Asian Journal of Chemistry; Vol. 23, No. 9 (2011), 3969-3974

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

Synthesis and Pharmacological Screening of Novel (2-(4-Methyl-2-oxo-2*H*-chromen-7-yloxy)-N-(benzo[d]thiazol-2-yl))acetamide Derivatives

ASHISH GAWAI[1,*], SANJIB DAS[1], MAHESH NEMADE[2] and SANDEEP WATHORE[2]

[1]Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh-786 004, India
[2]TVES's College of Pharmacy, Nehru Vidyanagar, Faizpur-425 503, India

*Corresponding author: Fax: +91 373 2370323; Tel: +91 373 2370254; E-mail: ashishgawai82@gmail.com

(*Received*: 20 October 2010; *Accepted*: 14 May 2011) AJC-9946

A new series of 2-(4-methyl-2-oxo-2*H*-chromen-7-yloxy)-N-(benzo[d]thiazol-2-yl)acetamide derivatives (**4a-k**) was synthesized and evaluated for their D_2 and $5HT_2$ antagonistic activity as a measure of atypical antipsychotic property. Compounds (**4a-k**) were synthesized by refluxing various N-(benzothiazol-2-yl)-2-chloroacetamides substituted derivatives (**3a-k**) with 7-hydroxy-4 methyl-2*H*-chromen-2-one (**1**) in acetonitrile and anhydrous K_2CO_3. N-(Benzothiazol-2-yl)-2-chloroacetamides substituted derivatives (**3a-k**) were prepared from the chloroacetyl chloride with various 2-amino benzothiazole substituted derivatives (**2a-k**). The synthesized compounds were characterized with the help of spectral and analytical data. Most of these compounds showed dopamine D_2 receptor antagonistic activity from moderate to high affinity along with serotonin 5-HT_2 receptor blockage activity: a property that has been suggested as necessary for atypicality. The D_2 and 5-HT_2 receptor blockage activity was evaluated by inhibition of apomorphine-induced climbing behaviour and 5HTP induced head twitches in mice, respectively.

Key Words: Schizophrenia, Atypical antipsychotics, Benzothiazole, Chromen-2-one.

INTRODUCTION

Antipsychotic drug treatment is the main therapeutic intervention for schizophrenia. Although the pathophysiology of the disease has yet to be clearly defined, the development of antipsychotic drugs in recent decades has been heavily influenced by the dopamine hypothesis, mainly supported by the capability of antipsychotic drugs of interfering with dopamine receptors *in vivo* and *in vitro* and by evidence that the clinical efficacy of typical antipsychotic drugs is correlated with their occupancy at dopamine D_2 receptors (D_2R)[1]. The most accepted model to explain the biochemical basis of schizophrenia postulates that dopaminergic activity has increased in the mesolimbic system of the brain[2]. In accordance with this, the pharmacological potencies of classical antipsychotics correlate with their affinities for D_2 receptors[3]. On the other hand, the extrapyramidal effects have been attributed to dopamine antagonism at nigrostriatal regions[4]. The "atypical" antipsychotics are characterized by a multireceptor affinity profile, which combines a potent antagonism for serotonin 5-HT with a dopamine D_2 and D_3 receptors blockade[5]. Second-generation antipsychotics combine D_2R occupancy and selective binding to certain subtypes of dopaminergic receptors[6] with activity at serotoninergic receptors such as 5-HT_{1A} receptors (5-$HT_{1A}R$) and 5-HT_{2A} receptors (5-$HT_{2A}R$), preferential 5-HT_2 in relation to D_2 antagonism[7], to provide drug therapies for resistant schizophrenic patients, with prompter therapeutic benefits and the improvement of cognitive symptoms[8].

In view of these reports, in the present work, it is worthwhile to synthesize series of 2-(4-methyl-2-oxo-2*H*-chromen-7-yloxy)-N-(benzo[d]thiazol-2-yl) acetamide derivatives (**4a-k**) and tested for dopamine D_2 as well as 5-HT receptor antagonist activity. The molecule that we had selected (chromen-2-one) was reported as selective dopamine antagonistic activity[9]. The molecule substituted with piperazine or piperidine was also evaluated for potential atypical antipsychotic activity[10] and 2-amino benzothiazole substituted derivatives were also reported for their 5HT affinity as potential atypical antipsychotics[11].

EXPERIMENTAL

Melting points were determined by open capillary method on Campbel electronic apparatus. The purity of the synthesized compounds was checked by TLC using pre-coated silica G_{254} plates and visualized in iodine and also by UV light. The IR spectra of synthesized compounds were recorded on a Jasco-V-5300 FTIR in potassium bromide discs. The ^1H NMR was recorded on a 300 MHz Jeol spectrophotometer in DMSO and using tetramethylsilane as internal standard.

