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SYNTHESIS, COMPUTATIONAL STUDY AND PRELIMINARY PHARMACOLOGICAL EVALUATION OF 2-[4-(2-CHLOROBENZYL/BENZOYL) SUBSTITUTED PIPERAZIN-1-YL]-N-PHENYLACETAMIDE: POTENTIAL ANTIPSYCHOTICS

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ABSTRACT
Benzyl and benzoyl substituted acetamides have been synthesized and evaluated as potential antipsychotic agents. The target compounds (4a-b) were prepared by reaction of substituted anilines with chloroacetylchloride which further treated with 2-chlorobenzyl or 2-chlorobenzoyl piperazine in presence of potassium carbonate and potassium iodide as catalyst in acetonitrile. The structures of the target compounds (4a-b) were characterized on the basis of their M.P., TLC, IR and ^{1}H-NMR data. Computational studies of target compounds (4a-b) were carried out by using software programs. The target compounds showed good similarity with respect to standard drugs. The target compounds (4a-b) showed inhibition of 5-HTP induced head twitches behavior and low induction of catalepsy in mice.

Keywords: Acetamides, benzyl/benzoyl piperazine, Computational studies, Catalepsy, Antipsychotic activity.

INTRODUCTION

Schizophrenia is a complex psychological disorder affecting about 1% of the population worldwide.[1] The vast amount of research directed towards the treatment of schizophrenia in recent years attests to the inadequacy of current methods of treatment and the need for new and improved therapeutic agents. The use of typical antipsychotics for the treatment of schizophrenia is associated with severe extrapyramidal side effects.[2] The adverse effects presented by classical antipsychotics along with their ineffectiveness in the treatment of negative symptoms of schizophrenia has encouraged the search for other drugs.[3]

MATERIALS AND METHODS

Melting points of the synthesized compounds were determined by open capillary method and are uncorrected. The infrared (IR) spectra of synthesized compounds were recorded in potassium bromide discs on Perkin Elmer Spectrum RX1. ^{1} H spectra was recorded on a Bruker DRX-300 spectrophotometer at 300 MHz in $CDCl_3$ containing TMS as an internal standard. All reagents were of commercial quality and were used without further purification. The progress of the reaction was monitored by thin layer chromatography (TLC) using silica gel G and spots were visualized in iodine chamber.

Synthesis of 2- Chloro –N- phenylacetamide

Aniline (0.04 mol) was dissolved in 10% sodium hydroxide (100 ml) and treated with chloroacetylchloride (0.04 mol) in dichloromethane (100 ml) at 0-5ºC. After 2 hour stirring, the layers were separated and the aqueous phase extracted with the additional portion of dichloromethane. The organic phases were combined and solvent was removed by vacuum distillation to afford the compound. Physical parameters for 2-chloro-N-phenylacetamides are following:
Molecular Formula: C_8H_8ClNO
Percentage Yield**:** 72.48 %
Melting point**:** 132-134^{0}C
R_f value**:** 0.73
Mobile phase**:** Ethyl acetate: n hexane (1:1)

General procedure for the synthesis of compounds (4a-b)

2-Chloro-N- phenylacetamide (0.005 mol) was dissolve in (100 ml) acetonitrile in a round bottom flask. Anhydrous K_2CO_3 (0.005 mol), catalytic amount of potassium iodide and 2-chloro benzyl / 2-chlorobenzoyl piperazines (0.005mol) were added in to above solution. The mixture was allowed to reflux with continuous stirring on magnetic stirrer for 7-8 hour. After completion of reaction the solvent was removed by vacuum distillation and residue was dissolve in water and dried to afford the target compounds.

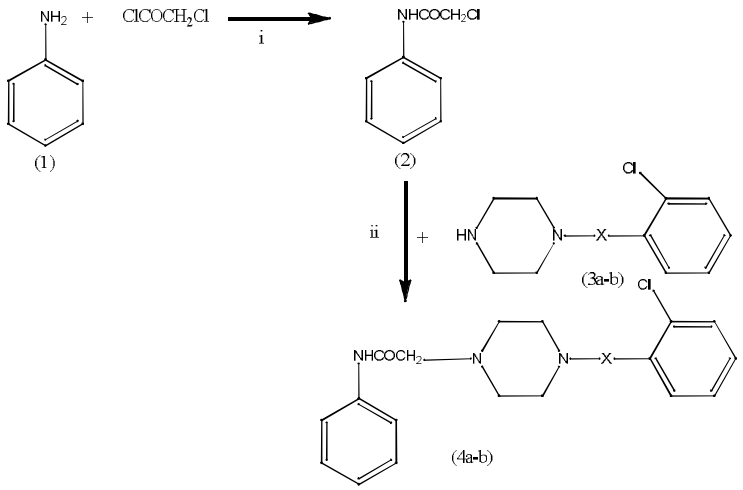

Figure 1: Synthesis of target compounds, reagents and condition: (i) NaOH: dichloromethane (ii) Acetonitrile: K_2CO_3, KI

