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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Benzo[*d*][1,3] oxathiols: synthesis and biological evaluation as potential atypical antipsychotic agents

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Abstract The present research paper reports the synthesis and biological evaluation of 6-(3-substitutedpropoxyl)benzo[*d*][1,3]oxathiol-2-ones as potential atypical antipsychotic agents. Accordingly, 10 derivatives with either amino or aryloxy substituents were synthesized. Potential antipsychotic activity of these compounds in terms of D_2 antagonism was evaluated by their ability to inhibit apomorphine-induced climbing behavior in mice and 5-HT_2 antagonistic activity of synthesized compounds was assessed by studying inhibition of 5-HTP-induced head twitches. Non-specific D_2 blockade was evaluated by studying propensity of these compounds to produce catalepsy in mice. All the synthesized compounds were found to exhibit D_2 and 5-HT_2 antagonist activity in behavioral models. However, they also induced mild to severe catalepsy. Among the 10 compounds tested, **5b** and **5e** exhibited maximum 'atypical antipsychotic activity like' profile.

Keywords Antipsychotic · 6-(3-Substitutedpropoxyl)benzo[*d*][1,3]oxathiol-2-one · Climbing behavior · Head twitches · Catalepsy

Introduction

The discovery of new effective drugs for the treatment of the psychiatric disorders such as schizophrenia still remains a top priority as it affects approximately 1% of the world population (Taverne *et al*., 1998). Schizophrenia is a chronic and severe disabling mental illness independent of sex, location, social class, or color of the skin (Evans *et al*., 2003). Active psychosis was ranked the third-most-disabling condition, after quadriplegia and dementia and before paraplegia and blindness (Aaron and David, 2004).

Although the pathophysiology of schizophrenia has not been fully established, dysfunction of dopamine neurotransmitter system within the brain is believed to play a vital role in symptoms expression and neuropsychological dysfunction of the illness (Ross and Ramsay, 2002). Since 1950s classical neuroleptic better known as typical antipsychotic such as chlorpromazine and haloperidol, which are potent dopamine D_2 receptor antagonists have provide clear efficacy against positive symptoms of schizophrenia (Navas *et al*., 1998). However, these drugs are relatively ineffective in the treatment of negative symptoms of the disease and also chronic administration of these drugs is frequently associated with serious extra pyramidal side effects (EPS) (Martin, 1997).

The discovery of newer atypical antipsychotic agents such as clozapine and olanzapine are focused on mixed dopamine D_2 and serotonin 5-HT_2 antagonist. Meltzer has postulated that mixed D_2/5-HT_2 antagonist that exhibit high affinity for 5-HT_2 receptor and moderate affinity for D_2 receptor are more likely to have good antipsychotic activity, treating positive as well as negative symptoms of schizophrenia with lower potency to produce EPS (Meltzer *et al*., 1989). Limitation of these atypical antipsychotics include substantial weight gain, agranulocyctosis, blood dyscrasias, and hyperglycemia on chronic medication (Wirshing *et al*., 1999; Lieberman *et al*., 1988; Lowe *et al*., 1991; Ravin and Masaguer, 2001). With a high refractive treatment incidence and low compliance due to tolerability, the search continues for novel atypical antipsychotics that

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have a better balance between efficacy and side effect profile to treat this complex disease.

For last few years, our research group has been actively working on exploring new lead molecules as potential antipsychotics. Previously in our laboratory 7-[3-(substituted amino)propoxyll]-4-methylchromen-2-one **a** (Aparna *et al*., 2005), coumarinoacetamide **b** (Bhosale *et al*., 2006), and 7-[4-(substituted phenylpiperazin-1-yl)-alkoxyl]-4-methylchromene-2-one **c** (Shelke *et al*., 2005) derivatives were synthesized and reported as potential antipsychotic agents (Fig. 1).

As a continuation of our work on antipsychotic agents that interact with D_2 and $5HT_2$ receptors, we hereby report synthesis and prepharmacological evaluation of 6-substituted-benzo[*d*][1,3]oxathiol-2-one as novel potential antipsychotic agents. As benzo[*d*] [1,3]oxathiol-2one **d** is the chemical bio-isoster of 4-methylchromen-2-one **e** as shown in Fig. 2, it was hypothesized that the present molecule may exhibit potential antipsychotic profile.

