

RESEARCH ARTICLE

“Synthesis, Characterization, and Antipsychotic Evaluation of Some Aryl Piperazine Congeners”

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ABSTRACT

In this proposal research work aryl piperazine derivatives will be synthesised because aryl piperazine currently the most important building blocks in drug discovery with a high number of positive hits encountered in biological screens of this heterocyclic and its congeners. A series N-(4-(benzo[d]thiazol-2-yl)phenyl)-2-[4-(arylsubstituted)piperazines-1-yl]acetamide and N-(4-(benzo[d]oxazol-2-yl)phenyl)-2-[4-(arylsubstituted)piperazines-1-yl]acetamide will be synthesized with different aryl piperazine substituents and their characterization such as melting point determination and Thin layer chromatography (TLC) also performed. After that pharmacological evaluation will be done for synthesized compounds. In pharmacological evaluation the antipsychotic activity determined by behaviour symptoms, Inhibition of 5-hydroxytryptophan (5-HTP) induced head twitches behavior and Induction of catalepsy.

Keywords: Aryl piperazine, congeners, characterization, melting point, thin layer chromatography (TLC), pharmacological evaluation, 5-hydroxytryptophan (5-HTP), catalepsy

INTRODUCTION

Piperazine is currently the most important building blocks in drug discovery with a high number of positive hits encountered in biological screens of this heterocyclic and its congeners.^[1-3] A literature survey revealed that piperazine derivatives are important pharmacophores across a number of different therapeutic areas and they act as antifungal, antipsychotic, antimicrobial, antioxidant, and antimalarial.^[1-8]

Antipsychotic agents

The term antipsychotic and neuroleptic are used interchangeably to denote a group of drugs that have been used mainly for treating schizophrenia

but is also effective in some other psychoses and agitated states.^[9-17]

Nature of psychosis and schizophrenia

The term “psychosis” denotes a variety of mental disorders, but the term antipsychotic drugs also known as a neuroleptic drug, antischizophrenic drugs or major tranquillizers conventionally refers to those used to treat schizophrenia, one of the most common and debilitating forms of florid mental illness.^[18-26] Pharmacologically, they are characterized as dopamine receptor antagonists, though many of them also act on other targets, particularly 5-hydroxytryptamine receptors.^[27-32]

Mechanism of action

Antipsychotics block postsynaptic dopamine receptors. **D1** and **D2** receptors are associated with antipsychotic efficacy. Other (D1, D2, D3, D4, and D5) dopaminergic receptors have been isolated

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but not characterized as to their action.^[33-35] D2 receptors are cited as responsible for antipsychotic-induced movement disorders with D1 receptors modulating the intensity of these side effects. Nearly 65–70% of patients with schizophrenia respond to traditional (those with primarily D2 blocking action) antipsychotic agents.^[35-39] Newer atypical antipsychotic agents (i.e., Clozapine) have effects on multiple dopaminergic receptors and have been effective in patients whose traditional antipsychotics have been ineffective.^[40-44] Clozapine, olanzapine, and risperidone are effective for negative symptoms as well.^[45-49]

MATERIALS AND METHODS

Reagents and solvent

The substituted aryl piperazines were purchased from chemical labs. All the standard drugs were purchased from Sigma. All other chemicals and solvents were purchased from CDH. All chemicals used were of analytical grades and purified before used. The glassware's used were properly cleaned and dried before use and suitably calibrated. The synthesis was followed in three steps [Figure 1].

