole		45.137	58.019	22.514		
Clozapine		48.353	47.943	29.246		

Number of animal, n =6, $p<0.05$, LIC = experimental %inhibition of climbing behavior, PIC = predicted %inhibition of climbing behavior.

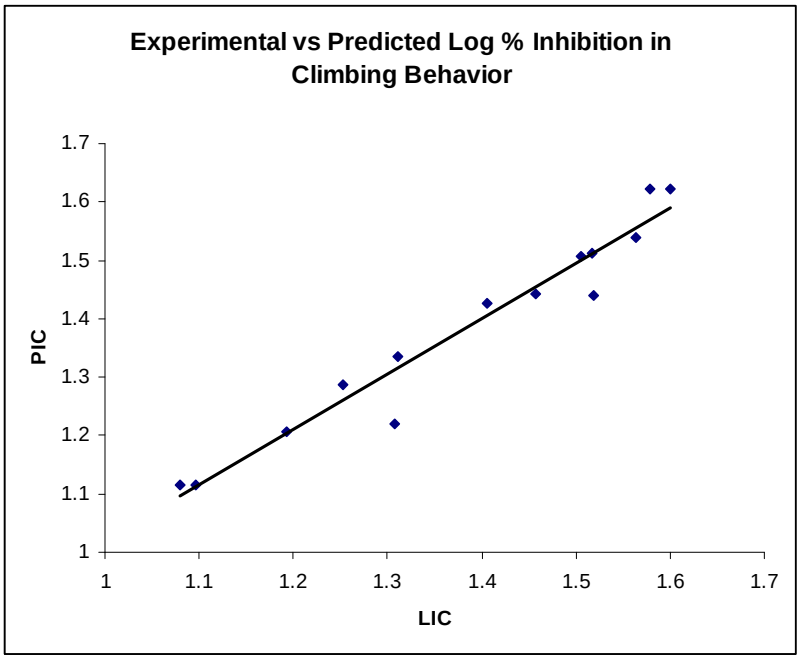


Fig 1. The correlation graph between LIC and PIC

3. Results and discussion

The synthesis of the target compounds was accomplished as shown in **Scheme 1**. 6-Hydroxybenzo[*d*][1,3]oxathiol-2one **1** was prepared as described in literature [15]. 6-(3-chloropropoxyl)benzo[*d*][1,3]oxathiol-2-one **2** was synthesized by refluxing **1** with 1-bromo-3-chloropropane in acetonitrile in presence of K_2CO_3 for 24h. Title compounds **3a-3n** were obtained by refluxing different substituted aryl piperazines with **2** in presence of K_2CO_3 in acetonitrile. Yields of final compounds were in the range of 49-65% after recrystallisation from methanol–water. Structure confirmation of synthesized compounds was done by IR, ^{1}H-NMR, ^{13}C-NMR, MS and elemental analysis. The various derivatives synthesized are illustrated in **Table 1.**

Disappearance of –OH stretching at 3410 cm^{-1} in the IR spectrum and appearance of peak at δ 2.24, 3.80, and 4.15 ppm in the ^{1}H-NMR spectrum and comparison of the melting points conformed the structure of compound **2**. IR spectrum of prototype compound **3a** showed prominent IR absorption bands of aromatic skeleton near 3019 cm^{-1} and a sharp peak at 1772 cm^{-1} for the ester carbonyl group. ^{1}H-NMR of **3a** displayed a multiplet at δ 2.19 for methylene protons (–CH_2-) of the propyl chain. A triplet peak at δ 2.69 corresponded to the four aliphatic protons of piperazines ring and two methylene protons of the propyl chain attached to it. Further a triplet peak at δ 3.27 was seen for four methylene protons of the piperazine ring. The two protons of the –OCH_2 group appeared as a triplet at δ 4.13. The eight protons of the aromatic exhibited multiplets at δ 6.76-7.52. The ^{13}C-NMR of **3a** showed peak at 28.19, 48.22, and 52.49 due to the three aliphatic carbons of propyl chain. While the two peaks at δ 54.53, 67.62 were observed for the four aliphatic carbons of piperazine ring. Peaks for twelve carbons in the aromatic region δ 110.48-151.68 underlined the presence of required aromatic skeleton. The ^{13}C-NMR spectrum indicated presence of carbonyl carbon with a peak at δ 171.11. Finally the structure of **3a** was confirmed by ESI MS, which showed the molecular ion peak *m/z* 371.3 (M+ H^+).