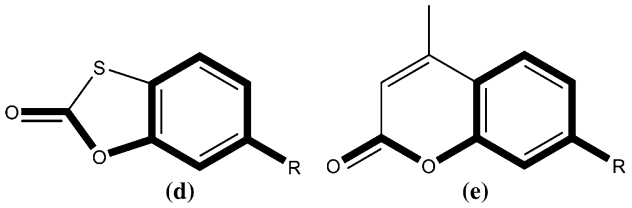


Fig. 2 6-Substituted-benzo[*d*][1,3]oxathiol-2one **d** as chemical bio-isoter of 7-substituted-4-methyl chromen-2-one **e**

Methods and materials

Chemistry

All the chemicals used in the synthesis were procured from Qualigen and purified prior to use. The completion of reaction was monitored by thin layer chromatography performed on Merck precoated silica gel F_{254} plates. The melting points were determined by open capillary method on Campbel electronic apparatus and are uncorrected. The IR spectrum of synthesized compounds was recorded on Jasco V-5300 FT-IR in potassium bromide disks. The ^1H NMR spectrum was recorded using NMR Varian Mercury 300 MHz using trimethyl silane (TMS) as internal standard.

The title compound 6-(3-substituted propoxyl)-benzo [*d*][1,3]oxathiol-2one was synthesized in four-step process as per Scheme 1. The various derivatives synthesized are illustrated in Table 1.

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

Solution of potassium thiocyanate (20 g, 0.41 mol) in water (25 ml) was added while stirring at room temperature to a solution of resorcinol (5.5 g, 0.5 mol) and crystallized copper sulfate (25 g, 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 2-N sodium carbonate solution (25 ml) to yield compound **2** as colorless crystals.

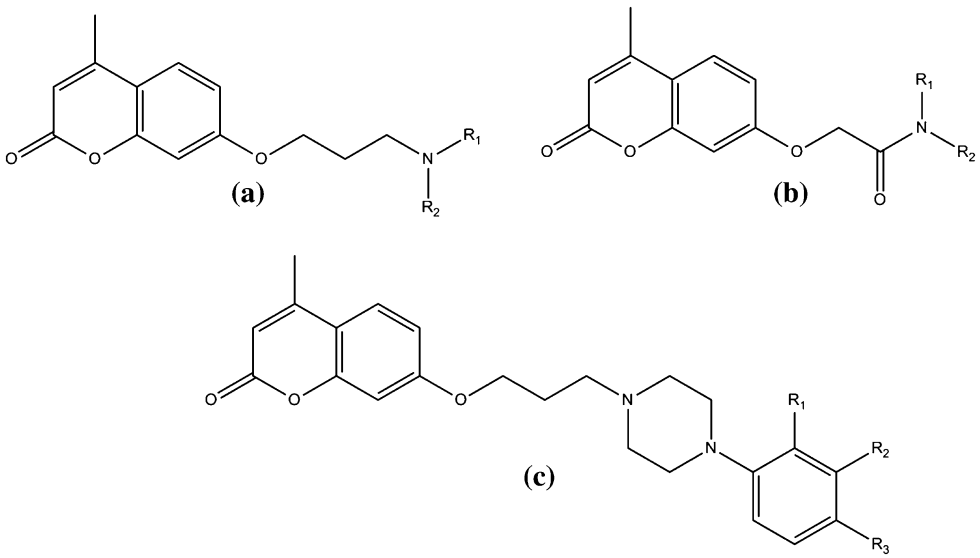


Fig. 1 Previously synthesized antipsychotic compounds by **a** Aparna *et al*. (2005) **b** Bhosale *et al*. (2006) **c** Shelke *et al*. (2005)

Scheme 1 Synthetic protocol for title compound. **a** KSCN, $CuSO_4$, H_2O; **b** 10% Hcl; **c** Br–$(CH_2)_3$–Cl, K_2CO_3, CH_3CN; **d** sec amine/phenol, K_2CO_3, CH_3CN. For R: refer Table 1