2-(4-(2-Chlorobenzyl) piperazine-1-yl)-N-phenylacetamide

Yield: 67 % , M. P.: 94-96°C , R_f : 0.63, I R (KBr) – 3401(NH Str.), 3018(CH Str. Aromatic), 2943(CH Str. Aliphatic), 1600(C=O Str. Amide), 1537(C=C Str. Aromatic), 1346(CN Str. Aromatic), 1218(CN Str. Aliphatic). ^{1}HNMR (300 MHz; $CDCl_3$) 2.57-3.87 (m, 8H, pip ring), 4.8 (d, 2H, COCH2) 7.10-7.55 (m, 10 H, Ar H), 9.85 (s, 1H , NH), Anal. Calcd for $C_{19}H_{22}ClN_3O$ = C- 66.37, H-6.45, Cl-10.31, N-12.22, O-4.65.

2-(4-(2-chlorobenzoyl) piperazine-1-yl)-N-phenylacetamide

Yield: 62 %, M. P.: 180-182°C, R_f : 0.42, I R (KBr) – 3392(NH Str.), 3010(CH Str. Aromatic), 2920(CH Str. Aliphatic), 1635(C=O Str. Amide), 1593(C=C Str. Aromatic), 1363(CN Str. Aromatic), 1249(CN Str. Aliphatic), ^{1}HNMR (300 MHz; $CDCl_3$) 2.30-3.56 (m, 8H, pip ring), 4.4 (d, 2H, $COCH_2$) 7.12-7.35 (m, 10 H, Ar H), 9.45 (s, 1H , NH), Anal. Calcd for $C_{19}H_{20}ClN_3O_2$ = C-63.77, H-5.63, Cl-9.91, N-11.74, O-8.94.

COMPUTATION OF PHYSIOCHEMICAL PROPERTIES

A set of molecular parameters was computed for the target compounds as well as three standard drugs clozapine, ketanserine and risperidone using Chem 3D ultra version 12.0 are shown in

Table1. The important molecular parameters for antipsychotics are log P and topological polar surface area. Literature review suggests that TPSA is a measure of a molecule's hydrogen bonding capacity and its value should not exceed certain limit if the compound is intended to be CNS active. Two differing limits have been proposed: van de Waterbeemed et al.[4] suggest a limit of 90 A^2, where, Kelder et al.[5]suggest 60-70 A^2.

Similarity calculations

The physicochemical similarity of the target compounds was calculated with respect to standard drugs [6] and shown in Table 2.

Firstly, the distance 'di' of a particular target compound 'j' to drug molecules e.g., clozapine was calculated by the formula:

$$d_i^2 = \sum_{j=1}^{n} (1-Xi,j\ /Xi,std)^2\ /n$$

Where, Xi, j is the value of molecular parameter 'i' for compound 'j', Xi, std is the value of the same molecular parameter for the standard drug, e.g., clozapine, ketanserine and risperidone. Then, the similarity of compound 'j' to the standard drug was calculated as: Similarity (%) = (1-R) x 100. Where R =$\sqrt{d^2}$ is the quadratic mean (root mean square), a measure of central tendency.

Statistical analysis

Table 1: Calculation of molecular properties of synthesized compounds and standard drugs

Cpd Name	Log P	MW[a]	MR[b]	SAS[c]	MSA[d]	SEV[e]	TPSA[f]	MTI[g]	WI[h]	Ova[i]
4a	2.80	343.85	97.83	572.44	310.59	279.02	35.58	12063	1619	1.50
4b	2.24	357.83	97.86	576.45	312.99	275.10	52.65	12860	1758	1.53
CLZ[j]	3.71	326.82	94.58	508.99	259.12	215.89	30.87	8127	1082	1.48
KET[k]	2.37	395.43	106.67	589.34	298.72	253.38	69.72	18646	2596	1.54
RIS[l]	2.10	410.48	114.21	690.02	375.09	351.81	57.5	20311	2793	1.55

[a]Molecular weight, [b]Molar refractivity, [c]Connolly solvent accessible surface area, [d]Connolly molecular surface area, [e]Connolly solvent excluded volume, [f]Topological polar surface area, [g]Molecular topological index, [h]Wienner index, [i]Ovality, [j]Clozapine, [k]Ketanserin, [l]Risperidone

Table 2: Similarity values of synthesized compounds with respect to standard drugs

Compound Code	Similarity [a,b] (in %) to		
	Clozapine	Ketanserin	Risperidone
4a	20 %	27 %	20.32 %
4b	58.7 %	46.72%	35.57 %

[a](1 - R) X 100 where R = quadratic mean (root mean square mean).
[b]Calcd. from physicochemical properties: Molecular weight; Molar refractivity; Connolly solvent accessible surface area; Connolly molecular surface area; Connolly solvent excluded volume; Topological polar surface area; Molecular topological index; Wiener index.