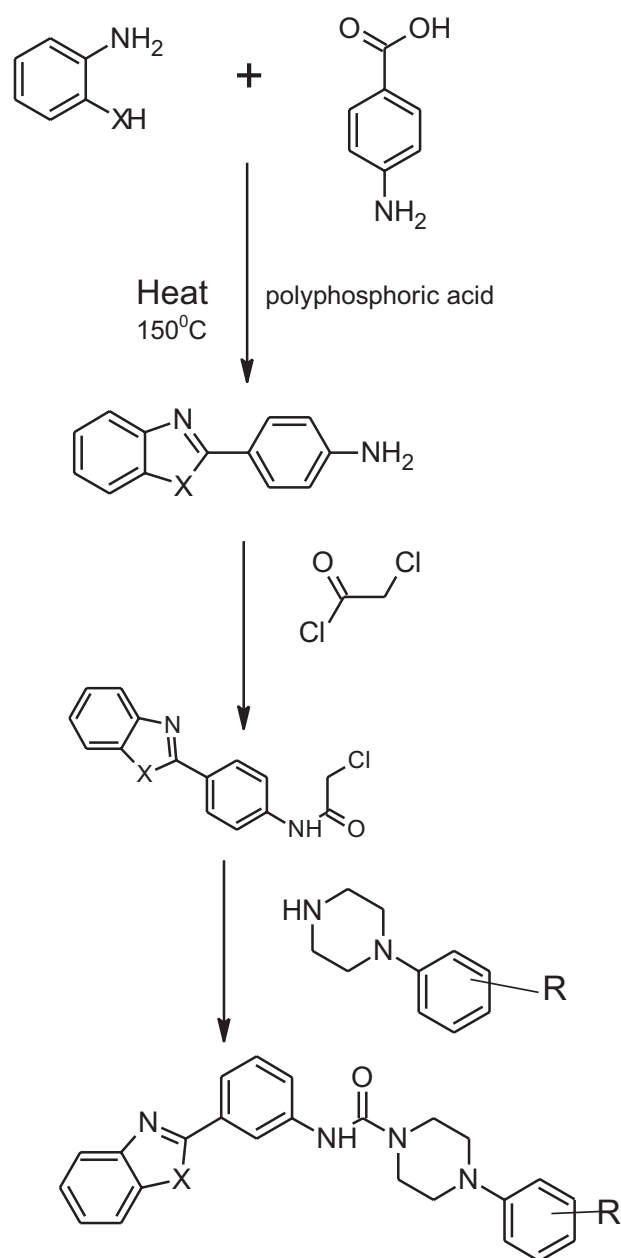
Preparation of series A

Step 1 Synthesis of 2-(4-aminophenyl)benzothiazole

Mixed equal moles of 2-aminothiophenol and 4-aminobenzoic acid in the same mole of polyphosphoric acid was heated for 4 h at 220°C. The reaction mixture was cooled and neutralized with freshly prepared 10% sodium carbonate ice-cold solution. The solution was left overnight, and the precipitate was settled down. The solution was filtered and crude product so obtained was dried and recrystallized from methanol to obtain the final compound.^[10,12]

Step 2 Synthesis of N-[4-(1, 3-benzothiazole-2-yl)phenyl]-2-chloroacetamide

0.02 mole of 2-(4-aminophenyl)benzothiazole was dissolved in acetonitrile (50 ml) and 0.02 mole of anhydrous potassium carbonate. The reaction mixture was refluxed for 2 h with continuous stirring. After cooling dropwise addition of 0.04



Where X = S, O

R = different substitution

Figure 1: Route for the synthesis of compounds

mole chloroacetyl chloride in acetonitrile was done. After complete addition, the reaction mixture was further refluxed for 16 h with continuous stirring. The reaction mixture was then cooled, filtered and the solvent was removed by vacuum distillation and obtained residue wash with an excess of water. The crude product was recrystallized from ethanol to obtain the compound.^[10,12,13]

Step 3

- Synthesis of N-(4-(benzo[d]thiazol-2-yl)phenyl)-2-(4-phenylpiperazin-1-yl)acetamide (**D1**)
- Synthesis of N-(4-(benzo[d]thiazol-2-yl)phenyl)-2-(4-p-tolylpiperazin-1-yl)acetamide (**D2**)
- Synthesis of N-(4-(benzo[d]thiazol-2-yl)phenyl)-2-(4-(3-chlorophenyl) piperazin-1-yl)acetamide (**D3**)
- Synthesis of N-(4-(benzo[d]thiazol-2-yl)phenyl)-2-(4-(2-methoxyphenyl) piperazin-1-yl)acetamide (**D4**)
- Synthesis of N-(4-(benzo[d]thiazol-2-yl)phenyl)-2-(4-(2-ethoxyphenyl) piperazin-1-yl)acetamide (**D5**)
- Synthesis of N-(4-(benzo[d]thiazol-2-yl)phenyl)-2-(4-(3-bromophenyl) piperazin-1-yl)acetamide (**D6**)

0.0025 mole of N-[4-(1,3-benzothiazole-2-yl)phenyl]-2-chloroacetamide was dissolved in ethylmethylketone (20 ml) and 0.0025 mole anhydrous sodium carbonate was added. The reaction mixture was refluxed for ½ h with continuous stirring. N-phenylpiperazine derivatives (**D1–D6**) (0.0025 mole) in ethylmethylketone and catalytic amount of sodium iodide were added. After complete addition, the reaction mixture allowed to reflux for 10–12 h with continuous stirring. After completion of reaction, the reaction mixture was filtered and the solvent was removed by vacuum distillation and obtained residue wash with an excess of water. The crude product was recrystallized from ethanol to obtain compound.

Preparation of series B**Step 1 Synthesis of 2-(4-aminophenyl)benzoxazole**

Mixed equal moles of 2-aminophenol and 4-aminobenzoic acid in polyphosphoric acid were heated for 4 h at 220°C. The reaction mixture was cooled and neutralized with freshly prepared 10% sodium carbonate ice-cold solution. The solution was left overnight and the precipitate was settled down. The solution was filtered and crude product so obtained was dried and recrystallized from methanol to obtain the final compound.