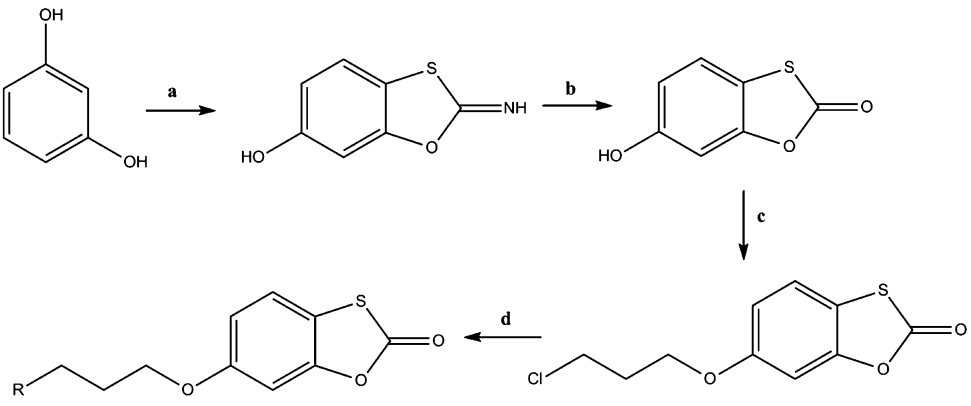
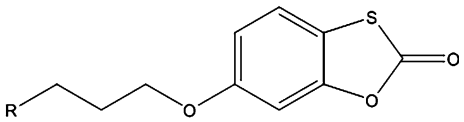


Table 1 Synthesized derivatives with biological evaluation results



Compound	R	Percentage inhibition of climbing behavior[a]	Percentage inhibition of head twitches[b]	% Catalepsy induction[b]
5a	Piperidinyl	51.20	67.32	41.00
5b	Morpholinyl	69.58	71.47	39.27
5c	Diethylamino	53.28	63.39	37.11
5d	Piperazinyl	62.33	68.24	42.39
5e	1,2,4-Triazolyl	69.96	79.28	36.98
5f	Naphthalen-2-yloxy	46.95	61.15	41.22
5g	Naphthalen-1-yloxy	39.03	58.27	49.21
5h	4-Chlorophenoxy	49.33	77.93	33.71
5i	*p*-Tolyloxy	52.44	77.32	39.48
5j	4-Nitrophenoxy	67.26	80.01	43.92
Aripiprazole[b]		62.36	80.19	29.34

$P < 0.05$, number of animals, $n = 6$

[a] 60 mg/kg

[b] 25 mg/kg

Yield: 7.0 g (84%), mp: 149°C, molecular formula: $C_7H_5NO_2S$ (167), elemental analysis: calcd. C 50.29, H 3.01, N 8.38, O 19.14, S 19.18; found C 50.15, H 2.96, N 8.24, O 19.44, S 19.21. IR ν_{max} (cm^{-1}) (KBr): 3411, 3384, 3022, 1706, 1654, 1226.

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

A solution of **2** (5.01 g, 0.03 mol) in 10% hydrochloric acid (50 ml) was heated for 15 min on the steam bath. Compound **3** separated on cooling in the form of fine crystals (Werner, 1943).

Yield: 4.5 g (89%), mp: 158°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. ^1H 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).

Synthesis of 6-(3-chloropropoxyl)benzo[d][1,3]oxathiol-2-one ***4***

A mixture of **3** (2.83 g, 0.017 mol), 1-bromo-3-chloropropane (2.5 ml, 0.025 mol) and anhydrous K_2CO_3 (3.5 g, 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 **4**.

Yield: 2.63 g (63%), mp: 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. ^1H 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–).

*General method of synthesis for compounds **5a–5e***

A mixture of **4** (4.88 g, 0.02 mol), appropriate sec amine (0.02 mol) and anhydrous K_2CO_3 (3.50 g, 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 vacuum. The residue was dissolved in methylene dichloride. The solution was washed with water and then with 10% HCl. The organic layer was then washed again with water and dried overnight on anhydrous sodium sulfate. Methylene dichloride was removed under vacuum to afford residue. The residue was then recrystallised from ethanol–water to yield the desired compound.

*6-[3-(Piperidin-1-yl)propoxyl]benzo[d][1,3]oxathiol-2-one **5a***

Yield: 3.28 g (56%), mp: 92°C, molecular formula: $C_{15}H_{19}NO_3S$ (293), elemental analysis: calcd. C 61.41, H 6.53, N 4.77, O 16.36, S 10.93, found C 61.27, H 6.78, N 4.69, O 16.48, S 10.78. IR ν_{max} (cm^{-1}) (KBr): 3017, 2941, 1720, 1423, 1150, 1045. ^1H NMR (δ ppm; DMSO-d_6): 6.81(s, 1H, C_7–H), 6.73 (d, 2H, C_4–H, and C_5–H), 4.16 (t, 2H, –OCH_2–), 3.89 (t, 2H, –CH_2CH_2N–), 1.63 (m, 6H, C_3'–H, C_4'–H, C_5'–H), 2.65 (t, 4H, C_2'–H, and C_6'–H), 2.85 (m, 2H, –CH_2–).

