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NEW 7-(2-(BENZOL[*d*]THIAZOL-2-YLAMINO)ETHOXY)-4-METHYL-2*H*-CHROMEN-2-ONE DERIVATIES WITH ATYPICAL ANTIPSYCHOTIC ACTIVITY

Gawai Ashish[1]*, Das Sanjib[2], Yashwant Pathak[3]

[1]Anuradha College of Pharmacy, Dept. of Quality Assurance

Chikhli, Dist-Buldana. M.S., INDIA

drashishgawai@gmail.com

[2]School of Pharmacy, Department Pharmaceutical Sciences

Assam University,Silchar, Assam-786004, INDIA

dr_sanjib@sify.com

[3] School of Pharmacy, University of South Florida Health, Tampa, Florida, USA

ABSTRACT

A new series of 7-(2-(benzo[d]thiazol-2-ylamino)ethoxy)-4-methyl-2H-chromen-2-one derivatives(4a-4k) was synthesized and evaluated for their D_2 and $5HT_2$ antagonistic activity as a measure of atypical antipsychotic property. Compounds 7-(2-(benzo[d]thiazol-2-ylamino)ethoxy)-4-methyl-2H-chromen-2-one derivatives (4a-4k) was synthesized by refluxing 2-amino benzothiazoles substituted derivatives (3a-3k) and 7-(2-Chloroethoxy)-4-methyl-2H-chromen-2-one (2) in dry pyridine. 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 potency along with serotonin 5-HT_2 receptor blockage activity: a property that has been suggested to be necessary for atypical nature of antipshycotic agents. The D_2 and 5-HT_2 receptor blockage activity was evaluated by inhibition of apomorphine-induced climbing behavior and 5HTP induced head twitches in mice respectively.

KEYWORDS: Schizophrenia, Atypical Antipsychotics, Benzothiazole. Chromen-2-one

RESUMO

Uma nova série de derivados de 7-(2-benzo[d]tiazol-2-ilamino)etoxi-4-metil-2H-cromeno-2-ona foram sintetizados e avaliados para suas propriedades D_2 e $5HT_2$ antagónicas e medida de propriedade antipsicótica. A maioria destes compostos mostraram atividade antagônica do receptor da dopamina e bloqueio da atividade do receptor 5-HT2 da serotonina, propriedades necessárias para a atividade atípica de agentes antipsicóticos. Os efeitos foram confirmados em camundongos.

PALAVRAS CHAVE: Esquizofrenia, Antipsicótico Atípico, Benzotiazol, Cromeno-2-ona

Corresponding Author: Dr. Ashish A. Gawai, Associate Professor, Anuradha College of Pharmacy, Chikhli-443201, Dist-Buldana, M.S, India.

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INTRODUCTION

A number of psychiatric disorders, including anxiety, depression, schizophrenia and neurodegenerative disorder like Parkinson's disease are known to involved defects in the function of neural pathways sustained by the neurotransmitters dopamine and serotonin[1, 2, 3]. Antipsychotic drugs antagonising central dopaminergic receptors have been used for several decades in the treatment of psychiatric disorder schizophrenia[4]. Although these drugs can reduce the positive symptoms of schizophrenia, they unfortunately often induce extapyramidal side effects and are furthermore often not able to control the negative symptoms. The antipsychotic action has been suggested due to a blockade of the mesocorticolimbic dopaminergic system[5, 6]. In accordance with this, the pharmacological potencies of classical antipsychotics correlate with their affinities for dopamine D_2 receptors[7]. The last decade has witnessed the discovery of the multiplicity of serotonin 5-HT receptors[8, 9, 10] and several 5-HT ligands have been studied with regard to their affinity, specificity and potential therapeutic application. The current status of antipsychotic agents and our previous works, synthesis and Pharmacological screening of new coumarinoacetamides[11], synthesis and neuroleptic activity of new **Coumarinoacetamides** with special reference to atypical antipsychotic activity[12] have led to the design and synthesis of new series of novel **2-(4-methyl-2-oxo-2*H*-chromen-7-yloxy)-N-(benzo[*d*]thiazol-2-yl) acetamide derivatives** (In Press). These compounds shown antipsychotic and analgesic activity assuming their interaction with serotoninergic 5HT and Dopaminergic D_2 receptor property. In an effort to increase such properties and gain access to new neuroleptic agents with or without reduced extrapyramidal side-effects, we have synthesized benzothiazole derivatives attached with Chromen-2-one moiety by ethoxy polar side chain linkage. Benzothiazole derivatives were reported to have 5HT antagonistic property[13] where as Chromen-2-one moiety was reported for their dopaminergic D_2 antagonistic activity[14]. The combination of these two antagonistic moieties could possibly lead to a new series of antipsychotic drugs with reduced CNS side-effects.