Step 2 Synthesis of N-[4-(1,3-benzoxazole-2-yl)phenyl]-2-chloroacetamide

0.02 mole of 2-(4-aminophenyl)benzoxazole was dissolved in acetonitrile (50 ml), and 0.02 mole anhydrous potassium carbonate was added. The reaction mixture was refluxed for 2 h with continuous stirring. After cooling dropwise addition of 0.04 mole chloroacetyl chloride in acetonitrile was added. After complete addition, the reaction mixture was further refluxed for 16 h with continuous stirring. The reaction mixture was then cooled, filtered and solvent was removed by vacuum distillation and obtained residue wash with an excess of water. The crude product was recrystallized from ethanol to obtain compound.

Step 3

- Synthesis of N-(4-(benzo[d]oxazol-2-yl)phenyl)-2-(4-phenylpiperazin-1-yl)acetamide (**G1**)
- Synthesis of N-(4-(benzo[d]oxazol-2-yl)phenyl)-2-(4-p-tolylpiperazin-1-yl)acetamide (**G2**)
- Synthesis of N-(4-(benzo[d]oxazol-2-yl)phenyl)-2-(4-(3-chlorophenyl)piperazin-1-yl)acetamide (**G3**)
- Synthesis of N-(4-(benzo[d]oxazol-2-yl)phenyl)-2-(4-(2-methoxyphenyl)piperazin-1-yl)acetamide (**G4**)
- Synthesis of N-(4-(benzo[d]oxazol-2-yl)phenyl)-2-(4-(2-ethoxy phenyl)piperazin-1-yl)acetamide (**G5**)
- Synthesis of N-(4-(benzo[d] oxazol -2-yl)phenyl)-2-(4-(3-bromophenyl)piperazin-1-yl)acetamide (**G6**)

0.0025 mole of N-[4-(1,3-benzoxazol-2-yl)phenyl]-2-chloroacetamide (0.717 g) was dissolved in ethylmethylketone (20 ml) and 0.0025 mole anhydrous sodium carbonate was added. The reaction mixture was refluxed for ½ h with continuous stirring. N-phenylpiperazine derivatives (**G1–G6**) (0.0025 mole) in ethylmethylketone and catalytic amount of sodium iodide were added. After complete addition, the reaction mixture allowed to reflux for 10–12 h with continuous stirring. After completion of reaction, the reaction mixture was filtered and the solvent

was removed by vacuum distillation and obtained residue wash with an excess of water. The crude product was recrystallized from ethanol to obtain compound.

Characterization of synthesized compounds

The reactions progress was monitored by the thin-layer chromatography (TLC). The TLC of the compounds was performed on the precoated silica gel G plates using iodine vapors for detection of the spots. The melting points of the synthesized compounds as well as intermediate were determined by open capillary methods and are uncorrected [Table 1].

Pharmacological evaluation

All the target compounds were subjected to pharmacological evaluation to determine their behavior symptoms, inhibition of 5-hydroxytryptophan (5-HTP)-induced head twitches behavior and induction of catalepsy studies.

Behavior symptoms

Swiss albino mice (six mice in each group) of either sex (26–28 g) were used and kept in a plastic cage. All derivatives at their respective doses were given to animals. Each cage contained one animal only. The changes in the behavior symptoms were noted down for an interval of 30 min for 3 h, and then after 24 h, the cages were inspected for any mortality of the animals [Table 2].

Inhibition of 5-HTP-induced head twitches behavior

Swiss albino mice in the control group ($n = 6$) were injected with pargyline (75 mg/kg, i. p) to prevent the rapid degradation of 5-HTP. Thirty minute later, the test compound was administered. After a further 30 min, the mice received 5-HTP (50 mg/kg, s. c). The mice were returned to the test cages and then head twitches were assessed at 10 min intervals for 30 min, starting 20 min after the 5-HTP treatment. Head twitches were monitored using the following scoring system, 0-absent, 1-moderate,