*6-[3-(Morpholin-4-yl)propoxyl]benzo[d][1,3]oxathiol-2-one **5b***

Yield: 3.24 g (55%), mp: 98°C, molecular formula: $C_{14}H_{17}NO_4S$ (295), elemental analysis: calcd. C 56.93, H 5.80, N 4.74, O 21.67, S 10.86; found. C 57.09, H 5.91, N 4.67, O 21.67, S 10.66. IR ν_{max} (cm^{-1}) (KBr): 3006, 2953, 1734, 1440, 1355, 1045. ^1H NMR (δ ppm; DMSO-d_6): 6.81(s, 1H, C_7–H), 6.73 (d, 2H, C_4–H, and C_5–H), 4.15 (t, 2H, –OCH_2–), 4.02 (t, 4H, C_2'–H, and C_6'–H), 3.87 (t, 2H, –CH_2CH_2N–), 3.81 (t, 4H, C_3'–H, and C_5'–H), 2.85 (m, 2H, –CH_2–).

*6-[3-(Diethylamino)propoxyl]benzo[d][1,3]oxathiol-2-one **5c***

Yield: 2.92 g (52%), mp: 84°C, molecular formula: $C_{14}H_{17}NO_4S$ (281), elemental analysis: calcd. C 59.76, H 6.81, N 4.98, O 17.06, S 11.40; found C 59.68, H 6.77, N 4.81, O 17.38, S 11.36. IR ν_{max} (cm^{-1}) (KBr): 3073, 2941, 1710, 1406. ^1H NMR (δ ppm, DMSO d_6): 6.81(s, 1H, C_7–H), 6.71 (d, 2H, C_4–H, and C_5–H), 4.15 (t, 2H, –OCH_2), 3.81 (t, 2H, –CH_2CH_2N–), 3.72 (q, 4H, NCH_2–), 2.87 (m, 2H, –CH_2–), 1.6(t, 6H –CH_3).

*6-[3-(Piperazin-1-yl)propoxyl]benzo[d][1,3]oxathiol-2-one **5d***

Yield: 3.82 g (65%), mp: 126°C, molecular formula: $C_{14}H_{18}N_2O_3S$ (294), elemental analysis: calcd. C 57.12, H 6.16, N 9.52, O 16.31, S 10.89; found C 57.08, H 6.12, N 9.47, O 16.47, S 10.86. IR ν_{max} (cm^{-1}) (KBr): 3290, 3018, 2964, 1720, 1587, 1410. ^1H NMR (δ, ppm, DMSO d_6): 9.36 (s, 1H, NH), 6.81(s, 1H, C_7–H), 6.71 (d, 2H, C_4–H, and C_5–H), 4.15 (t, 2H, –OCH_2), 3.84 (t, 2H, –CH_2CH_2N–), 3.75 (m, 4H C_2'–H, and C_6'–H), 3.73(m, 4H C_3'–H, and C_5'–H), 2.87 (m, 2H, –CH_2–).

*6-[3-(4H-1,2,4-Triazol-4-yl)propoxyl]benzo[d][1,3]oxathiol-2-one **5e***

Yield: 3.21 g (58%), mp: 133°C, molecular formula $C_{12}H_{11}N_3O_3S$ (277), elemental analysis: calcd. C 51.98, H 4.00, N 15.15, O 17.31, S 11.56; found C 51.91, H 3.86, N 15.11, O 17.63, S 11.49. IR ν_{max} (cm^{-1}) (KBr): 3080, 2964, 1728, 1427, 1392,1379, 1188. ^1H NMR (δ ppm, DMSO d_6): 6.80 (s, 1H, C_7–H), 6.73 (d, 2H, C_4–H, and C5–H), 4.15 (t, 2H, –OCH_2), 3.86 (t, 2H, –CH_2N), 3.25 (s, 2H, C_3'–H, and C_5'–H), 2.85 (m, 2H, –CH_2–).