General method of synthesis of 7-hydroxy-4 methyl-2*H*-chromen-2-one (1) (Scheme-I): The method of Pechmann and Duisberg[12] was followed for the preparation of 7-hydroxy-4-methyl-2*H*-chromen-2-one (**1**). 100 mL of conc. H_2SO_4 was kept in an ice-bath. When temperature reached to 10 ºC, a solution of resorcinol (10 g, 0.091 mol) and ethylacetoacetate (13 mL, 0.103 mol) was added with continuous stirring for 2 h. The temperature was maintained below 10 ºC throughout the addition. The reaction mixture was kept at room temperature for 18 h after which it was poured with vigorous stirring into the mixture of 200 g of crushed ice and 300 mL of distilled water. Precipitate was collected by vacuum filtration washed with cold water (325 mL). The solid was dissolved in 150 mL of 5 % NaOH, filtered and 2 M H_2SO_4 (55 mL) was added to it with vigorous stirring until the solution was acidic. The crude 7-hydroxy-4 methyl-2*H*-chromen-2-one (**1**) was collected by filtration at the pump, washed with cold water and dried. The product was recrystallized from ethanol.

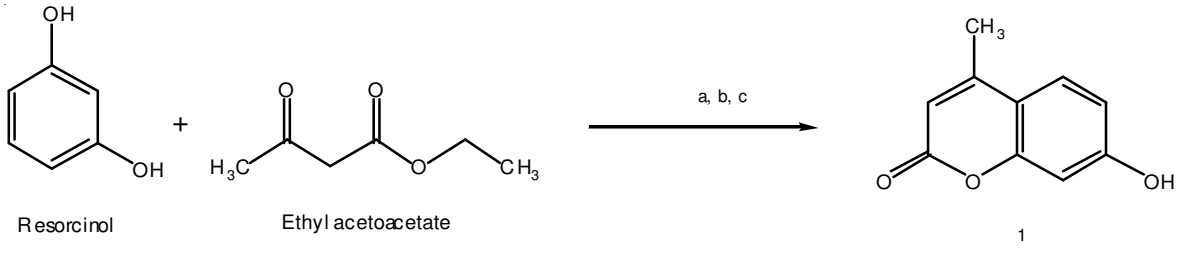
General method of synthesis of 2-amino benzothiazoles substituted derivatives (2a-k) (Scheme-II): For the synthesis of 2-amino benzothiaoles substituted derivatives[13] following method was used. To glacial acetic acid (20 mL) precooled to 5 ºC were added 8 g (0.08 mol) of potassium thiocyanate and 1.45 g (0.01 mol) of substituted aniline. The mixture was placed in freezing mixture of ice and salt and mechanically stirred while 1.6 mL of bromine in 6 mL of glacial acetic acid was added from dropping funnel at such a rate that the temp doesn't rise beyond 0 ºC. After all the bromine has been added within 105 min, the solution was stirred for an addition 2 h at 0 ºC and kept at room temp for 10 h. It was then allowed to stand overnight during which period an orange precipitate settled at the bottom, 6 mL water was added quickly and slurry was heated at 85 ºC on steam bath and filtered hot. The orange residue was placed in a reaction flask and treated with 10 mL of glacial acetic acid, heated again to 85 ºC and filtered hot. The combined filtrate was cooled and neutralized with concentrated ammonia to pH 6 when dark yellow precipitate was collected and recrystallized from benzene.

General method of synthesis of N-(benzo[d]thiazol-2-yl)-2-chloroacetamide substituted derivatives (3a-k) (Scheme-III): 2-Amino benzothiazole substituted derivatives (**2a-k**) (0.01 mol) was dissolved in 10 mL of acetonitrile. Anhydrous K_2CO_3 (0.01 mol) was added to the solution. Chloroacetyl-chloride (0.01 mol) was added drop wise to the mixture in the round bottom flask over a period of 15 min. The reaction was refluxed for 18 h. The filtrate was removed under vacuum using molecular distiller to afford dry solid. The solid obtained was dissolved in dichloromethane; the organic layer was washed with water and dried over anhydrous sodium sulfate. The organic layer was separated and evaporated to dryness to afford crude products **3a-k**, which were then recrystallized using ethanol.