Table 1: Physical Characters of synthesized compounds

Physical characteristics	D1	D2	D3	D4	D5	D6	G1	G2	G3	G4	G5	G6
State	Solid	Solid	Solid	Solid	Solid	Solid	Solid	Solid	Solid	Solid	Solid	Solid
Solubility	CHCl ₃ , alcohol	CHCl ₃ , alcohol	CHCl ₃ , alcohol	CHCl ₃ , alcohol	CHCl ₃ , alcohol	CHCl ₃ , alcohol	CHCl ₃ , alcohol	CHCl ₃ , alcohol	CHCl ₃ , alcohol	CHCl ₃ , alcohol	CHCl ₃ , alcohol	CHCl ₃ , alcohol
Melting point	105°C–107°C	110°C–113°C	112°C–115°C	106°C–109°C	104°C–106°C	103°C–105°C	114°C–116°C	118°C–120°C	119°C–122°C	111°C–114°C	114°C–116°C	106°C–109°C
Rf	0.46	0.38	0.35	0.42	0.44	0.40	0.33	0.42	0.43	0.37	0.33	0.41
Mobile phase	Hexane: Ethyl acetate (1:1)	Hexane: Ethyl acetate (1:1)	Hexane: Ethyl acetate (1:1)	Hexane: Ethyl acetate (1:1)	Hexane: Ethyl acetate (1:1)	Hexane: Ethyl acetate (1:1)	Hexane: Ethyl acetate (1:2)	Hexane: Ethyl acetate (1:2)	Hexane: Ethyl acetate (1:2)	Hexane: Ethyl acetate (1:2)	Hexane: Ethyl acetate (1:2)	Hexane: Ethyl acetate (1:2)
Molecular formula	C ₂₅ H ₂₄ N ₄ O ₅	C ₂₆ H ₂₆ N ₄ O ₅	C ₂₅ H ₂₃ CIN ₄ O ₅	C ₂₆ H ₂₆ N ₄ O ₂ S	C ₂₇ H ₂₈ N ₄ O ₂ S	C ₂₅ H ₂₃ BrN ₄ O ₅	C ₂₅ H ₂₄ N ₄ O ₅	C ₂₆ H ₂₆ N ₄ O ₂	C ₂₅ H ₂₃ CIN ₄ O ₂	C ₂₆ H ₂₆ N ₄ O ₃	C ₂₇ H ₂₈ N ₄ O ₃	C ₂₅ H ₂₃ BrN ₄ O ₂

Table 2: Behavioral symptoms of synthesized compounds

Compound	Behavioral symptoms	Observation at Interval of				
		30 min	60 min	90 min	120 min	180 min
D ₁	Sedation	-	-	-	-	-
	Sleep	-	-	-	-	-
	Hyperactivity	-	-	-	-	-
	Convulsion	-	-	-	-	-
D ₂	Sedation	-	-	-	-	-
	Sleep	-	-	-	-	-
	Hyperactivity	-	-	-	-	-
	Convulsion	-	-	-	-	-
D ₃	Sedation	-	-	-	-	-
	Sleep	-	-	-	-	-
	Hyperactivity	-	-	-	-	-
	Convulsion	-	-	-	-	-
D ₄	Sedation	-	-	-	-	-
	Sleep	-	-	-	-	-
	Hyperactivity	-	-	-	-	-
	Convulsion	-	-	-	-	-
D ₅	Sedation	-	-	-	-	-
	Sleep	-	-	-	-	-
	Hyperactivity	-	-	-	-	-
	Convulsion	-	-	-	-	-
D ₆	Sedation	-	-	-	-	-
	Sleep	-	-	-	-	-
	Hyperactivity	-	-	-	-	-
	Convulsion	-	-	-	-	-
G ₁	Sedation	-	-	-	-	-
	Sleep	-	-	-	-	-
	Hyperactivity	-	-	-	-	-
	Convulsion	-	-	-	-	-
G ₂	Sedation	-	-	-	-	-
	Sleep	-	-	-	-	-
	Hyperactivity	-	-	-	-	-
	Convulsion	-	-	-	-	-
G ₃	Sedation	-	-	-	-	-
	Sleep	-	-	-	-	-
	Hyperactivity	-	-	-	-	-
	Convulsion	-	-	-	-	-
G ₄	Sedation	-	-	-	-	-
	Sleep	-	-	-	-	-
	Hyperactivity	-	-	-	-	-
	Convulsion	-	-	-	-	-
G ₅	Sedation	-	-	-	-	-
	Sleep	-	-	-	-	-
	Hyperactivity	-	-	-	-	-
	Convulsion	-	-	-	-	-
G ₆	Sedation	-	-	-	-	-
	Sleep	-	-	-	-	-
	Hyperactivity	-	-	-	-	-
	Convulsion	-	-	-	-	-

+++ Marked effect, ++ Moderate effect, + Mild effect, - Absence of effect

and 2-marked. A maximum of 8 scores is possible. An observer made all observations unaware of the specific drug treatments [Table 3 and Figure 2].

Induction of catalepsy

Catalepsy was induced in albino mice ($n = 6$) with haloperidol (1.0 mg/kg, i. p) and was assessed at 30 min intervals until 120 min and at the end of 240 min by means of a standard bar test. Catalepsy was assessed in terms of the time (s) for which the mouse maintained an imposed position with both front limbs extended and resting on a 4 cm high wooden bar (1.0 cm diameter). The endpoint of catalepsy was considered to occur when both front paws were removed from the bar or if the animal moved its head in an exploratory manner. The severity of the cataleptic behavior was scored as one if maintained the imposed posture for at least 20 s and every additional 20 s one extra point was given. A cutoff time of 1100 s was applied during the recording of observations. The animals

were returned to their individual home cages in between determinations. All observations were made between 10.00 and 16.00 h in a quiet room