All the target compounds were converted to water soluble hydrochloride salts for pharmacological evaluation. Male Swiss albino mice were used for pharmacological evaluation. The preliminary antipsychotic profile of the synthesized compounds was evaluated by inhibition of apomorphine induced mesh climbing behavior for antipsychotic potential , antagonism of 5-HTP induced head twitches for anti-serotonergic activity and induction of catalepsy for its ability to cause EPS. Doses were selected by initial titration at different dose level. All the values were

expressed as percentage inhibition of respective behaviour model relative to control group and depicted in Table 1.

The aim of the undertaken research work was to make an effort in the direction of synthesizing molecules which would have a capability to reduce the catalepsy. Here we are reporting potential antipsychotic profile of different aryl piperazine derivatives taking compound 6-(3-(4-phenylpiperazin-1-yl)propoxy)benzo[*d*][1,3] oxathiol-2-one **3a**, as our lead compound. Inhibition of apomorphine induced climbing behavior is a direct measure of compound's antipsychotic potential. Compounds having hydrophobic and bulky group at *ortho* position of the aryl moiety as in **3b, 3e, 3h** produced statistically significant reversal of apomorphine induced mesh climbing than at *meta* and *para* position **3c, 3d, 3f, 3g**. Presence of halogen atom with both electronegative and steric properties at *ortho* position of aryl moiety **3e** revealed relatively higher antipsychotic potential activity than other substituent. Substitution on the *meta* position of the aryl ring **3f**, **3k** comparatively has no influence on the antipsychotic potential than **3a**, except **3c**. Further, an appreciable increase in antipsychotic potential was observed in *ortho-meta* di-substituted compounds bearing steric and hydrophobic moieties as in **3l** and **3n**. Introduction of halogen atoms at *para* position of the aryl ring i.e. **3g, 3h** almost suppressed the antipsychotic potential.

In the absence of *in vitro* binding assays the binding of our molecules to specific serotonin receptors could not be ascertained. However from the literature it is known that serotonergic neurotransmission has positive influence on dopaminergic tone in the medial prefrontal cortex and reduce EPS. So the inhibition of 5-HTP induced head twitches model was selected in order to assess the antiserotonergic activity of the compounds. The 5-HTP induced head twitches study of the compounds revealed that substitution at *meta* position of aryl ring **3c, 3f, 3k** enhanced activity compared to substituent at other positions. Presence of bulky or electron rich moiety at *para* position of aryl ring **3d**, **3g** has better antagonism of 5-HTP induced head twitches than substitution at *ortho* position **3b**, **3e**. Replacement of methyl group with more bulky group like methoxy **3h**, **3i** decreases the activity. Presence of halogens at both *ortho* and *meta* **3l**, **3n** position of the aryl ring shows better antagonism of 5-HTP induced head twitches than methyl groups.

The catalepsy induction of all the synthesized compounds could not be interpreted logically since catalepsy induction is a result of interplay of ligand receptor interactions. However it is seen that di substituted compound **3l**, **3m**, and **3n** exhibit minimum catalepsy induction comparable with aripiprazole and clozapine.

The QSAR result for antipsychotic potential produce highly predictive models that having goodness of fit 0.9489. The two best descriptors selected on the basis of importance in biological activity are square of the dipole moment divided by the molecular volume (dip^2/V) and weakly polar component of the total solvent accessible surface area (WPSA).

The statistically significant equation derived was as follows:

$EIC = 1.8285 (\pm 0.0340) - 2.8430(\pm 2.2808)\ dip^2/V + 0.0068((\pm 0.0006)\ WPSA$

N (number of compounds) = 14, $r^2_{cv} = 0.9223$, $r^2 = 0.9489$, F = 102.1, s = 0.0438

From the above equation we concluded that dip^2/V contributed more in the above QSAR equation than WPSA which means electron density distribution and volume in molecule play a vital role in antipsychotic potential activity. As it negatively correlates with the biological activity presence of electron withdrawing group having comparatively larger volume decreases the antipsychotic potential. It explains the activity of compounds **4k, 4m** as both contain large volume of electrostatic surface but having less dipole and vice-versa with compound **4l**. The second parameter WPSA contributed relatively less in the above QSAR but as it positively correlates with biological activity. Also it interprets the activity of compounds **4l** and **4n**. As compound **4l** contain halogen it has more polar component of the total solvent accessible surface area than the **4n**.