*General method of synthesis of compounds **5f–5j***

A mixture of **4** (4.88 g, 0.02 mol), appropriate phenol (0.02 mol), and anhydrous K_2CO_3 (3.50 g, 0.025 mol) was refluxed in acetonitrile for 36 h. The reaction mixture was filtered and concentrated under vacuum, residue dissolved in methylene dichloride and washed with water and then with 5% NaOH. Organic layer was again washed with water and dried over anhydrous sodium sulfate. The filtrate was concentrated under vacuum to provide crude solid. It was than recrystallised from absolute ethanol to yield desired compound.

6-[3-(Naphthalen-1-yloxy)propoxyl]benzo[d][1,3]oxathiol-2-one ***5f***

Yield: 2.81 g (40%), mp: 130°C, molecular formula: $C_{20}H_{16}O_4S$ (352), elemental analysis: calcd. C 68.16, H 4.58, O 18.16, S 9.10; found C 68.09, H 4.51, O 18.34, S 9.06. IR ν_{max} (cm^{-1}) (KBr): 3107, 2943, 1709, 1402, 1070. ^1H NMR (δ ppm, $CDCl_3$): 7.73 (s, 1H, C_8'–H), 7.65 (d, 1H, C_2'–H), 7.42 (t, 1H, C_5'–H), 7.31 (t, 1H, C_6'–H), 7.08–7.14 (d, 3H, C_3'–H, C_4'–H, and C_7'–H), 6.84 (s, 1H, C_7–H), 6.73 (d, 2H, C_4–H, and C_5–H), 4.15 (t, 2H, –OCH_2), 4.02 (t, 2H, –CH_2O), 2.24 (m, 2H, –CH_2–).

6-[3-(Naphthalen-2-yloxy)propoxyl]benzo[d][1,3]oxathiol-2-one ***5g***

Yield: 3.02 g (43%), mp: 128°C, molecular formula: $C_{20}H_{16}O_4S$ (352), elemental analysis: calcd. C 68.16, H 4.58, O 18.16, S 9.10; found C 68.21, H 4.55, O 18.23, S 9.01. IR ν_{max} (cm^{-1}) (KBr): 2998, 2953, 1709, 1425,1216. ^1H NMR (δ ppm, $CDCl_3$): 8.15 (t, 1H, C_3'–H), 7.72 (t, 1H, C_6'–H), 7.47 (t, 1H, C_7'–H), 7.45 (d, 1H, C_1'–H), 7.39 (d, 1H, C_8–H), 7.27 (d, 1H, C_5'–H), 7.22 (d, 1H, C_4'–H), 6.87 (d, 1H, C_4–H), 6.81 (d, 2H, C_5–H, and C_7–H), 4.15 (t, 2H, –OCH_2), 4.01 (t, 2H, –CH_2O), 2.29 (m, 2H, –CH_2–).

6-[3-(4-Chlorophenoxy)propoxyl]benzo[d][1,3]oxathiol-2-one ***5h***

Yield: 3.97 g (59%), mp: 112°C, molecular formula: $C_{16}H_{13}ClO_4S$ (337), elemental analysis: calcd. C 57.06, H 3.89, Cl 10.53, O 19.00, S 9.52; found C 57.11, H 3.78, Cl 10.51, O 19.11, S 9.49. IR ν_{max} (cm^{-1}) (KBr): 3004, 2973, 1700, 1458, 1367, 1201. ^1H NMR (δ, ppm, $CDCl_3$): 8.16 (d, 2H, C_3'–H, and C_5'–H), 7.33 (d, 2H, C_2'–H, and C_6'–H), 6.87 (d, 1H, C_4–H), 6.83 (d, 2H, C_5–H, and C_7–H), 4.15 (t, 2H, –OCH_2), 3.98 (t, 2H, –CH_2O), 2.31 (m, 2H, –CH_2–).

6-[3-(p-Tolyloxy)propoxyl]benzo[d][1,3]oxathiol-2-one ***5i***

Yield: 3.47 g (55%), mp: 105°C, molecular formula: $C_{17}H_{16}O_4S$ (316), elemental analysis: calcd. C 64.54, H 5.10, O 20.23, S 10.13; found C 64.41, H 5.03, O 20.46, S 10.10. IR ν_{max} (cm^{-1}) (KBr): 3371, 3078, 2920, 1720, 1427, 1361. ^1H NMR (δ, ppm, $CDCl_3$): 8.07 (d, 2H, C_3'–H, and C_5'–H), 7.24 (d, 2H, C_2'–H, and C_6'–H), 6.87 (d, 1H C_4–H), 6.84 and 6.81 (d, 2H, C_5–H, and C_7–H), 4.18 (d, 2H, –OCH_2), 3.99 (t, 2H, –CH_2O), 2.27 (m, 2H, –CH_2–), 2.38 (m, 3H, –CH_3).