General method of synthesis 2-(4-methyl-2-oxo-2*H*-chromen-7-yloxy)-N-(benzo[d]thiazol-2-yl)acetamide derivatives (4a-4k) (Secheme-IV): A mixture of **1**, compounds **3a-k** (0.01 mol) and anhydrous K_2CO_3 (0.01 mol) was added to the reaction flask and refluxed in acetonitrile for 24 h. The filtrate was removed under vacuum using molecular distiller to afford dry solid. The solid obtained was dissolved in dichloromethane. The organic layer was washed with water and dried over anhydrous sodium sulfate. The organic layer was separated and evaporated to dryness to afford crude products **4a-k**, which were then recrystallized using acetic acid.

Pharmacological method: Pharmacological evaluation of atypical antipsychotic activity was performed by testing their ability to inhibit apomorphine induced climbing behaviour and 5HTP induced head twitches in mice.

Animals: Albino Swiss male mice, 20-25 g were maintained on standard pallet diet and given tap water *ad libitum*. The experiments were performed in a quiet room with an

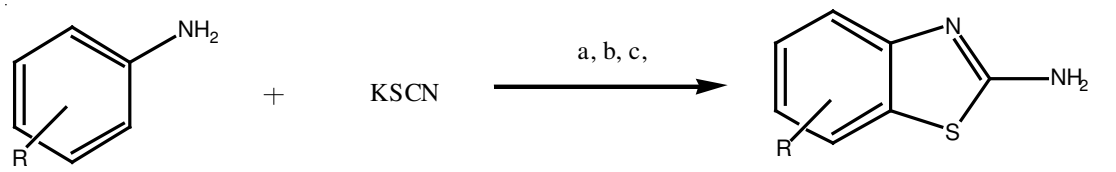


Resorcinol Ethyl acetoacetate 1

7-hydroxy-4-methyl-2*H*-chromen-2-one

(a) conc. H_2SO_4, (b) 5 % NaOH, (c) 2M H_2SO_4

Scheme-I: Synthesis of 7-hydroxy-4-methyl-2*H*-chromen-2-one (**1**)



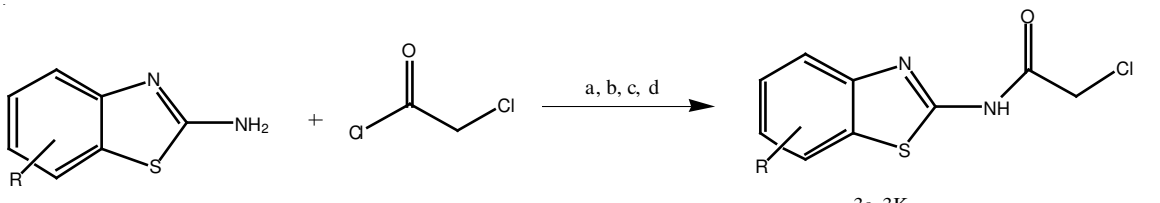
Sub. Amines

2-amino sub. benzothiazole derivatives

2 a-2K

(a) Gl. acetic acid, (b) bromine, (c) benzene

Scheme-II: Synthesis 2-amino benzothiazole substituted derivatives (**2a-k**)



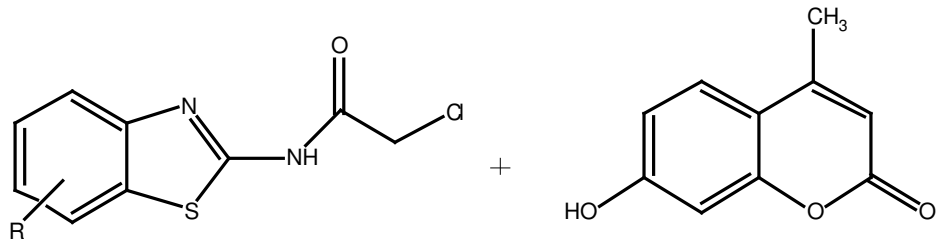
2a-2k
2-amino sub. benzothiazole derivatives

Chloroacetyl Chloride

3a-3K
N-(benzo[*d*]thiazol-2-yl)-2-chloroacetamide sub. derivatives

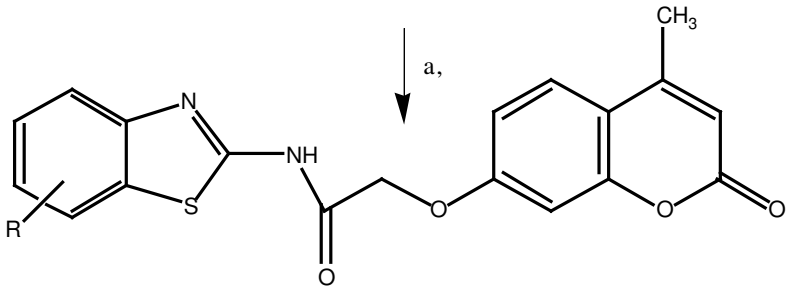
(a) Acetonitrile, (b) anhydrous K_2CO_3, (c) Dichlormethane, (d) ethanol

