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6-(4-(4-Substituted phenylpiperazin-1-yl)butoxy)benzo[*d*][1,3]oxathiol-2-one: Synthesis and biological evaluation as potential antipsychotic agents

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ABSTRACT

A series of 6-(4-(4-substituted phenylpiperazin-1-yl)butoxy)benzo[d][1,3]oxathiol-2-one was synthesized. The anti-dopaminergic and anti-serotonergic activities of the synthesized compounds were evaluated as an approach to identify novel antipsychotic agent. 6-(4-(4-Substituted phenylpiperazin-1-yl)butoxy)benzo[d][1,3]oxathiol-2-ones were synthesized by reacting 6-(4-chlorobutoxy)benzo[d][1,3]oxathiol-2-one with substituted phenyl piperazines and were characterized by IR, ^{1}H-NMR, C^{13}-NMR, MS and elemental analysis. The anti-dopaminergic activity was evaluated by their ability to inhibit apomorphine induced climbing behavior and the anti-serotonergic activity of synthesized compounds was assessed by studying inhibition of 5-HTP induced head twitches in mice. The intensity of catalepsy induced by synthesised compounds was evaluated against haloperidol induced catalepsy. The pharmacological testing revealed that the compound ***4l,*** *6-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)benzo[d][1,3]oxathiol-2-one and* ***4n*** *6-(4-(4-(2,3-dimethylphenyl)piperazin-1-yl)butoxy)benzo[d][1,3]oxathiol-2-one showed better antipsychotic profile with lower incidence of catalepsy induction.*

Keywords: 6-(4-(4-substituted phenylpiperazin-1-yl)butoxy)benzo[*d*][1,3]oxathiol-2-one, Antipsychotic, Climbing behavior; Head twitches; Catalepsy.

INTRODUCTION

Schizophrenia is a complex mental disorder affecting about 1% of the total world population [1]. The symptoms related to schizophrenia are characterized by the presence of “positive symptoms" which include mostly auditory hallucination, delusion, disorganized thought and "negative

symptoms" include alogia, inability to experience pleasure, 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 affect (EPS) [4] and hyperprolactinemia [5]. The second generation atypical antipsychotics like clozapine, risperidone, olanzapine, and ziprazidone block both dopaminergic and serotonergic transmission and alleviate both positive and negative symptoms of the disorder [6]. The anti-serotonergic activities have inhibitory influence on dopaminergic neurons at the level of the midbrain as well as at the terminal regions of the nigrostriatal and mesocortical dopaminergic pathways [7]. Atypical antipsychotics block the serotonergic transmission and induce a sustained enhancement in dopaminergic tone in the medial prefrontal cortex [8]. Although, several classes of atypical antipsychotics are currently being used, their clinical limitations and adverse effects, such as weight gain, blood dyscrasia, hyperglycemia, agranulocytosis etc. are forcing development of efficient and safe drugs for treatment of psychosis [9-11].

Previously we have investigated a series of 6-(3-substitutedpropoxyl)benzo [*d*][1,3]oxathiol-2-ones as novel centrally acting anti-dopaminergic and anti-serotonergic agent [12]. However, these compounds also induced mild to severe catalepsy because of comparatively weaker anti-serotonergic activity. Thus for striking a better balance between efficacy and side effect profile to treat this complex disease, we hereby have linked various 4-(substituted phenyl) piperazines in benzo[*d*][1,3]oxathiol-2-ones with a butyl linker. Rationale for selecting arylpiperazines was their reported anti-serotonergic activity with decreased induction of EPS [13, 14].

MATERIALS AND METHODS

Chemistry

All the chemicals and solvents used were of synthetic grade and were purified prior to use. The melting points were determined by open capillary method on Veego VMP-D digital melting point apparatus and are uncorrected. The IR spectrum of synthesized compounds was recorded on Jasco FT-IR 4100 in potassium bromide. The ^{1}H-NMR and ^{13}C-NMR spectra was recorded using NMR Varian Mercury plus 300 MHz using tetramethyl silane (TMS) as internal standard for ^{1}H-NMR. Electron spray ionization mass spectra were recorded by Varian 410 prostar binary LC with 500MS IT PDA detector. The completion of reaction was monitored by thin layer chromatography performed on Merck precoated silica gel F_{254} plates. Results of elemental analysis are within ± 0.4 % range of theoretical values for all the compounds. All the target compounds were converted to water soluble hydrochloride salts for evaluation of pharmacological activity. The various derivatives synthesized are illustrated in Table 1.