Table 3: Inhibition of 5-hydroxytryptophan (5-HTP)-induced head twitches behavior synthesized compounds

Compound	Total Head Twitches Score
D ₁	3.17±0.16
D ₂	3.67±0.51
D ₃	4.16±0.41
D ₄	2.66±0.21
D ₅	3.20±0.21
D ₆	2.89±0.25
G ₁	3.33±0.61
G ₂	3.50±0.42
G ₃	3.83±0.31
G ₄	2.83±0.40
G ₅	3.43±0.22
G ₆	2.92±0.23
Control	6.50±0.42
Aripiprazole	1.83±0.30

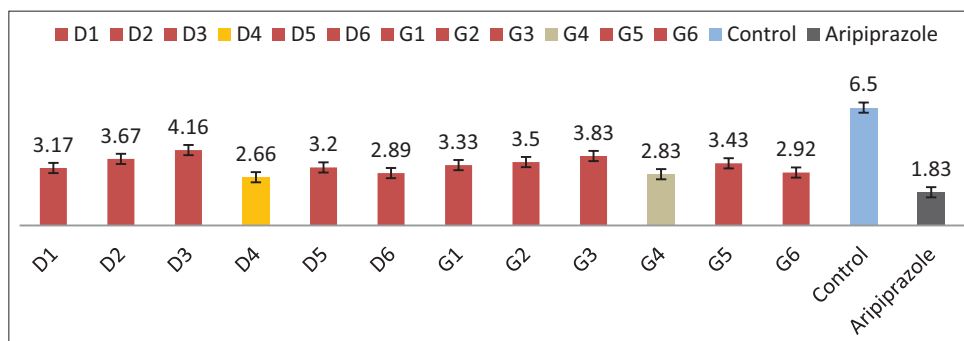


Figure 2: Inhibition of 5-hydroxytryptophan-induced head twitches behavior of synthesized compounds

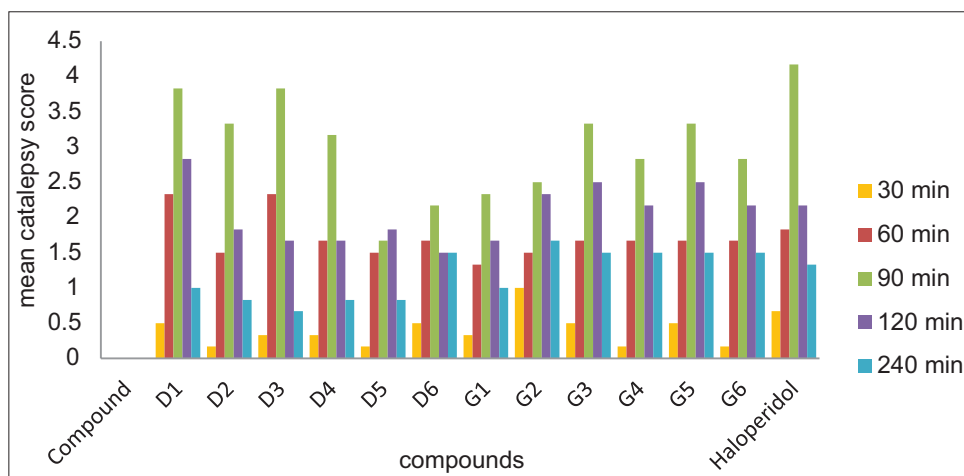


Figure 3: Induction of catalepsy shown by synthesized compounds

Table 4: Induction of catalepsy shown by synthesized compounds

Compound	Mean catalepsy score				
	30 min	60 min	90 min	120 min	240 min
D ₁	0.50±0.22	2.33±0.33	3.83±0.31	2.83±0.31	1.00±0.36
D ₂	0.17±0.16	1.50±0.22	3.33±0.33	1.83±0.31	0.83±0.16
D ₃	0.33±0.21	2.33±0.33	3.83±0.40	1.67±0.33	0.67±0.21
D ₄	0.33±0.21	1.67±0.21	3.17±0.31	1.67±0.33	0.83±0.31
D ₅	0.17±0.16	1.50±0.22	1.67±0.21	1.83±0.31	0.83±0.16
D ₆	0.50±0.22	1.67±0.21	2.17±0.31	1.50±0.22	1.50±0.22
G ₁	0.33±0.21	1.33±0.33	2.33±0.21	1.67±0.33	1.00±0.26
G ₂	1.00±0.26	1.50±0.20	2.50±0.22	2.33±0.21	1.67±0.21
G ₃	0.50±0.22	1.67±0.21	3.33±0.21	2.50±0.22	1.50±0.22
G ₄	0.17±0.16	1.67±0.21	2.83±0.31	2.17±0.31	1.50±0.22
G ₅	0.50±0.22	1.67±0.21	3.33±0.21	2.50±0.22	1.50±0.22
G ₆	0.17±0.16	1.67±0.21	2.83±0.31	2.17±0.31	1.50±0.22
Haloperidol	0.67±0.21	1.83±0.31	4.17±0.40	2.17±0.31	1.33±0.21

at 23–25°C. The animals in the test group were administered with test drugs instead of haloperidol and the remaining procedure for assessment of catalepsy was same as inhibition 5-HTP-induced head twitches behavior [Table 4 and Figure 3].