Scheme-III: Synthesis of N-(benzo[d]thiazol-2-yl)-2-chloroacetamide substituted derivatives (**3a-3k**)



3a-3K
N-(benzo[*d*]thiazol-2-yl)-2-chloroacetamide sub. derivatives

1
7-hydroxy-4-methyl-2*H*-chromen-2-one



4a-4k
2-(4-methyl-2-oxo-2*H*-chromen-7-yloxy)-*N*-(benzo[*d*]thiazol-2-yl)acetamide

(a) Acetonitrile, (b) anhydrous K_2CO_3, (c) Dichlormethane, (d) ethanol

Scheme-4: Synthesis of final compounds (**4a-k**)

ambient temperature of 22 ± 2 ºC and between 12-18 h each day to avoid behavioural changes resulting from circadian rhythm. The test compounds were suspended in 3 % gum acacia in water for injection. All the injections were given intraperitoneally (i.p.). The effects of the test compounds and vehicle control (3 % gum acacia 5 mL/Kg) on drug induced models were observed by injecting test compounds 0.5 h prior to the apomorphine or 5HTP.

Apomorphine induced climbing behaviour[14]: The animals were grouped randomly containing six animals in each group. The test groups received the dose of test compounds at 5 mg/kg body weight. The control and standard group received 3 % gum acacia 5 mL/kg and olanzepine 1 mg/kg body weight, respectively. Climbing behaviour was assessed in the animals by placing them individually in cylindrical wire mesh cage (height 18 cm, diameter 14 cm) 5 min after administration of apomorphine (1.0 mg/kg). The animals were kept in the cage and observed at the interval of 10, 20, 30 min after the administration of apomorphine. The following score was assigned to an individual animal: 0, when all four paws on the floor; 1, when two paws on the mesh and 2, when all the four paws on the mesh. The score was summed up for each animal. Data were expressed as percentage of blockage of climbing relative to apomorphine-treated control mice.

5-HTP induced head twitches[15]: The mice were grouped and administered test compounds and control similarly but the standard group received olanzepine (1 mg/kg, b.w). The head twitches in mice were counted after 20 min of 5-HTP (100 mg/kg, b.w.) administration at an interval of 5 min and for a period of 1 h.

RESULTS AND DISCUSSION

The physicochemical characterization of the target compounds were summarized in Table-1. All synthesized compounds were subjected for analytical study for confirmation of the structure by using FTIR spectroscopy and ^{1}H NMR spectroscopy as mention below.

7-Hydroxy-4-methyl-2*H*-chromen-2-one (1): The method of Pechman and Duisberg was followed for the synthesis of 7-hydroxy-4 methyl-2*H*-chromen-2-one. Yield: 51 %; m.p.

181-182 ºC; R_f: 0.45 [benzene; ethyl acetate: 4:1] IR (KBr, ν_{max}, cm^{-1}): 3500 (-OH), 2957 (aromatic C-H) 1680 (C=O), 1601-1452 (C=C), 1336-1159 (-C-CO-O), 1215 (-C-O phenol) and 746 (C-H out of plane), ^{1}H NMR (DMSO): 10.5 (b, 1H, -OH), 7.51-7.53 (d, 1H, C5-H), 6.6-6.9 (m, 2H, C_6-H), 6.06 (s, 1H, C_3-H), 2.29 (s, 3H, C_4-CH_3).

2-(4-Methyl-2-oxo-2*H*-chromen-7-yloxy)-N-(benzo[d]-thiazol-2-yl)acetamide (4a): IR (KBr, ν_{max}, cm^{-1}): 3375 (N-H), 3080 (C-H), 2914 (C-H), 1734 (C=O), 1440 (C=C), 1261 (C-N), 879 (C-H). ^{1}H NMR (δ, ppm, DMSO): 9.84 (s, 1H, N-H), 7.55 (m, 2H, $C_{5'}$-H and $C_{6'}$-H in benzothiazole), 8.17 (d, 2H, $C_{4'}$-H and $C_{7'}$-H in benzothiazole), 7.16 (d, 1H, in chromen-2-one), 6.63 (s, 2H, C_6-H and C_8-H in chromen-2-one), 6.02 (s, 1H, C_3-H in chromen-2-one) 4.84 (s, 2H, -CH_2 in the linkage), 1.89 (s, 3H, -CH_3 in chromen-2-one).