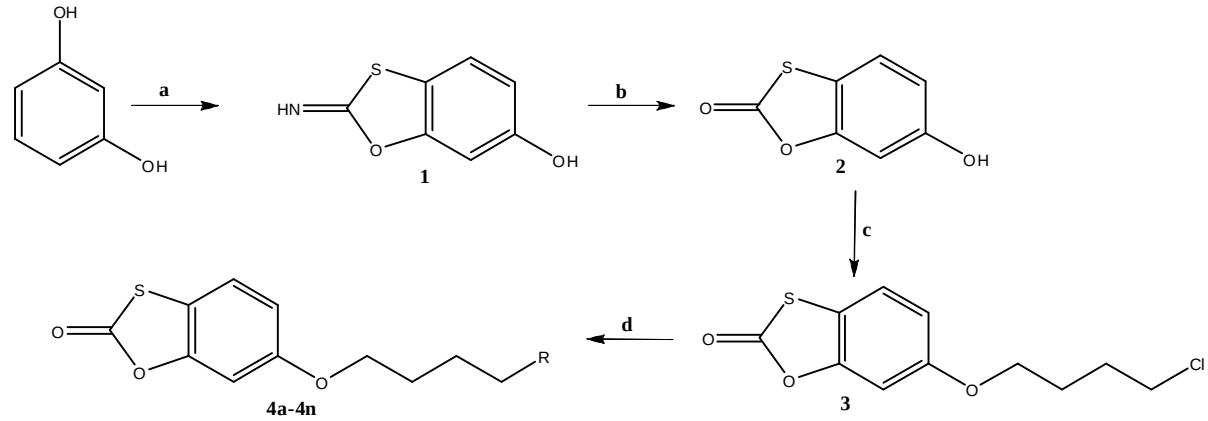
2-iminobenzo[d][1,3]oxathiol-6-ol **1**

Solution of potassium thiocyanate (0.41 mol) in water (25 mL) was added while stirring at room temperature to a solution of resorcinol (0.5 mol) and crystallized copper sulfate (0.15 mol) in water (125 mL). The black precipitate initially formed during stirring became colorless. The precipitate was then filtered and the filtrate was mixed with 2N sodium carbonate solution (25 mL) to yield compound **1** as colorless crystals.

Yield: 84%. mp:149^{0}C. IR ν_{max} (cm^{-1}) (KBr): 3411, 3384, 3022, 1706, 1654, 1226. Elemental analysis $C_7H_5NO_2S$ Calcd. (Found): C, 50.29 (50.15); H, 3.01 (2.96); N, 8.38 (8.24); O, 19.14 (19.21).

6-hydroxybenzo[d][1,3]oxathiol-2-one **2**
A solution of **1** (0.03 mol) in 10% hydrochloric acid (50 mL) was heated for 15 min on the steam bath. Compound **2** separated on cooling in the form of fine crystals.
Yield: 89%. mp: 158^{0}C. 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 and 6.71 (d, 2H, C_4-H and C_5-H), 5.21 (s, 1H, OH). Elemental analysis $C_7H_4O_3S$ Calcd. (Found): C, 49.99 (49.78); H, 2.40 (2.36)l; O, 28.54 (28.59); S, 19.07 (19.07).

6-(4-chlorobutoxy)benzo[d][1,3]oxathiol-2-one **3**
A mixture of **2** (0.017 mol), 1-bromo-4-chlorobutane (0.025 mol) and anhydrous K_2CO_3 (0.025 mol) in acetonitrile (30 mL) was refluxed for 24 h. The solvent was removed under vacuum. The residue was dissolved in methylene dichloride and washed with water and latter with 5% NaOH solution. The organic layer was then 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 **3**.
Yield: 63%. mp: 67-69˚C. Molecular formula: $C_{11}H_{11}ClO_3S$ (258).. IR ν_{max} (cm^{-1})(KBr):3047, 2983, 1713, 1559, 1041. ^{1}H-NMR (δ ppm; $CDCl_3$): 6.84 (s, 1H, C_7-H), 6.80 (d, 2H, C_4-H and C_5-H), 4.04 (t, 2H, -OCH_2.), 3.49 (t, 2H, -CH_2Cl), 2.07 (m, 4H, -CH_2-CH_2-). Elemental analysis $C_{11}H_{11}ClO_3S$ Calcd. (Found): C, 51.07 (51.21); H, 4.29 (4.13); Cl, 13.70 (13.81); O, 18.55 (18.43); S, 12.39 (12.42).