RESULTS AND DISCUSSION

Synthetic scheme

There are three different series prepared, in which different derivatives are prepared.

The synthetic work will proceed as follows:

CONCLUSION

Series of new aryl piperazine were synthesized and were prepared using the pathway shown in schemes. The target compounds were prepared by chloroacetylation of amines as 2-(4-aminophenyl) benzothiazole and 2-(4-aminophenyl)benzoxazole followed by condensation with respect to substituted phenylpiperazines in ethylmethylketone in the presence of sodium carbonate and sodium iodide as a catalyst which afforded the target compounds. All the reactions were monitored by TLC. The final products were purified by recrystallization and characterized by their physical parameters. All the target compounds were subjected to pharmacological evaluation for behavior symptoms; inhibition of 5-HTP-induced head twitches behavior

and induction of catalepsy studies. All synthesized compounds shown antipsychotic activity and compound D₄ showed statistically significant inhibition of 5-HTP-induced head twitches (ED_{min} = 20 mg/kg) and minimum induction of catalepsy (ED_{min} = 60 mg/kg). Thus, the compound D₄ emerged as most potent and contributed to an atypical antipsychotic like profile. It may be concluded that the series of arylpiperazines were synthesized and their pharmacological evaluation showed potential antipsychotic activity in an animal model.

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REFERENCES

1. Al-Harthy T, Zoghaib WM, Pflüger M, Schöpel M, Önder K, Reitsammer M, *et al.* Design, synthesis, and cytotoxicity of 5-fluoro-2-methyl-6-(4-aryl-piperazin-1-yl) benzoxazoles. *Molecules* 2016;21:E1290.
2. Alang G, Kaur R, Kaur G, Singh A, Singla P. Synthesis and antibacterial activity of some new benzothiazole derivatives. *Acta Pharm Sci* 2010;52:213-8.
3. Al-Talib M, Al-Soud YA, Abussaud M, Khshashneh S. Synthesis and biological evaluation of new benzothiazoles as antimicrobial agents. *Arabian J Chem* 2016;9:926-30.