2-(4-Methyl-2-oxo-2*H*-chromen-7-yloxy)-N-(6-chlorobenzo[d]thiazol-2-yl) acetamide (4b): IR (KBr, ν_{max}, cm^{-1}): 3269 (N-H), 3063 (C-H), 2941 (C-H), 1672 (C=O), 1410 (C=C), 1261 (C-Cl), 831 (C-H). ^{1}H NMR (δ, ppm, DMSO): 10.14 (s, 1H, N-H), 8.15 (m, 2H, $C_{4'}$-H and $C_{7'}$-H in benzothiazole), 7.84 (d, 1H, $C_{5'}$-H), 7.27 (d, 1H, C_5-H in chromen-2-one), 6.53 (s, 2H, C_6-H and C_8-H in chromen-2-one), 5.93 (s, 1H, C_3-H in chromen-2-one) 4.90 (s, 2H, -CH_2 in the linkage), 1.71 (s, 3H, -CH_3 in chromen-2-one).

2-(4-Methyl-2-oxo-2*H*-chromen-7-yloxy)-N-(6-methoxybenzo[d]thiazol-2-yl) acetamide (4c): IR (KBr, ν_{max}, cm^{-1}): 3319 (N-H), 3065 (C-H), 2854 (C-H), 1699 (C=O), 1456 (C=C), 1392 (C-O), 1257 (C-N), 860 (C-H). ^{1}H NMR (δ, ppm, DMSO): 9.38 (s, 1H, N-H), 8.27 (d, 2H, $C_{4'}$-H, in benzothiazole), 7.73 (s, 1H, $C_{7'}$-H in benzothiazole), 7.03 (s, 1H, $C_{5'}$-H in benzothiazole) 7.41 (d, 1H, in chromen-2-one), 7.02 (s, 2H, C_6-H and C_8-H in chromen-2-one), 5.47(s, 1H, C_3-H in chromen-2-one), 4.12 (s, 2H, -CH_2 in the linkage), 3.13 (s, 3H, -CH_3 in methoxy of benzothaizole), 2.05 (s, 3H, -CH_3 in chromen-2-one).

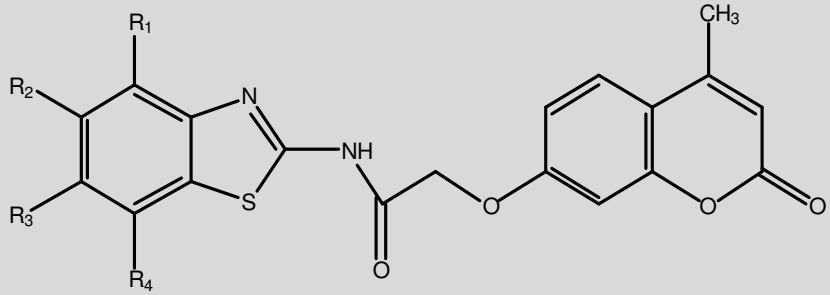
2-(4-Methyl-2-oxo-2*H*-chromen-7-yloxy)-N-(6-nitro-benzo[d]thiazol-2-yl)acetamide (4d): IR (KBr, ν_{max}, cm^{-1}): 3306 (N-H), 3092 (C-H), 2918 (C-H), 1709 (C=O), 1581 (C=C), 1390 (C-O), 1235 (C-N), 837 (C-H). ^{1}H NMR (δ, ppm, $CDCl_3$): 10.00 (s, 1H, N-H), 9.11 (s, 1H, $C_{7'}$-H, in benzothiazole), 8.30 (d, 2H, $C_{4'}$-H and $C_{5'}$-H in benzothiazole), 7.20 (d, 1H, C_5-H in chromen-2-one), 6.40 (dd, 2H, C6-H and C_8-H in chromen-2-one), 5.42 (s, 1H, C_3-H in chromen-2-one) 4.30 (s, 2H, -CH_2 in the linkage), 1.34 (s, 3H, -CH_3 in chromen-2-one).

2-(4-Methyl-2-oxo-2*H*-chromen-7-yloxy)-N-(4-chloro-benzo[d]thiazol-2-yl)acetamide (4e): IR (KBr, ν_{max}, cm^{-1}): 3306 (N-H), 3090 (C-H), 2920 (C-H), 1711 (C=O), 1565 (C=C), 1390 (C-O), 1205 (C-Cl), 837 (CH). ^{1}H NMR (δ, ppm, DMSO): 9.45 (s, 1H, N-H), 8.03 (d, 1H, $C_{7'}$-H in benzothiazole) 7.53 (m, 2H, $C_{5'}$-H and $C_{6'}$-H in benzothiazole), 7.00 (d, 1H, C_5-H in chromen-2-one), 6.17 (d, 2H, in chromen-2-one), 5.39 (s, 1H, C_3-H in chromen-2-one) 4.04 (s, 2H, -CH_2 in the linkage), 1.70 (s, 3H, -CH_3 in chromen-2-one).