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

General procedure for synthesis of 6-(4-(4-substitutedphenylpiperazin-1-yl)butoxy)benzo[d][1,3]oxathiol-2-one **4a-4n**
A mixture of **3** (0.02 mol), substitutedphenyl piperazines (0.02 mol) and anhydrous K_2CO_3 (0.025 mol) was added to the reaction flask and refluxed in acetonitrile for 18 h. The reaction

mixture was filtered and the filtrate was concentrated under vaccum. The residue was dissolved in methylene dichloride and was washed with water and then with 10% HCl. The organic layer was then washed again with water and dried overnight on anhydrous sodium sulphate. Methylene dichloride was removed under vacuum to afford residue. The residue was then recrystallized from ethanol-water to yield the desired compounds **4a-4n.**

Following products were synthesized using above method:
6-(4-(4-phenylpiperazin-1-yl)butoxy)benzo[d][1,3]oxathiol-2-one **4a** : Yield 59 %; mp 102-104 ºC; IR (KBr, ν cm^{-1}): 3061, 2967, 1709, 1536, 1023. ^{1}H-NMR (δ ppm; $CDCl_3$) 7.13-6.78 (m, 8H, ArH), 4.01 (t, 2H, -OC$\underline{H}_2$-), 3.11 (t, 4H, -C$\underline{H}_2$-N-C$\underline{H}_2$-), 2.62 (t, 6H, -C$\underline{H}_2$-N(C$\underline{H}_2$-)C$\underline{H}_2$-), 1.96 (m, 4H, -C$\underline{H}_2$-C$\underline{H}_2$-). ^{13}C-NMR (δ; $CDCl_3$): 171.16, 151.74, 148.34, 145.41, 132.17, 130.72, 129.27, 117.34, 113.97, 113.27, 109.37, 63.51, 53.27, 51.31, 47.97, 27.82, 26.98. MS (APCI) *m/z*: 384.9 (M^+; 100%). Elemental analysis $C_{21}H_{24}N_2O_3S$ Calcd. (Found): C, 65.60 (65.73); H, 6.29 (6.18); N, 7.29 (7.26); O, 12.48 (12.44); S, 8.34 (8.39).

6-(4-(4-o-tolylpiperazin-1-yl)butoxy)benzo[d][1,3]oxathiol-2-one **4b:** Yield 62 %; mp 119-121 ºC; IR (KBr, ν cm^{-1}): 3060, 2968, 1712, 1544, 1020. ^{1}H-NMR (δ ppm; $CDCl_3$) 7.09-6.82 (m, 7H, ArH), 3.97 (t, 2H, -OC$\underline{H}_2$-), 3.12 (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$\underline{H}_2$-), 2.22 (s, 3H, -C$\underline{H}_3$-), 1.98 (m, 4H, -C$\underline{H}_2$-C$\underline{H}_2$-). Elemental analysis $C_{22}H_{26}N_2O_3S$ Calcd. (Found): C, 66.30 (66.47); H, 6.58 (6.51); N, 7.03 (6.92); O, 12.04 (12.14); S, 8.05 (7.96).

6-(4-(4-m-tolylpiperazin-1-yl)butoxy)benzo[d][1,3]oxathiol-2-one **4c:** Yield 61 %; mp 123-125 ºC; IR (KBr, ν cm^{-1}): 3067, 2962, 1709, 1536, 1019. ^{1}H-NMR (δ ppm; $CDCl_3$) 7.11-6.86 (m, 7H, ArH), 3.94 (t, 2H, -OC$\underline{H}_2$-), 3.08 (t, 4H, -C$\underline{H}_2$-N-C$\underline{H}_2$-), 2.68 (t, 6H, -C$\underline{H}_2$-N(C$\underline{H}_2$-)C$\underline{H}_2$-), 2.17 (s, 3H, -C$\underline{H}_3$-), 2.00 (m, 4H, -C$\underline{H}_2$-C$\underline{H}_2$-).

6-(4-(4-p-tolylpiperazin-1-yl)butoxy)benzo[d][1,3]oxathiol-2-one **4d:** Yield 63 %; mp 129-131 ºC; IR (KBr, ν cm^{-1}): 3063, 2973, 1714, 1584, 1022. ^{1}H-NMR (δ ppm; $CDCl_3$) 7.06-6.88 (m, 7H, ArH), 3.90 (t, 2H, -OC$\underline{H}_2$-), 3.13 (t, 4H, -C$\underline{H}_2$-N-C$\underline{H}_2$-), 2.70 (t, 6H, -C$\underline{H}_2$-N(C$\underline{H}_2$-)C$\underline{H}_2$-), 2.19 (s, 3H, -C$\underline{H}_3$-), 1.94 (m, 4H, -C$\underline{H}_2$-C$\underline{H}_2$-).