MATERIAL AND METHODS

Melting points were determined by open capillary method on Campbell electronic apparatus and are uncorrected. The purity of the synthesized compounds was checked by TLC using precoated silica G_{254} plates and visualized in iodine and UV light. The IR spectra of synthesized compounds were recorded by a Jasco-V-5300 FTIR in potassium bromide discs. The ^{1}H NMR was recorded on a 300 MHz JEOL spectrophotometer in DMSO and $CHCl_3$ using tetramethylsilane as internal standard.

EXPERIMENTAL METHODS

The general methods of synthesis exemplified are illustrated as below.

General method of synthesis of 7-hydroxy-4 methyl-2*H*-chromen-2-one (1)

(Scheme 1)

The method of Pechmann and Duisberg[15] was followed for the preparation of 7-hydroxy-4 methyl-2*H*-chromen-2-one (1). 100ml of conc. H_2SO_4 was kept in an ice-bath. When temperature fell below 10^0C, a solution of resorcinol (10gm, 0.091 moles) and ethylacetoacetate (13ml, 0.103 moles) was added with continuous stirring for 2hr. The temperature was maintained below 10^0C throughout the addition. The reaction mixture was kept at room temperature for 18 hr after which it was poured with vigorous stirring into the mixture of 200gm of crushed ice and 300ml of distilled water. Precipitate was collected by vacuum filtration and washed with cold water (325ml). The solid was dissolved in 150ml of 5% NaOH, filtered, and 2M H_2SO_4 (55ml) 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.

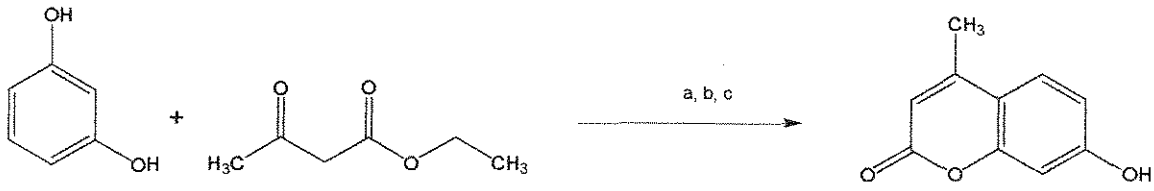
General method of synthesis of 7-(2-Chloroethoxy)-4-methyl-2*H*-chromen-2-one (2), (Scheme 2)

7-hydroxy-4-methyl-2H-chromen-2-one (1) (0.01 mol) was dissolved in 10ml acetonitrile with anhydrous K_2CO_3 (0.01 mol) was added to the solution. 1-Bromo 2-Chloroethane (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 18h. 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 **(2)** which was then recrystallized using ethanol.

General method of synthesis of 2-amino benzothiazoles substituted derivatives (3a-3k) (Scheme 3)

2-amino benzothiazole substituted derivatives was synthesis by following method[16]. To glacial acetic acid (20ml) precooled to 5^0C were added 8gm (0.08mol) of potassium thiocynate and 1.45gm (0.01mol) of substituted aniline. The mixture was placed in freezing mixture of ice and salt and mechanically stirred while 1.6ml of bromine in 6ml of glacial acetic acid was added from dropping funnel at such a rate that the temperature doesn't rise beyond 0^0C. After addition of bromine for 105 minutes, the solution was stirred for an additional 2 hours at 0^0C and at room temperature for 10 hour. It was then allowed to stand overnight during which period an orange precipitate was settled at the bottom where 6ml water was added quickly and slurry was heated at 85^0C on steam bath and filtered in hot condition. The orange residue was placed in a reaction flask and treated with 10ml of glacial acetic acid, heated again to 85^0 and filtered in hot state. The combined filtrate was cooled and neutralized with concentrated