2-(4-Methyl-2-oxo-2*H*-chromen-7-yloxy)-N-(6-fluoro-benzo[d]thiazol-2-yl)acetamid (4f): IR (KBr, ν_{max}, cm^{-1}): 3070 (NH), 2922 (ArCH), 2918 (CH), 1703 (C=O), 1596 (C=C), 1342 (C-O), 1205 (C-F), 850 (C-H). ^{1}H NMR (δ, ppm,$CDCl_3$): 10.10 (s, 1H, N-H), 8.13 (m, 1H, $C_{4'}$-H, in benzothiazole), 7.90 (d, 1H, $C_{5'}$-H benzothiazole), 7.92 (d, 1H, $C_{7'}$-H benzothiazole) 7.02 (d, 1H, in chromen-2-one), 6.53 (m, 2H, C_6-H and C_8-H in chromen-2-one), 5.86 (s, 1H, C_3-H in chromen-2-one) 4.36 (s, 2H, -CH_2 in the linkage), 1.71 (s, 3H, -CH_3 in chromen-2-one).

2-(4-Methyl-2-oxo-2*H*-chromen-7-yloxy)-N-(5-chloro-6-fluorobenzo[d]thiazol-2-yl)acetamide (4g): IR (KBr, ν_{max},

TABLE-1
PHYSICOCHEMICAL CHARACTERIZATION OF SYNTHESIZED COMPOUNDS (**4a-4k**)



4a-4k

Compound	m.f.	R_1	R_2	R_3	Yield (%)	m.p. (ºC)*	R_f**
4a	$C_{19}H_{14}N_2O_4S$	–	–	–	48	140-141	0.56
4b	$C_{19}H_{13}ClN_2O_4S$	–	–	Cl	53	153-154	0.64
4c	$C_{20}H_{16}N_2O_5S$	–	–	OCH_3	58	174-175	0.60
4d	$C_{19}H_{13}N_3O_6S$	–	–	NO_2	42	159-160	0.48
4e	$C_{19}H_{13}ClN_2O_4S$	Cl	–	-	38	148-149	0.63
4f	$C_{19}H_{13}FN_2O_4S$	–	–	F	48	162-163	0.57
4g	$C_{19}H_{12}ClFN_2O_4S$	–	Cl	F	56	170	0.49
4h	$C_{20}H_{16}N_2O_4S$	CH_3	–	–	35	138-139	0.53
4i	$C_{20}H_{16}N_2O_4S$	–	–	CH_3	57	144	0.62
4j	$C_{19}H_{13}ClN_2O_4S$	–	Cl	–	18	167-168	0.48
4k	$C_{19}H_{13}BrN_2O_4S$	Br	–	–	13	155-157	0.60

*Melting points were uncorrected. **Mobile phase for (**4a-4k**), [benzene; ethyl acetate:4;1].

cm^{-1}): 3423 (N-H), 3078 (C-H), 2920 (C-H), 1720 (C=O), 1539 (C=C), 1136 (C-Cl), 1203 (C-F), ^{1}H NMR (δ, ppm, $CDCl_3$): 10.04 (s, 1H, N-H), 9.35 (s, 1H, C_4-H, in benzothiazole), 8.40 (d, 1H, C_7-H in benzothiazole), 7.45 (d, 1H, C_5-H in chromen-2-one), 7.00 (d, 2H, C_6-H and C_8-H in chromen-2-one), 6.10 (s, 1H, C_3-H in chromen-2-one) 4.93 (s, 2H, -CH_2 in the linkage), 2.18 (s, 3H, -CH_3 in chromen-2-one).