6-(4-(4-(2-chlorophenyl)piperazin-1-yl)butoxy)benzo[d][1,3]oxathiol-2-one **4e:** Yield 62 %; mp 108-110 ºC; IR (KBr, ν cm^{-1}): 3059, 2979, 1705, 1592, 1021. ^{1}H-NMR (δ ppm; $CDCl_3$) 7.09-6.97 (m, 7H, ArH), 3.94 (t, 2H, -OC$\underline{H}_2$-), 3.16 (t, 4H, -C$\underline{H}_2$-N-C$\underline{H}_2$-), 2.67 (t, 6H, -C$\underline{H}_2$-N(C$\underline{H}_2$-)C$\underline{H}_2$-), 1.98 (m, 4H, -C$\underline{H}_2$-C$\underline{H}_2$-). MS (APCI) *m/z*: 418.7 (M^+; 100%). Elemental analysis $C_{21}H_{23}ClN_2O_3S$ Calcd. (Found): C, 60.21 (59.99); H, 5.53 (5.61); Cl, 8.46 (8.34); N, 6.69 (6.71); O, 11.46 (11.67); S, 7.65(7.68).

6-(4-(4-(3-chlorophenyl)piperazin-1-yl)butoxy)benzo[d][1,3]oxathiol-2-one **4f:** Yield 57 %; mp 111-113 ºC; IR (KBr, ν cm^{-1}): 3051, 2989, 1700, 1586, 1052. ^{1}H-NMR (δ ppm; $CDCl_3$) 7.14-6.90 (m, 7H, ArH), 3.91 (t, 2H, -OC$\underline{H}_2$-), 3.20 (t, 4H, -C$\underline{H}_2$-N-C$\underline{H}_2$-), 2.63 (t, 6H, -C$\underline{H}_2$-N(C$\underline{H}_2$-)C$\underline{H}_2$-), 1.96 (m, 4H, -C$\underline{H}_2$-C$\underline{H}_2$-).

6-(4-(4-(4-chlorophenyl)piperazin-1-yl)butoxy)benzo[d][1,3]oxathiol-2-one **4g:** Yield 60 %; mp 119-121 ºC; IR (KBr, ν cm^{-1}): 3061, 2978, 1708, 1569, 1019. ^{1}H-NMR (δ ppm; $CDCl_3$) 7.14-

6.90 (m, 7H, ArH), 3.93 (t, 2H, -OC$\underline{H}_2$-), 3.21 (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$\underline{H}_2$-), 1.99 (m, 4H, -C$\underline{H}_2$-C$\underline{H}_2$-).

6-(4-(4-(2-methoxyphenyl)piperazin-1-yl)butoxy)benzo[d][1,3]oxathiol-2-one **4h:** Yield 57 %; mp 110-112 ºC; ; IR (KBr, ν cm^{-1}): 3069, 2931, 1701, 1545, 1019. ^{1}H-NMR (δ ppm; $CDCl_3$) 7.16-6.98 (m, 7H, ArH), 3.92 (t, 2H, -OC$\underline{H}_2$-), 3.88 (s, 3H, -OCH_3), 3.19 (t, 4H, -C$\underline{H}_2$-N-C$\underline{H}_2$-), 2.68 (t, 6H, -C$\underline{H}_2$-N(C$\underline{H}_2$-)C$\underline{H}_2$-), 2.01 (m, 4H, -C$\underline{H}_2$-C$\underline{H}_2$-). MS (APCI) *m/z*: 418.7 (M^+; 100%). Elemental analysis $C_{22}H_{26}N_2O_4S$ Calcd. (Found): C, 63.75 (63.71); H, 6.32 (6.29); N, 6.76 (6.73); O, 15.44 (15.56); S, 7.74 (7.68).