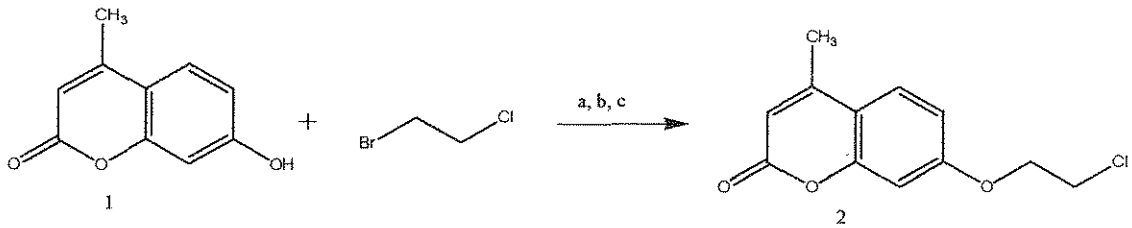
Scheme 1: Synthesis of 7-hydroxy-4 methyl-2*H*-chromen-2-one (1)



Resorcinol Ethyl acetoacetate 1

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

Scheme 2: Synthesis of 7-(2-Chloroethoxy)-4-methyl-2*H*-chormen-2-one



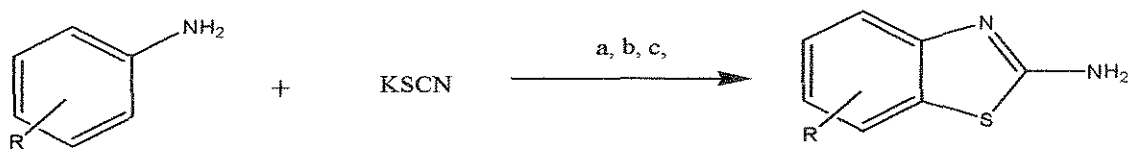
1 7-hydroxy 4-methyl coumarin

1 Bromo 2 Chloroethane

2 7-(2-Chloroethoxy)-4-methyl-2H-chromen-2-one

a. Acetonitrile, b. anhydrousK_2CO_3, c. Dichloromethane

Scheme 3: Synthesis 2-amino Benzothiazole substituted derivatives (3a-3k)



Sub. Amines

Sub. 2-amino Benzothiazole 3a-3k

a. Gl. Acetic Acid, b. Bromine, c. Benzene

ammonia to pH 6 when dark yellow precipitate was collected and recrystallised from benzene.

General method of synthesis 7-(2-(benzo[*d*]thiazol-2-ylamino)ethoxy)-4-methyl-2*H*-chromen-2-one derivatives (4a-4k) (Scheme 4)

A mixture of **7-(2-Chloroethoxy)-4-methyl-2*H*-chromen-2-one (2)** with compounds **3a-3k** (0.01 mol) was added to the reaction flask and refluxed in dry pyridine for 24 hours. The solvent was distilled off. The mixture was collected and poured on to cursed ice. The solid product was filtered and recrystallised from ethanol.

Pharmacological Evaluation of Atypical Antipsychotics Activity:

Pharmacological evaluation of atypical antipsychotic activity was performed by testing their ability to inhibit apomorphine induced climbing behavior (Figure 1) and 5HTP induced head twitches in mice (Figure 2).

Animals: Albino Swiss male mice, 20-25 g were maintained on standard pallet diet and given tap water *ad libidum*. The experiments were performed in a quiet room with an ambient temperature of 22^{0+}-2^{0}C and between 12.00- 18.00 hrs each day to avoid behavioral 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 5ml/Kg) on drug induced models were observed by injecting test compounds 30 minutes prior to the apomorphine and 5HTP.

Apomorphine induced Climbing Behavior[17]

The animals were grouped randomly containing six animals in each group. The test groups received dose of test compounds 5 mg/kg body weight. The control and standard group received 3% gum acacia 5ml/kg and olanzepine 1mg/kg body weight respectively. Climbing behaviour was assessed in the animals by placing them individually in cylindrical wire mesh cage (height 18cm, diameter 14 cm) 5 minute after administration of apomorphine (1.0 mg/kg) The animals were kept in the cage, and observed at the interval of 10, 20, 30 minute 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 Twiches[18]

The mice were grouped and administered test compounds at 5 mg/kg and control group 3 % gum acacia but the standard group received olanzepine (1 mg/kg, b.w). The head twitches in mice were counted after 20 minutes of 5-HTP (100mg/kg) administration at an interval of 5 minutes and for a period of 1hour.