2-(4-Methyl-2-oxo-2*H*-chromen-7-yloxy)-N-(4-methyl-benzo[d]thiazol-2-yl)acetamide (4h): IR (KBr, ν_{max}, cm^{-1}): 3371 (N-H), 3078 (C-H), 2920 (C-H), 1720 (C=O), 1563 (C=C), 1203 (C-N), 841 (C-H), ^{1}H NMR (δ, ppm,$CDCl_3$): 8.04 (s, 1H, N-H), 7.55 (d, 1H, C_5-H, in benzothiazole), 7.82 (m, 1H, C_6-H in benzothiazole), 7.10 (m, 1H, in benzothiazole), 6.33 (m, 2H, C_6-H and C_8-H in chromen-2-one), 7.02 (s, 1H, C_5-H in chromen-2-one), 5.93 (s, 1H, C_3-H in chromen-2-one), 4.84 (s, 2H, -CH_2 in the linkage), 2.30 (s, 3H, -CH_3 in benzothaizole), 1.70 (s, 3H, -CH_3 in chromen-2-one).

2-(4-Methyl-2-oxo-2H-chromen-7-yloxy)-N-(6-methyl-benzo[d]thiazol-2-yl)acetamide (4i): IR (KBr, ν_{max}, cm^{-1}): 265 (N-H), 3005 (C-H), 2891 (C-H), 1743 (C=O), 1528 (C=C), 1332 (C-N), 851 (C-H). ^{1}H NMR (δ, ppm, DMSO): 8.04 (s, 1H, N-H), 8.11 (d, 1H, C_4-H, in benzothiazole), 7.70 (d, 1H, C_7-H in benzothiazole), 7.20 (m, 1H, in benzothiazole), 6.00 (m, 2H, C_6-H and C_8-H in chromen-2-one), 7.11 (s, 1H, C_5-H in chromen-2-one), 5.10 (s, 1H, C_3-H in chromen-2-one), 4.40 (s, 2H, -CH_2 in the linkage), 2.55 (s, 3H, C6-H in benzothiazole), 1.70 (s, 3H, -CH_3 in chromen-2-one).

2-(4-Methyl-2-oxo-2*H*-chromen-7-yloxy)-N-(5-chloro-benzo[d]thiazol-2-yl)acetamide (4j): IR (KBr, ν_{max}, cm^{-1}): 3359 (N-H), 3026 (C-H), 2901 (C-H), 1678 (C=O), 1468 (C=C), 1147 (C-Cl), 816 (C-H), ^{1}H NMR (δ, ppm, DMSO): 8.44 (s, 1H, N-H), 8.25 (s, 1H, C4'-H, in benzothiazole), 8.00 (d, 1H, C_7-H in benzothiazole), 7.60 (d, 1H, in chromen-2-one), 6.60 (m, 2H, C_6-H and C_8-H in chromen-2-one), 7.12 (s, 1H, C_3-H in chromen-2-one) 4.00 (s, 2H, -CH_2 in the linkage), 1.63 (s, 3H, -CH_3 in chromen-2-one).

2-(4-Methyl-2-oxo-2*H*-chromen-7-yloxy)-N-(5-bromo-benzo[d]thiazol-2-yl)acetamide (4k): IR (KBr, ν_{max}, cm^{-1}): 3265 (N-H), 3005 (C-H), 2891 (C-H), 1743 (C=O), 1528 (C=C), 1332 (C-N), 851 (C-H), ^{1}H NMR (δ, ppm, DMSO): 8.14 (s, 1H, N-H), 7.90 (m, 1H, C_5-H in benzothiazole), 7.60 (m, 2H, C_5-H and C_6-H in benzothiazole), 7.16 (d, 1H, in chromen-2-one), 6.50 (s, 2H, C_6-H and C_8-H in chromen-2-one), 5.80 (s, 1H, C_3-H in chromen-2-one) 4.70 (s, 2H, -CH_2 in the linkage), 1.70 (s, 3H, -CH_3 in chromen-2-one).

Pharmacological results: The affinity of the synthesized compounds for the dopamine D_2 and Serotonin 5HT receptors was measured by pharmacological screening of apomorphine induced psychosis (Fig. 1) and 5HTP induced head twitches (Fig. 2) on Swiss albino mice. All compounds had shown high dopamine D_2 and serotonin 5HT receptors antagonistic affinity.

Conclusion

Present study suggests that all the synthesized compounds provide a chemical class of compounds that showed significant antipsychotic activity in pharmacological model predictive of D_2 antagonist activity and also had significant antagonistic activity at 5-HT receptor, an index of hypothesized atypical profile. The compounds which were substituted with chloro, bromo at *ortho* position and nitro, methyl and chloro at *meta* position showed significant dopamine D_2 receptor antagonistic activity and the compounds which were substituted with chloro, bromo at *ortho* position and chloro, fluoro and methoxy at *meta* position showed significant 5HT receptor antagonistic activity. From this data, it is concluded that compounds 2-(4-methyl-2-oxo-2*H*-chromen-7-yloxy)-N-(4-chloro-benzo[d]-thiazol-2-yl)acetamide (**4e**) and 2-(4-methyl-2-oxo-2*H*-chromen-7-yloxy)-N-(5-chlorobenzo[d]thiazol-2-yl)acetamide (**4j**) have better atypical antipsychotic profile. Detail toxicity study is required for characterization of the compounds for the therapeutic utility.