4. Conclusions

On the basis of above observation, it could be said that many of the synthesized compounds have considerable antipsychotic potential. The analogous **3l** and **3n,** which have unique antipsychotic potential and anti-serotonergic activity with lower potency of catalepsy

induction, were identified as potential antipsychotic compounds. The QSAR information can be used for better development of potential antipsychotic agents.

Acknowledgements

The authors are thankful to AICTE, New Delhi for providing financial support for this research work. Authors acknowledge assistance of Serum Institute of India, Pune for providing animals for pharmacological studies and Indian Institute of Technology-Bombay, Mumbai for carrying out spectral analysis.

References

[1] N. C.Andreasen, Brain Res. Rev. **31**, 106 (2000).
[2] B.Capuano, I. T. Crosby, E. Lioyd, J. Curr. Med. Chem. **9**, 521 (2002).
[3] R. R. J Lewine, L. Rogg, H. Y. Meltzer, Schizophr.Bull. **9**, 368 (1983).
[4] D. E.Casey, Clin. Psychopharmacol. **10,** 105 (1995).
[5] A.Wieck, P. Haddad, Brit. Med. J. **324**, 250 (2002).
[6] H. Y. Meltzer, S. Matsubaras, J. Lee, C. Psychopharmacol. Bull. 1989, 25, 390.
[7] S.Kapur, G. Remington, Am. J. Psychiat. **042**, 355 (1987).
[8] M. Naughton, J. B. Mulrooney, B. E. Leonard, Hum. Psychopharmacol. Clin. Exp. **15**, 397 (2000).
[9] D. A.Wirshing, W. C. Wirshing, L. Kysar, M. A. Berisford, D. Goldstein, J. Pashdag, J. Mintz, S. R. Marder, J. Clin. Psychiatry. **60**, 358 (1999).
[10] J. A. Lieberman, C. A. Johns, J. M. Kane, K. Rai, A. V. Pisciotta, B. L. Saltz, A. Howard, J. Clin. Psychiatry. **49**, 271 (1988).
[11] J. A. Lowe, T. F Seeger, A. A. Nagel, H. R. Howard, P. A. Seymour, J. H. Heym, F. E. Ewing, M. E. Newman, A. W. Schmidt, J. S. Furman, L. A. Vincent, P. R. Maloney, G. L. Robinson, L. S. Reynolds, F. J. Vinick, J. Med. Chem. **34**, 1860 (1991).
[12] R. C. Dash, M. R. Suryawanshi, S. M. Shelke, S. H. Bhosale, K. R. Mahadik, Med. Chem. Res. DOI 10.1007/s00044-009-9278-5.Accepted and to be published in Medicinal Chemistry Research.
[13] E. M. Gregory, J. Robert, J. Elgin, R. M. Joanne, B. D. Coralie, M. K. James, J. B. William, P. S. Richard, L. D. Deena, L. F. Cynthia, K. S. Malcom, J. Med. Chem. **32**, 1052 (1989).
[14] B. Stefaia, G. Sandra, C. Giuseppe, F. Silva, T. Francesco, B. Marianna, C. Nicoletta, R. Sindu, S. C. Salvatore, B. Matteo, D. A. Mari, B. Marghrerita, N. Vitoi, F. Isabella, N. Ettore, C. Alfredo, M. Tiziana, S. N. Karin, T. A. Jesper, S. K. Jorgan, D. M. Jens, F. Caterina, J. Med. Chem. **52**, 151 (2009).
[15] G. Werner, US Patent No. 2332418, 1943.
[16] S. R. Kesten, T. G. Heffner, S. J. Johnson, T. A. Pugsley, J. L. Wright, G. L. D.Wise J. Med. Chem. **42**, 3718 (1999).
[17] S. H. Kim, G. S. Rhee, S. Oh, W. K. Park, Behav. Brain. Res. **100**, 135 (1999).
[18] R. T. Khisti, S. N. Mandhane, C. T. Chopde, Neurosci. Lett. **251** , 85 (1998).
[19] Maestro, version 9.0, Schrödinger, LLC, New York, NY, 2009.
[20] MacroModel, version 9.7, Schrödinger, LLC, New York, NY, 2009.
[21] QikProp, version 3.2, Schrödinger, LLC, New York, NY, 2009.
[22] Strike, version 1.8, Schrödinger, LLC, New York, NY, 2009.