6-[3-(4-Nitrophenoxy)propoxyl]benzo[d][1,3]oxathiol-2-one ***5j***

Yield: 2.91 g (42%), mp: 111°C, molecular formula: $C_{16}H_{13}NO_6S$ (347), elemental analysis: calcd. C 55.33, H 3.77, N 4.03, O 27.64, S 9.23; found C 55.28, H 3.61, N 4.17, O 27.66, S 9.28. IR ν_{max} (cm^{-1}) (KBr): 3000, 2933, 1751, 1505, 1539. ^1H NMR (δ, ppm, $CDCl_3$): 8.11 (d, 2H, C_3'–H, and C_5'–H), 7.22 (d, 2H, C_2'–H, and C_6'–H), 6.87 (d, 1H, C_4–H), 6.83 and 6.81 (d, 2H, C_5–H, and C_7–H), 4.15 (d, 2H, C_1–H), 4.00 (t, 2H, –CH_2O), 2.29 (m, 2H, m, 2H, –CH_2–).

Biological activity

Experimental groups

Adult male albino mice (22 ± 2 g) were used in this study. They were housed in a quiet and temperature-controlled room (25 ± 3°C) with 12-h light/dark cycle. Food and water were made freely available to the animals during the study. Six animals were housed in each cage. Assays were carried out at the same time of the day so as to avoid variation due to circadian rhythms. For behavioral study mice were divided into three groups—control, standard, and test each with six animals. Methyl cellulose was used for preparing suspension of drugs in water for injection (WFI). Route of administration was i.p except wherever mentioned. Aripiprazole was used as reference compound. All the 10 compounds showed maximum inhibition of climbing behavior at the dose 60 mg/kg. This dose was selected for further study.

Inhibition of climbing behavior

Ability of compound to inhibit apomorphine-induced climbing behavior is an index of its D_2-antagonism and hence of potential antipsychotic activity.

Climbing behavior was assessed in the animals by placing them individually in cylindrical wire mesh cage (height 18 cm, diameter 14 cm). Animals given control saline injections remained on the floor of cylinder, exhibiting normal exploratory behavior, while animal given apomorphine (1.0 mg/kg; s.c) climbed up the walls of the cylinders holding onto the wire mesh with their paws. Test or reference compound was given 30 min before administration of apomorphine. Climbing behavior was assessed at 5-min intervals for 30 min, starting from 5 min after apomorphine administration (Kesten *et al.*, 1999).

Data was expressed as percentage inhibition of climbing behavior relative to control group (Table 1).

Antagonism of head twitches

Antagonism of head twitches induced by L-5-hydroxytryptophan (5-HTP) in mice indicates 5-HT_2 antagonistic activity. Carbidopa (25 mg/kg) was administered 20 min after drug followed by administration of 5-HTP (100 mg/kg) after 30 min. The numbers of head twitches were counted for a period of 5 min after 20 min (Kim *et al*., 1999). Data was expressed as percentage inhibition of head twitches relative to control group (Table 1).

Catalepsy induction

Induction of catalepsy by compound is a reflection of its ability to cause EPS in humans. 20 min after drug administration, mouse was placed on a horizontal bar (2 mm in diameter) kept at a height of 2.5 cm from the platform, with its hind paws resting on the platform. The time span for which the mouse retained its forepaws on the horizontal bar during observation period of 5 min was recorded (Khisti *et al*., 1998). Data was expressed as percentage induction with respect to control group.

Statistical analysis

All the biological data was analyzed using one-way ANOVA. If the overall F ratio was significant, post hoc comparison was carried out by Dunnett's test. P value of less than 0.05 was considered statistically significant.

Result and discussion

The aim of the undertaken research work is to make an effort in the direction of synthesizing molecules with an atypical antipsychotic like D_2 and 5-HT_2 antagonist activity. Efforts were focused upon compounds possessing a pharmacological profile suggestive of significant antipsychotic activity and minimal induction of extrapyramidal side effects.