4. Arora P, Das S, Arora N, Gawai A, Baghel US. Synthesis and screening of some novel 7-Hydroxy 4-methylcoumarin derivatives for antipsychotic activity. *Int J Pharm Life Sci* 2010;1:113-8.
5. Arora P, Das S, Ranawat MS, Arora N, Gupta MM. Synthesis and biological evaluation of some novel chromene-2-one derivatives for antipsychotic activity. *J Chem Pharm Res* 2010;2:317-23.
6. Asiri AM, Khan SA. N-[1-(2, 5-Dimethyl-3-thienyl) ethylidene]-1, 3-benzothiazol-2-amine. *Molbank* 2010;M659:1-3.
7. Bali A, Sharma K, Bhalla A, Bala S, Reddy D, Singh A, *et al.* Synthesis, evaluation and computational studies on a series of acetophenone based 1-(aryloxypropyl)-4-(chloroaryl) piperazines as potential atypical antipsychotics. *Eur J Med Chem* 2010;45:2656-62.
8. Bhosale SH, Dash RC, Mahadik KR. 6-(4-(4-Substituted phenylpiperazin-1-yl)butoxy)benzo[d][1,3]oxathiol-2-one: Synthesis and biological evaluation as potential antipsychotic agents. *Der Pharm Chem* 2010;2:294-303.
9. Bhosale SH, Dash RC, Mahadik KR. Synthesis, pharmacological evaluation and qsar study of 6-[3-(4-substituted phenylpiperazin-1-Yl)propoxy] benzo[D][1,3]oxathiol-2-ones as potential antipsychotics. *Dig J Nanomater Biostruct* 2010;5:739-47.
10. Szulczyk D, Bielenica A, Dobrowolski MA, Dobrzycki L, Krawiecka M, Kuran B, *et al.* Synthesis and structure evaluation of new complex butylaryl piperazin-1-yl derivatives. *Med Chem Res* 2014;23:1519-36.
11. Caleta I, Kralj M, Marjanović M, Bertosa B, Tomić S, Pavlović G, *et al.* Novel cyano- and amidinobenzothiazole derivatives: Synthesis, antitumor evaluation, and X-ray and quantitative structure-activity relationship (QSAR) analysis. *J Med Chem* 2009;52:1744-56.
12. Chakraborty M, Jin KJ, Glover SA, Novak M. Characterization of the 4-(benzothiazol-2-yl) phenyl nitrenium ion from a putative metabolite of a model antitumor drug. *J Org Chem* 2010;75:5296-304.
13. Devmurari VP, Pandey S, Goyani MB, Nandanwar RR, Jivani NP, Perumal P. Synthesis and anticancer activity of some novel 2-substituted benzothiazole derivatives. *Int J ChemTech Res* 2010;2:681-9.
14. Gupta SD, Moorthy NS, Sanyal U. Synthesis, cytotoxic evaluation, *in silico* pharmacokinetic and QSAR study of some benzothiazole derivatives. *Int J Pharm Pharm Sci* 2010;2:57-62.
15. Gurdal EE, Durmaz I, Cetin-Atalay R, Yarim M. Cytotoxic activities of some benzothiazole-piperazine derivatives. *J Enzyme Inhib Med Chem* 2015;30:649-54.
16. Ha ST, Koh TM, Ong ST, Win YF. 2-[4-(Hexadecyloxy)-3-methoxyphenyl]-1,3-benzothiazole. *Molbank* 2009;M634:1-3.
17. Hu WP, Chen YK, Liao CC, Yu HS, Tsai YM, Huang SM, *et al.* Synthesis, and biological evaluation of 2-(4-aminophenyl)benzothiazole derivatives as photosensitizing agents. *Bioorg Med Chem* 2010;18:6197-207.
18. Kaya B, Yurttas L, Saglik BN, Levent S, Ozkay Y, Kaplancikli ZA, *et al.* Novel 1-(2-pyrimidin-2-yl) piperazine derivatives as selective monoamine oxidase (MAO)-A inhibitors. *J Enzyme Inhib Med Chem* 2017;32:193-202.
19. Kumar S, Pandey P, Srivastava Y, Kumar A. Synthesis, computational studies and pharmacological evaluation of some acetamides as serotonin antagonists. *Der Pharm Chem* 2011;3:195-200.
20. Kumar S, Wahi AK, Singh R. Synthesis and preliminary pharmacological evaluation of 2-[4-(Aryl substituted) piperazin-1-yl]-N-phenylacetamides: Potential antipsychotics. *Trop J Pharm Res* 2011;10:265-72.
21. Kumar S, Wahi AK, Singh R. Synthesis, computational studies and preliminary pharmacological evaluation of 2-[4-(aryl substituted) piperazin-1-yl] N, N-diphenylacetamides as potential antipsychotics. *Arabian J Chem* 2016;9:S1450-6.
22. Kumar S, Wahi AK, Singh R. Synthesis, computational studies and preliminary pharmacological evaluation of 2-[4-(aryl substituted) piperazin-1-yl] N, N-diphenylacetamides as potential antipsychotics. *Eur J Med Chem* 2011;46:4753-9.
23. Kumar S, Wahi AK, Singh R. Synthesis, computational studies and preliminary pharmacological evaluation of new aryl piperazines. *E J Chem* 2011;8:1044-51.
24. Kumar VM, Latha S, Shameer H, Jayachandran E, Sreenivasa GM. N-substituted-thiazolidin-4-ones: Synthesis and characterization of new novel potential anticonvulsant agents. *Arch Pharm Sci Res* 2009;1:138-49.
25. Lion CJ, Matthews CS, Wells G, Bradshaw TD, Stevens MF, Westwell AD, *et al.* Antitumour properties of fluorinated benzothiazole-substituted hydroxycyclohexa-2,5-dienones ('quinols'). *Bioorg Med Chem Lett* 2006;16:5005-8.
26. Liu Y, Qian J, Lou S, Xu Z. Gold(III)-catalyzed tandem reaction of O-arylhydroxylamines with 1,3-dicarbonyl compounds: Highly selective synthesis of 3-carbonylated benzofuran derivatives. *J Org Chem* 2010;75:6300-3.
27. Malik JK, Manvi FV, Nanjwade BK, Singh S. Synthesis and screening of some new 2-amino substituted benzothiazole derivatives for antifungal activity. *Drug Invent Today* 2009;1:32-4.
28. Mancini A, Chelini A, Di Capua A, Castelli L, Brogi S, Paolino M, *et al.* Synthesis and biological evaluation of a new class of benzothiazines as neuroprotective agents. *Eur J Med Chem* 2017;126:614-30.
29. Muench J, Hamer AM. Adverse effects of antipsychotic medications. *Am Fam Phys* 2010;81:617-22.
30. Ojha KG, Swarnkar PK, Kriplani P, Gupta GN. Synthesis and antibacterial activity of some new phenothiazine derivatives. *E J Chem* 2007;4:14-20.
31. Ozkay Y, Isikdag I, Incesu Z, Akalin G. Synthesis of 2-substituted-N-[4-(1-methyl-4,5-diphenyl-1H-imidazole-2-yl)phenyl]acetamide derivatives and evaluation of their anticancer activity. *Eur J Med Chem* 2010;45:3320-8.