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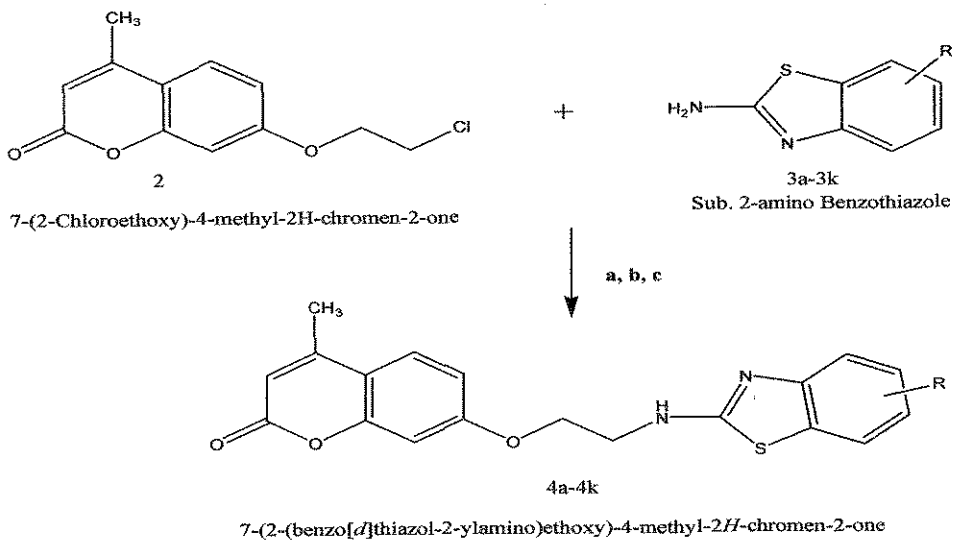
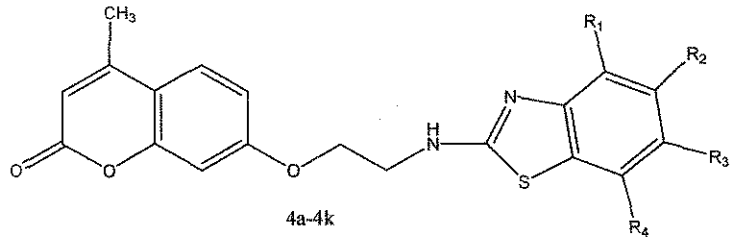
Scheme 4: Synthesis of 7-(2-(benzo[*d*]thiazol-2-ylamino)ethoxy)-4-methyl-2*H*-Chromen-2-one derivatives



a. dry pyridine, b. crushed ice, c. ethanol.

RESULTS AND DISCUSSION

Table-1. Physicochemical data of synthesized compounds **(4a-4k)**



4a-4k

Cmp	Mol. Formula	R_1	R_2	R_3	Elemental Analysis (%) C	H	N	Yield (%)	m. p (^{0}C)♦	Rf*
4a	$C_{19}H_{16}N_2O_3S$	-	-	-	64.7	4.5	7.9	80	180-182	0.60
4b	$C_{19}H_{15}ClN_2O_3S$	-	-	Cl	58.9	3.9	7.2	53	130	0.35
4c	$C_{20}H_{18}N_2O_4S$	-	-	OCH_3	62.8	4.7	7.3	69	170	0.5
4d	$C_{19}H_{15}N_3O_5S$	-	-	NO_2	57.1	3.7	10.5	73	160-161	0.63
4e	$C_{19}H_{15}ClN_2O_3S$	Cl	-	-	58.9	3.9	7.2	75	152-153	0.59
4f	$C_{19}H_{15}FN_2O_3S$	-	-	F	61.6	4.1	7.5	63	174	0.32
4g	$C_{19}H_{14}ClFN_2O_3S$	-	Cl	F	56.4	3.4	7.0	68	130-131	0.38
4h	$C_{20}H_{18}N_2O_3S$	CH_3	-	-	65.6	5.0	7.7	55	168-169	0.44
4i	$C_{20}H_{18}N_2O_3S$	-	-	CH_3	65.6	5.0	7.7	68	154-155	0.60
4j	$C_{19}H_{15}ClN_2O_3S$	-	Cl	-	59.0	3.9	7.3	18	149	0.49
4k	$C_{19}H_{15}BrN_2O_3S$	Br	-	-	52.9	3.5	6.5	13	134	0.55

♦ Melting points were uncorrected
*Mobile phase for (4a-4k) [Benzene; Ethyl acetate : 4;1]

7-Hydroxy-4-methyl chromen-2-one (1)

The method of Pechman and Duisberg was followed for the synthesis of 7-Hydroxy-4-methyl chromen-2-one. **Yield**: 51%; **m.p.** 181-182; **Rf**: 0.45 [benzene; ethyl acetate: 4:1] **IR (KBr) 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,C_5-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).