Preliminary Pharmacological Evaluation for Antipsychotic Effect

All the target compounds were subjected to preliminary pharmacological evaluation to determine their ability to inhibition of 5-hydroxy tryptophan (5-HTP) induced head twitches behavior and catalepsy studies. [7]

Prior permission of the animal ethics committee was obtained and all experiments were conducted according to the approved protocol (837/ac/04/CPCSEA).

Antagonism of 5-hydroxytryptophan (5-HTP) induced head twitches

Swiss albino mice in the control group (n=6) was injected with pargyline (75 mg/kg, i.p) in order to prevent the rapid degradation of 5-HTP. Thirty minutes later, the test compound was administered (40mg/kg). 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, 2-marked. A maximum of 8 score is possible.[8] (Fig 2) An observer made all observations unaware of the specific drug treatments.

The inhibition of 5-HTP induced head twitches behavior study showed that benzoyl analogue produced higher activity than benzyl analogue.

Table 3: Total mean head twitches score

S. No.	Compounds	Total Head Twitches
1	4a	4.2
2	4b	3.8
3	Control	6.4
4	Clozapine	0.86

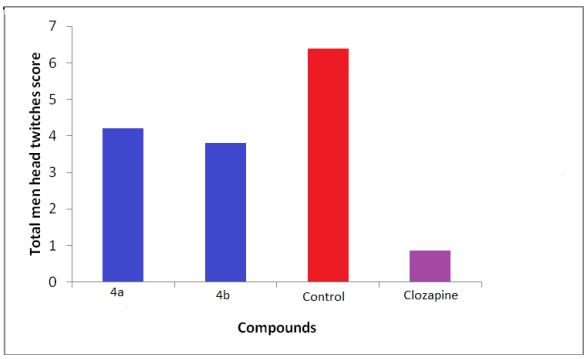

Fig 2: The effect of synthesized compounds (4a-b) on the 5-HTP induced head twitches behavior. Each column represents the mean of total head twitches score for group of six mice assessed at 10-min intervals for 30 min, starting 20 after the 5-HTP treatment. A score of 8 is maximum possible.

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 (sec.) 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. Severity of the cataleptic behavior was scored as 1 if maintained the imposed posture for at least 20 sec. and every additional 20 sec. one extra point was given. A cut-off time of 1100 sec. was applied during the recording of observations. The animals were returned to their individual home cages in between determinations. (Fig 3) All observations were made between 10.00 and 16.00 hrs in a quiet room at 23-25ºC. The animals in the test group were administered with test drugs (80mg/kg) instead of haloperidol and the remaining procedure for assessment of catalepsy was same as mentioned above.[9,10]

The Catalepsy results showed that new compounds (4a-b) were less cataletogenic than haloperidol. Among them benzoyl analogues exhibit the lowest propensity to produce catalepsy.

Table 4: Total mean catalepsy score

S. No.	Compound Code	Mean Catalepsy Score				
		30 min	60 min	90 min	120 min	240 min
1	4a	3.2	5.1	6.7	9.1	3.9
2	4b	2.5	4.0	5.7	7.8	3.4
3	Haloperidol	4.4	7.5	10.4	12.5	6.6

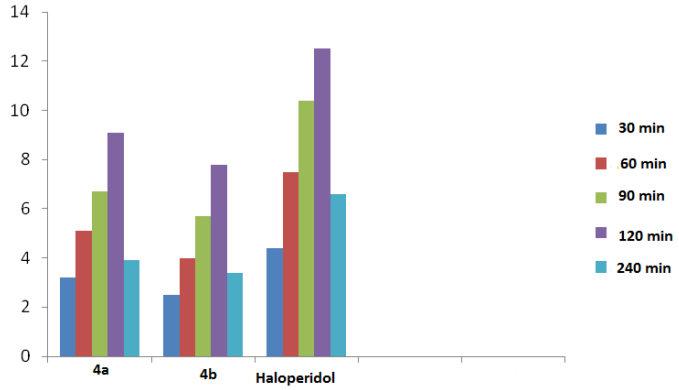

Fig 3: The effect of synthesized compounds on induction of catalepsy in mice and results are expressed as the mean .

RESULTS AND DISCUSSION

The target compounds (**4a-b**) were synthesized as outlined in Fig 1 and obtained in good yields (62 – 67 %). The purity of the compounds was monitored by TLC and the structures of the compounds were deduced on the basis of spectroscopic methods. A set of molecular parameters and physicochemical similarity of the target compounds was calculated with respect to the standard drugs. The compounds (**4a-b**) showed good structural similarity with respect to standard drugs (20-58%). The results from the pharmacological synthesized compounds (5-HTP) induced head twitches behavior and low propensity to induce catalepsy.

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