32. Pai NR, Pusalkar DA. Schizophrenic activity of 1, 2, 4-triazolo(4,3-A)-pyridine-3-(2h)-one-2[3-(4-(3-substituted phenyl)-1-piperaziny}alkyl] hydrochloride derivatives. *Int J Pharm Sci Res* 2010;5:108-14.
33. Pandurangan A, Sharma A, Sharma N, Sharma PK, Visht S. Synthesis and structural studies of novel benzothiazole derivative and evaluation of their antimicrobial activity. *Der Pharm Chem* 2010;2:316-24.
34. Patil ST, Bhatt PA. Synthesis and pharmacological screening of some benzoxazole derivatives as an anti-inflammatory agents. *Int J Pharm Res Dev* 2010;2:165-72.
35. Pelecanou M, Tzanopoulou S, Sagnou M, Petsotas MP, Gourni E, Loudos G. Evaluation of re and ^{99m}Tc complexes of 2-(4'-aminophenyl)benzothiazole as potential breast cancer radiopharmaceuticals. *J Med Chem* 2010;53:4633-41.
36. Prabhu PP, Pande S, Shastry CS. Synthesis and biological evaluation of schiff's bases of some new benzothiazole derivatives as antimicrobial agents. *Int J ChemTech Res* 2011;3:185-91.
37. Priyanka K, Sharma NK, Jha KK. Benzothiazole: The molecule of diverse biological activities. *Int J Curr Pharm Res* 2010;2:1-6.
38. Saleh OA, El Behery MF, Aboul-Enein MN, El-Azzouny AA. Anticonvulsant potential of certain N-(6-substitutedbenzo[d]thiazol-2-yl)-2-(4-substitutedpiperazin-1-yl)acetamides. *Egypt Pharm J* 2016;15:62-9.
39. Sekar NV, Borse BN, Gupta VD, Phatangare KR, Patil VS, Umaspe PG. Antimicrobial activity of novel 2-substituted benzimidazole, benzoxazole and benzothiazole derivatives. *Arabian J Chem* 2016;9:1-19.
40. Serdons K, Verduyck T, Vanderghinste D, Borghgraef P, Cleynhens J, Van Leuven F, *et al.* 11C-labelled PIB analogues as potential tracer agents for *in vivo* imaging of amyloid beta in Alzheimer's disease. *Eur J Med Chem* 2009;44:1415-26.
41. Shantakumar SM, Rajeeva B, Srinivasulu N. Synthesis and antimicrobial activity of some new 2-substituted benzothiazole derivatives. *E J Chem* 2009;6:775-9.
42. Sharma C, Yerande S, Chavan R, Bhosale AV. Synthesis of thienopyrimidines and their antipsychotic activity. *E J Chem* 2010;7:655-64.
43. Sharma V, Sharma KV. Synthesis and biological activity of some 3,5-diaryl-1-benzothiazolopyrazoline derivatives: Reaction of chalcones with 2-hyrazinobenzothiazoles. *E J Chem* 2009;6:348-56.
44. Siddiqui N, Rana A, Khan SA, Haque SE, Alam MS, Ahsan W, *et al.* Anticonvulsant and toxicity of newly synthesized 1-[2-(3,4-disubstitutedphenyl)-3-chloro-4-oxoazetidin-1-yl]-3-(6-substituted-1,3-benzothiazol-2-yl) ureas. *Acta Chim Slov* 2009;56:462-9.
45. Sridevi CH, Balaji K, Naidu A, Sudhakaran R. Antimicrobial evaluation and synthesis of some phenylpyrazolo benzothiazole quinoxaline derivatives. *E J Chem* 2009;6:866-70.
46. Srinivas A, Jukanti R, Sagar V, Ganta R, Manda S. Synthesis and *in vivo* anti-inflammatory activity of a novel series of benzoxazole derivatives. *Der Chem Sin* 2010;3:157-68.
47. Vedavathi M, Somashekar B, Sreenivasa GM, Jayachandran E. Synthesis, characterization and antimicrobial activity of fluoro benzothiazole incorporated with 1,3,4-thiadiazole. *J Pharm Sci Res* 2010;2:53-63.
48. Velingkar VS, Ahire DC, Kolhe NS, Shidore MM, Pokharna G. Synthesis, characterization, biological evaluation and ADME studies using *in silico* techniques of novel derivatives of benzothiazolyl-amides as non-acidic anti-inflammatory agents. *Int J Pharm Sci Res* 2011;2:197-202.
49. Zhu J, Chen Z, Xie H, Li S, Wu Y. A general and straightforward method for the synthesis of 2-trifluoromethylbenzothiazoles. *Org Lett* 2010;12:2434-6.