7-(2-Chloroethoxy)-4-methyl-2H-chromen-2-one (2)

Yield: 59% ; **m.p.** 120-121; **Rf**: 0.65 [benzene; ethyl acetate: 4:1] **IR (KBr) cm^{-1}**: 2931.6(aromatic C-H) 1724(C=O streching), 1682(aromatic C=C streching), 1386-1201(-C-CO-O), 1240(-C-O phenol), 644(C-Cl stretching) and 746(C-H out of plane), **^{1}H NMR (DMSO)**: 7.51(d,1H,C_5-H), 6.6-6.9(m,2H,C_6-H and C_8-H), 6(s,1H,C_3-H), 2.15(s,3H,C_4-CH_3). 4.20(t, 2H, O-CH_2 linkage), 4.12(t, 2H, Cl-CH_2 linkage)

7-(2-(benzo[d]thiazol-2-ylamino)ethoxy)-4-methyl-2H-chromen-2-one (4a)

IR (KBr): 3359.5(N-H stretching), 2990(Aromatic C-H stretching), 1688(C=O stretching), 1587-1440(C=C), 1248(C-N), 748(C-S stretching) **cm^{-1}**. **^{1}H NMR (δ, ppm, DMSO):** 8.6(t, 1H, N-H), 7.16(d,1H,C_5-H in Chromen-2-one), 6.6-6.9(d,2H,C_6-H and C_8-H in Chormen-2-one), 5.90(s,1H,C_3-H in Chromen-2-one), 2.3(s,3H,C_4-CH_3 in Chromen-2-one), 4.24(t,2H,O-CH_2 linkage), 4.12(t,2H,N-CH_2 linkage), 7.47(m,2H, $C_{5'}$-H,&$C_{6'}$-H in Benzothiazole), 8.10(d,2H,$C_{4'}$-H&$C_{7'}$H in benzothiazole)

7-(2-(6-Chlorobenzo[d]thiazol-2-ylamino)ethoxy)-4-methyl-2H-chromen-2-one (4b)

IR (KBr): 3211(N-H stretching), 2966(C-H stretching), 1732(C=O stret), 1458-1365 (C=C), 1277(C-N), 1171(CO-O-C stert), 781(C-S stretching) **cm^{-1}**. **^{1}H NMR (δ, ppm, DMSO):** 9.11(t,1H,N-H), 7.23(d,1H,C_5-H in Chromen-2-one), 6.6-6.9 (d,2H,C_6-H and C_8-H in Chormen-2-one), 6.05(s,1H,C_3-H in Chromen-2-one), 2.0(s,3H,C_4-CH_3 in Chromen-2-one). 4.5(t, 2H, O-CH_2 linkage), 4.60(t, 2H, NH-CH_2 linkage), 7.60(d, 1H, $C_{5'}$-H in Benzothiazole), 8.15(d, 2H, $C_{4'}$-H&$C_{7'}$H in benzothiazole)

7-(2-(6-methoxybenzo[d]thiazol-2-ylamino)ethoxy)-4-methyl-2H-chromen-2-one (4c)

IR (KBr): 3410(N-H), 2854(C-H), 1715(C=O), 1452(C=C), 1264(C-N), 1134(CO-O-C), 747(C-S) **cm^{-1}**. **^{1}H NMR (δ, ppm, $CDCl_3$):** 8.1(t,1H,N-H), 7.4(d,1H,C_5-H in Chromen-2-one), 6.5-6.9(d,2H,C_6-H and C_8-H in Chormen-2-one), 5.6(s,1H,C_3-H in Chromen-2-one), 2.1(s,3H,C_4-CH_3 in Chromen-2-one), 4.12(t,2H,O-CH_2 linkage), 4.0(t,2H,N-CH_2 linkage), 7.6(s,1H,$C_{7'}$-H in Benzothiazole), 8.1(d,1H,$C_{4'}$-H in benzothiazole), 7.1(d,1H,$C_{5'}$-H in benzothiazole), 3.7(S,3H,OCH_3 in benzothiazole)

7-(2-(6-nitrobenzo[d]thiazol-2-ylamino)ethoxy)-4-methyl-2H-chromen-2-one (4d)