6-(4-(4-(4-methoxyphenyl)piperazin-1-yl)butoxy)benzo[d][1,3]oxathiol-2-one **4i:** Yield 56 %; mp 122-124 ºC; IR(KBr, ν cm^{-1}): 3056, 2978, 1703, 1577, 1020. ^{1}H-NMR (δ ppm; $CDCl_3$) 7.14-6.96 (m, 7H, ArH), 3.94 (t, 2H, -OC$\underline{H}_2$-), 3.85 (s, 3H, -OCH_3), 3.21 (t, 4H, -C$\underline{H}_2$-N-C$\underline{H}_2$-), 2.65 (t, 6H, -C$\underline{H}_2$-N(C$\underline{H}_2$-)C$\underline{H}_2$-), 1.97 (m, 4H, -C$\underline{H}_2$-C$\underline{H}_2$-).

6-(4-(4-(4-fluorophenyl)piperazin-1-yl)butoxy)benzo[d][1,3]oxathiol-2-one **4j:** Yield 59 %; mp 138-140 ºC; IR(KBr, ν cm^{-1}): 3052, 2983, 1011, 1582, 1022. ^{1}H-NMR (δ ppm; $CDCl_3$) 7.11-6.95 (m, 7H, ArH), 3.91 (t, 2H, -OC$\underline{H}_2$-), 3.17 (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$\underline{H}_2$-), 1.95 (m, 4H, -C$\underline{H}_2$-C$\underline{H}_2$-). MS (APCI) *m/z*: 402.7 (M^+; 100%). Elemental analysis $C_{21}H_{23}FN_2O_3S$ Calcd. (Found): C, 62.67 (62.73); H, 5.76 (5.80); F, 4.72 (4.67); N, 6.96 (6.91); O, 11.93 (11.91); S, 7.97 (8.04).

6-(4-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)butoxy)benzo[d][1,3]oxathiol-2-one **4k:** Yield 57 %; mp 135-137 ºC; IR(KBr, ν cm^{-1}): 3083, 2979, 1703, 1562, 1027. ^{1}H-NMR (δ ppm; $CDCl_3$) 7.14-6.97 (m, 7H, ArH), 3.90 (t, 2H, -OC$\underline{H}_2$-), 3.16 (t, 4H, -C$\underline{H}_2$-N-C$\underline{H}_2$-), 2.66 (t, 6H, -C$\underline{H}_2$-N(C$\underline{H}_2$-)C$\underline{H}_2$-), 1.98 (m, 4H, -C$\underline{H}_2$-C$\underline{H}_2$-).

6-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)benzo[d][1,3]oxathiol-2-one **4l:** Yield 64 %; mp 133-135 ºC; IR(KBr, ν cm^{-1}): 3066, 2974, 1713, 1547, 1018. ^{1}H-NMR (δ ppm; $CDCl_3$) 7.07-6.99 (m, 6H, ArH), 3.94 (t, 2H, -OC$\underline{H}_2$-), 3.14 (t, 4H, -C$\underline{H}_2$-N-C$\underline{H}_2$-), 2.67 (t, 6H, -C$\underline{H}_2$-N(C$\underline{H}_2$-)C$\underline{H}_2$-), 1.99 (m, 4H, -C$\underline{H}_2$-C$\underline{H}_2$-). MS (APCI) *m/z*: 452.5 (M^+; 100%). Elemental analysis $C_{21}H_{22}Cl_2N_2O_3S$ Calcd. (Found): C, 55.63 (55.69); H, 4.89 (4.94); Cl, 15.64 (15.59); N, 6.18 (6.22); O, 10.59 (10.85); S, 7.07 (7.01).

6-(4-(4-(3,4-dichlorophenyl)piperazin-1-yl)butoxy)benzo[d][1,3]oxathiol-2-one **4m:** Yield : 63 %; mp 139-141 ºC; IR(KBr, ν cm^{-1}): 3054, 2983, 1709, 1536, 1015. ^{1}H-NMR (δ ppm; $CDCl_3$) 7.09-6.97 (m, 6H, ArH), 3.96 (t, 2H, -OC$\underline{H}_2$-), 3.16 (t, 4H, -C$\underline{H}_2$-N-C$\underline{H}_2$-), 2.69 (t, 6H, -C$\underline{H}_2$-N(C$\underline{H}_2$-)C$\underline{H}_2$-), 1.95 (m, 4H, -C$\underline{H}_2$-C$\underline{H}_2$-).