To evaluate the D_2 antagonist activity, inhibition of climbing behavior in mice induced by apomorphine was used as a model. Since apomorphine being dopamine agonist, inhibition of climbing induced by it could give idea regarding the D_2 antagonist activity of the test compound which is supposed to be direct reflection of its antipsychotic potential. 5-HT_2 antagonistic activity is one of the main features of atypical antipsychotics. As 5-HTP is used as precursor of serotonin which acts as non-selective agonist for serotonin receptor, inhibition of 5-HTP-induced head twitches can be regarded as a hint for 5-HT_2 antagonist activity.

The important thing of interest in the preliminary pharmacological screening was to determine the propensity of the synthesized compounds to cause side effects in terms of catalepsy. All the synthesized compounds displayed dose-dependent cataleptic activity from mild to severe, probably because of blockade of D_2 receptors in the nigrostriatal region. This could be considered as the reflection of probable EPS they may induce in humans.

Effect of morpholine, diethylamine substitution on the carbazole nucleus has been reported for D_2 and 5HT_2 antagonist activities (Masaguer *et al*., 2000). Effect of aryl piperazine substitution on bezothiazolin-2-one has been evaluated for D_2 and 5HT_2 antagonist activities (Taverne *et al*., 1998). We have selected these substituents in the amine series.

Thus, we investigated the effects of the changes in the secondary amine groups in the lead compound [**5a**–**5e**], the alicyclic group, such as piperidine [**5a**], morpholine [**5b**], piperazine [**5d**], diethyl amine [**5c**], and deactivated aromatic group 1,2,4-triazole [**5e**], on the inhibition of climbing behavior [D_2 antagonism]. Surprisingly the triazolo-substituted derivate showed more effect than the alicyclic groups piperidine, piperazine, and morpholine, whereas the diethyl amine derivative showed the decreased effect. Similar trend was observed on the inhibition to the head twitches [5HT_2 antagonism]. In catalepsy induction model, the triazolo and diethyl amine derivatives displayed least induction followed alicyclic amine derivatives. Thus, all the derivatives in amine series exhibited significant D_2 and 5-HT_2 antagonistic activity, although, at higher dose than the standard drug aripiprazole. However, all the derivatives in amine series exhibited slightly increased catalepsy induction as compared to aripiprazole.

Next, keeping the 6-propyoxyl-benzo[*d*][1,3]oxathiol-2-one moiety in the lead compound, changes in the aryl ether were investigated. In this series, 4-substituted phenyl derivatives were found to be more active than naphthyl derivatives with respect to D_2 and 5-HT_2 antagonistic activity. Interestingly again deactivated aromatic ring, *p*-nitro derivative [**5j**] showed maximum D_2 and 5-HT_2 antagonism effect. In catalepsy induction test, *p*-chlorophenyl derivative displayed least catalepsy induction, whereas all other derivatives in this series exhibited catalepsy induction in the same range. Thus, it is evident that derivatives in the ether series showed considerable D_2 and 5-HT_2 antagonistic activity, again at higher dose than aripiprazole. Derivatives in this series too displayed increased catalepsy induction.

In summary, from the combined results including inhibition of climbing behavior [D_2 antagonism], inhibition of head twitches [5HT_2] antagonism, and catalepsy induction, compound **5e** 6-[(1,2,4-triazololyl-propyloxyl)]benzo[*d*][1,3]oxathiol-2-one from secondary amine series and **5j**

6-[(4-nitrophenyl)-propyloxyl)]benzo[*d*][1,3]oxathiol-2-one from the ether series can be considered as lead compounds

Conclusion

Our studies suggest that all the 6-substituted-benzo[*d*]-[1,3]oxathiol-2-one derivatives showed significant D_2 and 5-HT_2 antagonist activity in behavioral models, an activity profile attributed to atypical antipsychotic agents. Thus, this research work has furnished a novel molecule with potential antipsychotic activity. However, the compounds under investigation suffered from a drawback of catalepsy induction in rodents, likely because of non-specific D_2 blockade. All the synthesized compounds were found to be less active than the reference drug aripiprazole. Nevertheless, taking into consideration 'atypical antipsychotic like' activity profile of the synthesized compounds, it will be interesting to investigate this lead molecule further. Thus, to improve the activity of this molecule, further research is in progress at our laboratory.

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