IR (KBr): 3341(N-H), 1685(C=O), 1588(C=C), 1310(C-O-O stretching), 1266(C-N), 754(C-N) **cm^{-1}**. **^{1}H NMR (δ, ppm, $CDCl_3$):** 8.5(t,1H,N-H), 7.5(d,1H,C_5-H in Chromen-2-one), 6.5-6.9(d,2H,C_6-H and C_8-H in Chormen-2-one), 6.2(s,1H,C_3-H in Chromen-2-one), 2.1(s,3H,C_4-CH_3 in Chromen-2-one). 4.0(t, 2H, O-CH_2 linkage), 4.2(t, 2H, N-CH_2 linkage), 8.47(m, 2H, $C_{4'}$-H & $C_{5'}$-H in Benzothiazole), 8.56 (s, 1H, $C_{7'}$-H in benzothiazole)

7-(2-(4-chlorobenzo[d]thiazol-2-ylamino)ethoxy)-4-methyl-2H-chromen-2-one (4e)
IR (KBr): 3310(N-H), 2920(C-H), 1734(C=O), 1504(C=C), 1140(C-O), 582(C-Cl), 781(C-S) **cm^{-1}**. **^{1}H NMR (δ, ppm, DMSO):** 9.1(t,1H,N-H), 7.20(d,1H,C_5-H in Chromen-2-one), 6.5-6.9(d,2H,C_6-H and C_8-H in Chormen-2-one), 6.1(s,1H,C_3-H in Chromen-2-one), 2.4(s,3H,C_4-CH_3 in Chromen-2-one). 4.2(t, 2H, O-CH_2 linkage), 4.62(t, 2H, N-CH_2 linkage), 7.4-7.6(m, 2H, $C_{5'}$-H &$C_{6'}$-H in Benzothiazole), 8.1 (d, 1H, $C_{7'}$-H in benzothiazole)

7-(2-(6-fluorobenzo[d]thiazol-2-ylamino)ethoxy)-4-methyl-2H-chromen-2-one (4f)
IR (KBr): 3327(N-H), 2922(Ar C-H), 1703(C=O), 1596-1334(C=C), 1135(C-O), 929 (C-F), 751(C-S) **cm-1. ^{1}H NMR (δ, ppm, DMSO):** 9.3(t,1H,N-H), 7.2(d,1H,C_5-H in Chromen-2-one), 6.4-6.9(d,2H,C_6-H and C_8-H in Chormen-2-one), 6.20(s,1H,C_3-H in Chromen-2-one), 2.32(s,3H,C_4-CH_3 in Chromen-2-one). 4.11(t, 2H, O-CH_2 linkage), 4.32(t, 2H, N-CH_2 linkage), 7.2-7.8(m, 2H, $C_{5'}$-H & $C_{7'}$-H in Benzothiazole), 8.01(d, 2H, $C_{4'}$-H in benzothiazole)

7-(2-(5-chloro-6-fluorobenzo[d]thiazol-2-ylamino)ethoxy)-4-methyl-2H-chromen-2-one (4g)
IR (KBr): 3360(N-H), 2920(C-H), 1720(C=O), 1589-1365(C=C), 667(C-Cl), 931(C-F), 1153(CO-O-C stretching), 1253.9(C-O-O) **cm^{-1}**. **^{1}H NMR (δ, ppm, DMSO):** 9.6(t, 1H,N-H), 7.26(d,1H,C_5-H in Chromen-2-one), 6.5-6.9(d,2H,C_6-H and C_8-H in Chormen-2-one), 6.13(s,1H,C_3-H in Chromen-2-one), 2.17(s,3H,C_4-CH_3 in Chromen-2-one), 4.34(t, 2H, O-CH_2 linkage), 4.48(t, 2H, N-CH_2 linkage), 7.89(s, 1H, $C_{7'}$-H in Benzothiazole), 8.30(s, 1H, $C_{4'}$-H in benzothiazole)