6-(4-(4-(2,3-dimethylphenyl)piperazin-1-yl)butoxy)benzo[d][1,3]oxathiol-2-one **4n:** Yield : 55 %; mp 143-145 ºC; IR(KBr, ν cm^{-1}): 3061, 2984, 1704, 1535, 1019. ^{1}H-NMR (δ ppm; $CDCl_3$) 7.09-6.97 (m, 6H, ArH), 3.96 (t, 2H, -OC$\underline{H}_2$-), 3.11 (t, 4H, -C$\underline{H}_2$-N-C$\underline{H}_2$-), 2.69 (t, 6H, -C$\underline{H}_2$-N(C$\underline{H}_2$-)C$\underline{H}_2$-), 2.20(s,, 3H, -CH_3), 2.14(s, 3H, -C$\underline{H}_3$), 1.99 (m, 4H, -C$\underline{H}_2$-C$\underline{H}_2$-). MS (APCI) *m/z*: 412.8 (M^+; 100%). Elemental analysis $C_{23}H_{28}N_2O_3S$ Calcd. (Found): C, 66.96 (67.08); H, 6.84 (6.73); N, 6.79 (6.89); O, 11.63 (11.68); S, 7.77 (7.62).

Pharmacology

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 (weighing in the range of 20-25 g) procured from Serum Institute of India, Pune were selected for the purpose of experiment. The animals were kept in suitable laboratory environment (22 ± 2 ^{0}C with 12h light/dark cycle) and feed ad libitum with standard food pellet. Animals were divided into 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). Route of administration was i.p. except wherever mentioned. Aripiprazole was used as a standard.

Inhibition of apomorphine induced climbing behavior

The relative anti-dopaminergic activity of the compounds has been determined on the basis of this test. 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).Test or standard compound was given 30 min before administration (15mg/kg) of apomorphine while animals in control group received 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 [15].

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 [16].

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), 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. 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 [17].

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 analyzed using Dunnet's t test. P values < 0.05 were considered to be significant. All the values were expressed as percentage inhibition of respected

behaviour model relative to control group and depicted in Table 1.

RESULTS AND DISCUSSION

Chemistry

Synthesis of 6-hydroxybenzo[*d*][1,3]oxathiol-2-one **2** was accomplished by following a earlier reported procedure [18] involving reaction of resorcinol with potassium thiocyanate in water containing copper sulfate. 6-(4-Chlorobutoxy)benzo[*d*][1,3]oxathiol-2-one **3** was synthesized by refluxing **2** with 1-bromo-4-chlorobutane in acetonitrile in presence of anhydrous K_2CO_3 for 24h. Title compounds **4a-4n** were obtained by refluxing different substituted aryl piperazines with **3** in presence of anhydrous K_2CO_3 in acetonitrile. Yields of final compounds were in the range of 55-64% after recrystallization from methanol–water.

The structures of **4a-4n** were in accordance with IR, ^{1}H-NMR, ^{13}C-NMR, MS and elemental analysis data. For example, IR spectrum of **4a** showed strong absorption peak of aromatic and aliphatic C-H stretching at 3061 and 2967 cm^{-1} respectively. The presence of C=O group was confirmed by peak at 1709 $cm^{-1.}$ ^{1}H-NMR spectrum of **4a** showed multiplet in the range of δ 7.13-6.78 integrating for eight protons confirm the presence of necessary aromatic system. The two protons of the $–OCH_2$ group appeared as a triplet at δ 4.13. The four methylene protons of the piperazine ring showed a triplet peak at δ 3.11. Further a triplet peak at δ 2.62 appeared for six aliphatic protons of piperazines ring and two methylene protons of the butyl chain attached to it. Further, the four protons of butyl chain were ascertained by the multiplet at δ 1.96. ^{13}C-NMR spectrum of **4a** showed the presence of carbonyl carbon with a peak at δ 171.16. Peaks for twelve carbons in the aromatic region δ 151.74-109.37 underlined the presence of required aromatic skeleton. The two peaks at δ 63.51, 53.27 were observed for the four aliphatic carbons of piperazine ring. Peaks at 51.31, 47.97, 27.82 and 26.98 were due to the four aliphatic carbons of butyl chain. Finally, a mass spectrum (ESI) showed a molecular ion peak at *m/z* 384.9 which is consistent with molecular weight of **4a**.

Pharmacology

The two established animal models namely inhibition of apomorphine induced climbing behavior and inhibition of 5-HTP induced head twitches in albino mice along with study of haloperidol induced catalepsy, were used to assess the antipsychotic potential of the test compounds. All the biological data was analyzed statistically and was expressed as percentage inhibition of climbing behavior, inhibition of 5-HTP induced head twitches and catalepsy induction relative to control group (Table 1). Taking compound 4**a** 6-(4-(4-phenylpiperazin-1-yl)butoxy)benzo[*d*][1,3]oxathiol-2-one as lead, substitution was carried out in the phenyl moiety and above mentioned behavioral studies were evaluated.