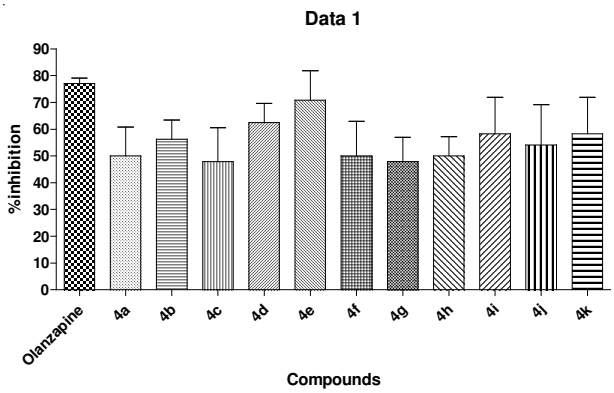


Fig. 1. Percentage inhibition of apomorphine induced climbing behaviour by synthesized compounds at the dose of 5 mg/kg. *n = 6, $p < 0.05$, $ dose of olanzapine was 1 mg/kg, apomorphine 1 mg/kg

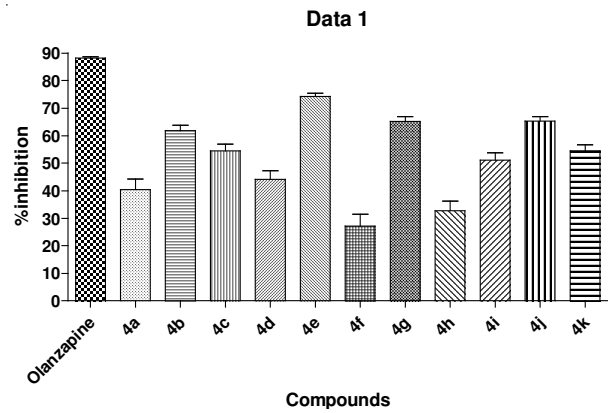


Fig. 2. Percentage inhibition of 5-HT induced head twitches by synthesized compounds at the dose of 5 mg/kg. *n = 6, $p < 0.05$, $ dose of olanzapine was 1 mg/kg

ACKNOWLEDGEMENTS

The authors acknowledged and thank TVES's college of Pharmacy, Faizpur, for providing animal activity on albino mice for biological evaluation of the compounds. Thanks are also due to University of Pune for providing ^{1}HNMR and elemental analysis, respectively.

REFERENCES

1. A. Carlsson, *Neuropsychopharmacology*, **1**, 179 (1988).
2. K.L. Davis, R.S. Kahn, G. Koi and M. Davidson, *Am. J. Psychiatry*, **148**, 1474 (1991).
3. I. Creese, D.R. Burt and S.H. Snyder, *Science*, **192**, 481 (1976).
4. B. Costall and R.J. Naylor, *Neuropharmacology*, **13**, 353 (1974).

5. M. Campbell, P.I. Young, D.N. Bateman, J.M. Smith and S.H. Thomas, *Br. J. Clin. Pharmacol*., **47**, 13 (1999).
6. S.A. West and C.B. Nemeroff, *Drugs Today*, **29**, 183 (1993).
7. H.Y. Meltzer, S. Matsubara and J.C. Lee, *Psychopharmacol. Bull*., **25**, 390 (1989).
8. R. Morphy and Z. Rankovic, *J. Med. Chem*., **48**, 6523 (2005).
9. R.K. Suzanne, G.H. Thomas and J.J. Stephen, *J. Med. Chem*., **42**, 3718 (1999).
10. J. Bolo, S. Gubert and L. Anglada, *J. Med. Chem*., **39**, 2962 (1996).
11. T. Taverne and O. Diouf, *J. Med. Chem*., **41**, 2010 (1998).
12. H. Pechmann and C. Duisberg, *Ber*, **16**, 2119 (1883).
13. G.M. Sreenivasa and E.S. Jayachandran, *Arch. Pharm. Sci. Res*., **1**, 150 (2009).
14. A.S. Davis, P. Jenner and C.D. Marsden, *Br. J. Pharmacol*., **87**, 129 (1986).
15. W. Chung, J.B. Park, U.G. Kang and S.K. Yong, *Pharmacol. Biochem. Behav*., **71**, 191 (2002).