7-(2-(4-methylbenzo[d]thiazol-2-ylamino)ethoxy)-4-methyl-2H-chromen-2-one (4h)
IR (KBr): 3342(N-H), 2920(C-H), 1693(C=O), 1565(C=C), 1259(C-N), 841(C-H out of plane), 1174(CO-O-C), 743(C-S Stretching) **cm^{-1}**. **^{1}H NMR (δ, ppm, DMSO):** 8.3(t, 1H,N-H), 7.10(d,1H,C_5-H in Chromen-2-one), 6.6-6.9(d,2H,C_6-H and C_8-H in Chormen-2-one), 5.90(s,1H,C_3-H in Chromen-2-one), 1.9(s,3H,C_4-CH_3 in Chromen-2-one) 4.3(t, 2H, O-CH_2 linkage), 4.10(t, 2H, N-CH_2 linkage), 7.3-7.4(m,2H,$C_{5'}$-H & $C_{6'}$-H in Benzothiazole), 8.0(d,1H,$C_{7'}$-H in benzothiazole), 2.35(s,3H,-CH_3 of Benzothiazole)

7-(2-(6-methylbenzo[d]thiazol-2-ylamino)ethoxy)-4-methyl-2H-chromen-2-one (4i)

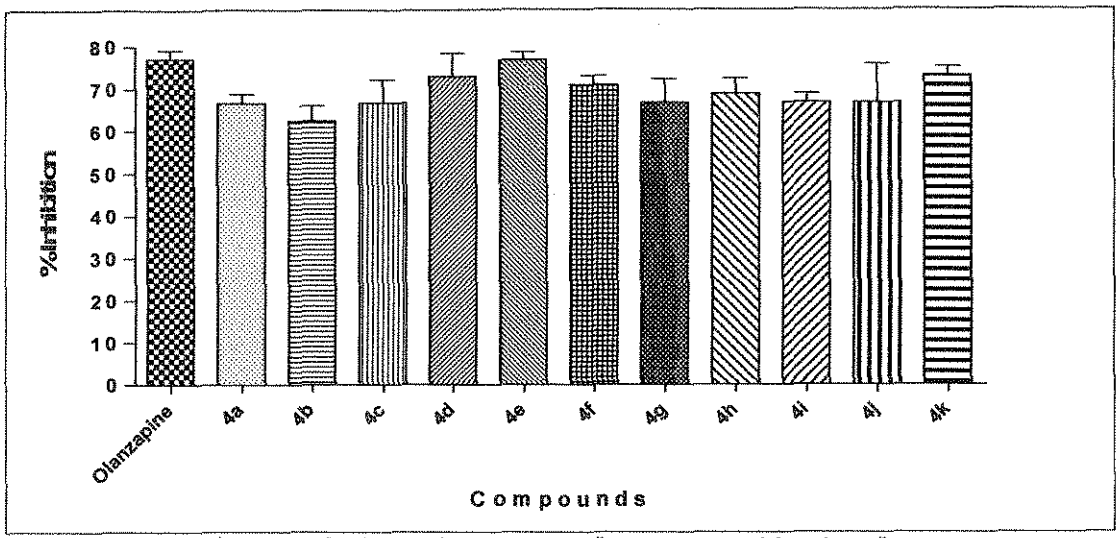
IR (KBr): 3095(N-H), 2991(C-H), 1611(C=O), 1428(C=C), 1282(C-N), 1184(CO-O-C), 851(C-H), 732(C-S stretching) **cm^{-1}**. **^{1}H NMR (δ, ppm, $CDCl_3$):** 8.1(t,1H,N-H), 6.96(d,1H,C_5-H in Chromen-2-one), 6.5-6.6(d,2H,C_6-H and C_8-H in Chormen-2-one), 6.0(s,1H,C_3-H in Chromen-2-one), 2.23(s,3H,C_4-CH_3 in Chromen-2-one). 4.34(t, 2H, O-CH_2 linkage), 4.17(t, 2H, N-CH_2 linkage), 7.9-8.1(m, 2H, $C_{4'}$-H & $C_{7'}$-H in benzothiazole), 7.4(d, 1H, $C_{5'}$-H in benzothiazole)

7-(2-(5-chlorobenzo[d]thiazol-2-ylamino)ethoxy)-4-methyl-2H-chromen-2-one (4j)
IR (KBr): 3089(N-H), 2972(C-H), 1708(C=O), 1555(C=C), 1246(C-N stretching), 1180(CO-O-C stretching), 816(C-H) **cm^{-1}**. **^{1}H NMR (δ, ppm, DMSO):** 8.6(t,1H,N-H), 7.16(d,1H,C_5-H in Chromen-2-one), 6.6-6.9(d,2H,C_6-H and C_8-H in Chormen-2-one), 5.90(s,1H,C_3-H in Chromen-2-one), 2.3(s,3H,C_4-CH_3 in Chromen-2-one), 4.24(t, 2H, O-CH_2 linkage), 4.12(t, 2H, N-CH_2 linkage), 7.56(m, 1H, $C_{6'}$-H in Benzothiazole), 8-8.2(d, 2H, $C_{4'}$-H & $C_{7'}$-H in benzothiazole)