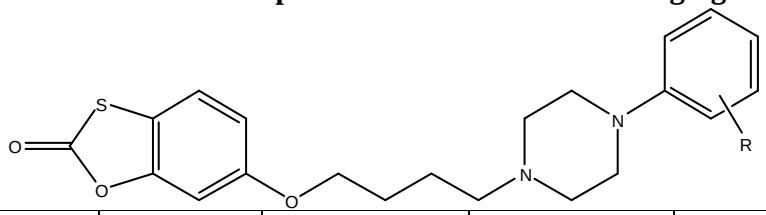
Substitution at *ortho* position in **4a** by methyl **4b** and chlorine **4e** resulted in the enhancement in anti-dopaminergic activity while presence of methoxy group **4h** reduced the anti-dopaminergic activity. Further substitution at *meta* position of aryl ring with methyl **4c**, chlorine **4f** and trifluromethyl **4k** decreased the anti-dopaminergic activity compared to lead **4a**. Presence of methyl **4d**, chloro **4g**, fluro **4j** and methoxy **4i** at *para* position of the phenyl ring significantly increased the anti-dopaminergic activity. As far as di-substituted compounds **4l**, **4m**

and **4n** resulted in significantly reverse the apomorphine induced climbing behavior.

In antagonism of 5-HTP induced head twitches, presence of methyl **4b**, chlorine **4e** and methoxy **4h** at *ortho* position of the phenyl ring resulted in increase anti-serotonergic activity. While in other mono-substituted compounds, any substitution at *meta* and *para* position of the phenyl ring decreased the anti-serotonergic activity. Further, an appreciable increase in anti-serotonergic activity was observed in *ortho-meta* di-substituted compounds bearing steric and hydrophobic moieties as in **4l** and **4n.** While presence of chlorine **4m** at both *meta* and *para* position of the aryl ring slightly reversed the 5-HTP induced head twitches as compare to **4a.**

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 **4l** and **4n** exhibit minimum catalepsy induction comparable with aripiprazole.

Table 1: In vivo data of the compounds 4a-4n at the dose 10mg/kg in albino mice



Compd.	R	%Inhibition of climbing behavior	%Inhibition of head twitches	%catalepsy induction
4a	H	26.641	28.376	21.429
4b	2-CH_3	27.493	32.732	39.327
4c	3-CH_3	22.932	24.436	31.862
4d	4-CH_3	35.653	27.024	28.162
4e	2-Cl	26.392	30.438	37.229
4f	3-Cl	21.137	25.517	36.318
4g	4-Cl	36.267	23.143	39.581
4h	2-OCH_3	22.663	29.347	22.659
4i	4-OCH_3	28.683	21.384	46.274
4j	4-F	30.701	26.693	26.956
4k	3-CF_3	21.359	24.637	26.343
4l	2,3-diCl	27.238	49.833	19.347
4m	3,4-diCl	30..354	32.001	26.624
4n	2,3-diCH_3	35.241	47.344	20.131
Aripiprazole[a]		45.137	58.019	22.514

n = 6; Data were analyzed by one-way ANOVA followed by Dunnett's test; P < 0.05 versus control

Figure 1: Plot of % inhibition of climbing behavior against compounds tested

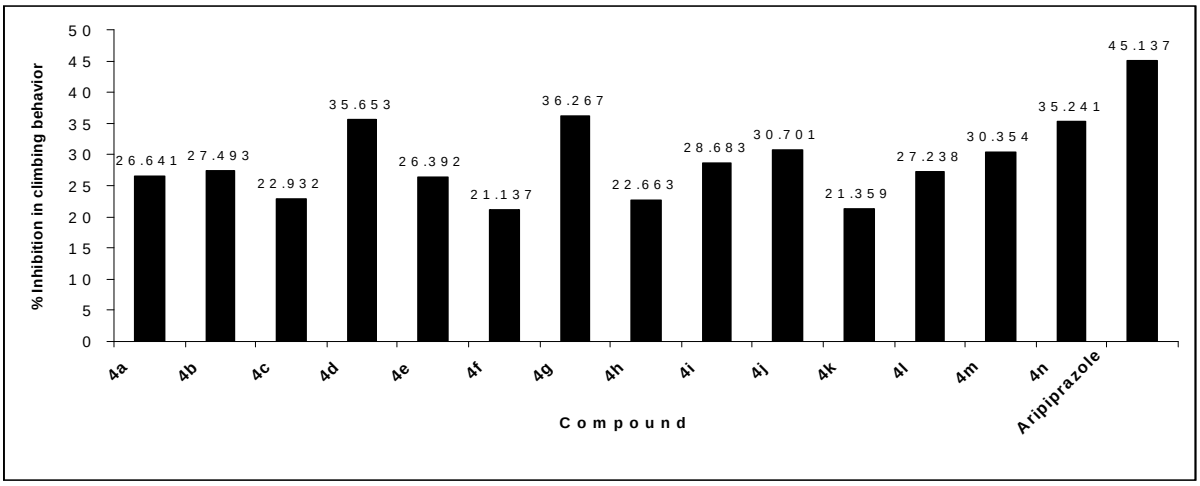
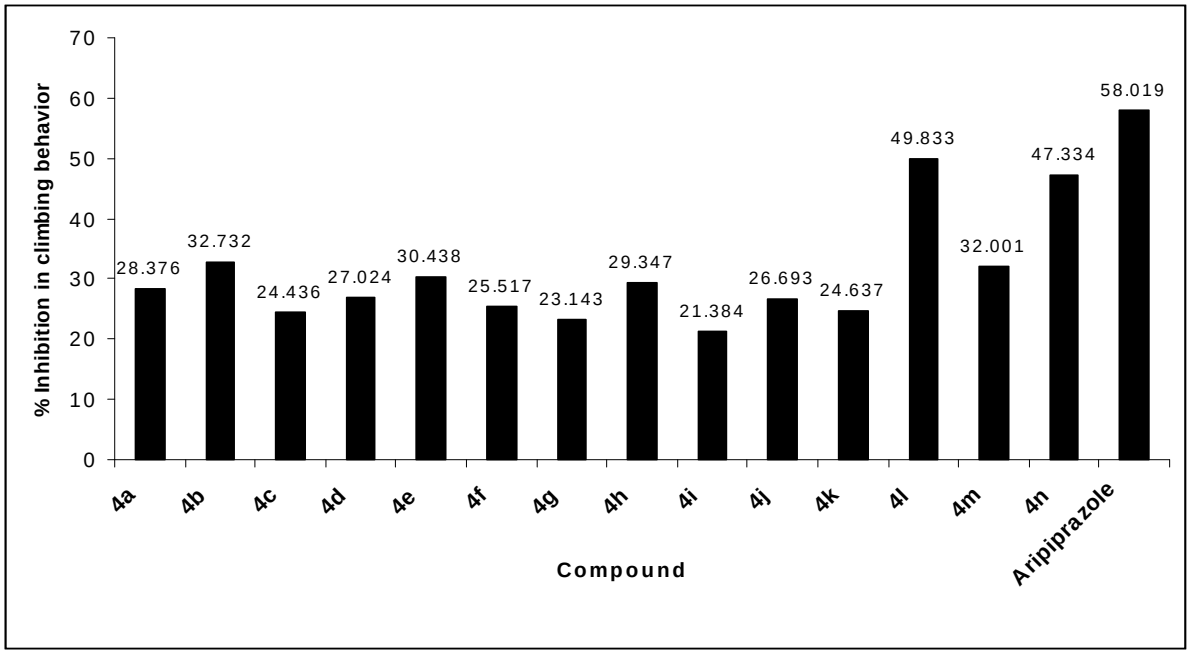


Figure 2: Plot of % inhibition of head twitches against compounds tested



CONCLUSION

The main objective of the present work was to study the effect of increased alkyl chain length of the linker and incorporation of aryl piperazines on the antipsychotic potential of the previously reported lead 6-(3-substitutedpropoxyl)benzo [*d*][1,3]oxathiol-2-ones . Accordingly a new series of 6-(4-(4-Substituted phenylpiperazin-1-yl)butoxy)benzo[*d*][1,3]oxathiol-2-one was synthesized and characterized using IR, ^{1}H-NMR, ^{13}C-NMR and MS. The antipsychotic potential of these

compounds was ascertained by evaluating their antidopaminergic activity , antiserotonergic activity and ability to induce catalepsy. All the synthesized compounds exhibited increased antidopaminergic and antiserotonergic activity as compared to our previous series also some of the new compounds showed less catalepsy even than aripiprazole.

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