7-(2-(4-bromobenzo[d]thiazol-2-ylamino)ethoxy)-4-methyl-2H-chromen-2-one (4k)
IR (KBr): 3267(N-H), 2891(C-H), 1732(C=O), 1492(C=C), 1226(C-N), 1056(CO-O-C), 701(C-S), 631(C-Cl) **cm^{-1}**. **^{1}H NMR (δ, ppm, DMSO):** 8.4(t,1H,N-H), 7.20 (d,1H,C_5-H in Chromen-2-one), 6.6-6.9(d,2H,C_6-H and C_8-H in Chormen-2-one), 6.10 (s,1H,C_3-H in Chromen-2-one), 2.1(s,3H,C_4-CH_3 in Chromen-2-one). 4.11(t, 2H, O-CH_2 linkage), 4.18(t, 2H, N-CH_2 linkage), 7.72(m, 1H, $C_{5'}$-H in benzothiazole), 8.1-8.2 (d, 2H, $C_{4'}$-H & $C_{7'}$-H in benzothiazole)

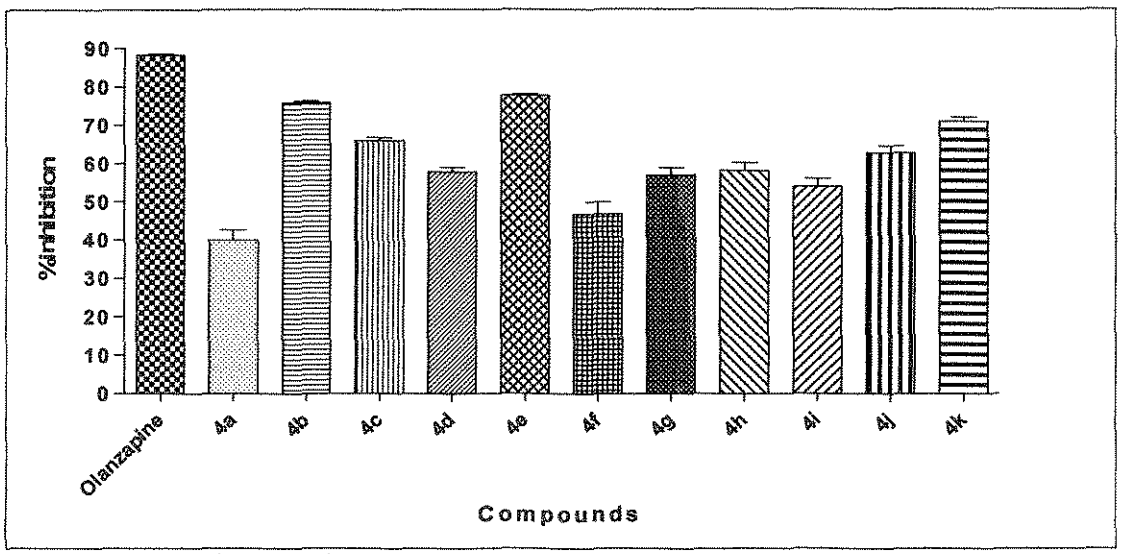
Pharmacological Results.

Figure 1. Percent Inhibition of apomorphine induced climbing behavior, at the dose of 5 mg/kg.



*n = 6, p < 0.05, $ Dose of Olanzapine was 1mg/kg, Apomorphine 1mg/kg

Figure 2. Percent Inhibition of 5-HT induced head twitches at the dose of 5 mg/kg.



*n = 6, p < 0.05, $ Dose of Olanzapine was 1mg/kg

CONCLUSIONS

Our 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 antipsychotic 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 we can conclude that compounds 7-(2-(4-chlorobenzo[*d*]thiazol-2-ylamino)ethoxy)-4-methyl-2*H*-chromen-2-one (4e) and 7-(2-(6-methoxybenzo[*d*]thiazol-2-ylamino)ethoxy)-4-methyl-2*H*-chromen-2-one (4c) have better atypical antipsychotic profile. A detailed toxicity study is required for characterization of the compounds for the therapeutic utility.

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