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Synthesis, computational studies and preliminary pharmacological evaluation of new acetamides: Potential antipsychotics

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ABSTRACT

A series of acetamides have been synthesized and evaluated as potential antipsychotic agents. The target compounds (3a-e) were prepared by reaction of substituted anilines with chloroacetylchloride which further treated with benzyl or benzoyl piperazine in presence of potassium carbonate and potassium iodide as catalyst in acetonitrile. The structures of the target compounds (3a-e) were characterized on the basis of their M.P., TLC, IR and ^{1}H-NMR data. Computational studies of target compounds (3a-e) were carried out by using software programs. The target compounds showed good similarity with respect to standard drugs. The target compounds (3a-e) 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 has been referred to as the cancer of mental illnesses [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

Experimental

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-(substituted phenyl) acetamide

Substituted anilines (0.04 mol) were dissolved in 10% sodium hydroxide (100 ml) and treated with chloroacetylchloride (3.18 ml, 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 compounds.

Table 1 Physical parameters of 2-Chloro-N-(Substituted phenyl) acetamide

Compounds	Molecular formula	Melting point (°C)	Percentage yield (%)	Rf value
2-Chloro-N-phenylacetamide	$C_8H_8Cl\ NO$	132-134	72.48	0.73
2-Chloro-N-(3-chlorophenyl)acetamide	$C_8H_7Cl_2NO$	65-68	76.07	0.64
2-Chloro-N-(2-fluorophenyl)acetamide	$C8H_7ClFNO$	82-86	73.29	0.68

General procedure for the synthesis of compounds (3a-e)

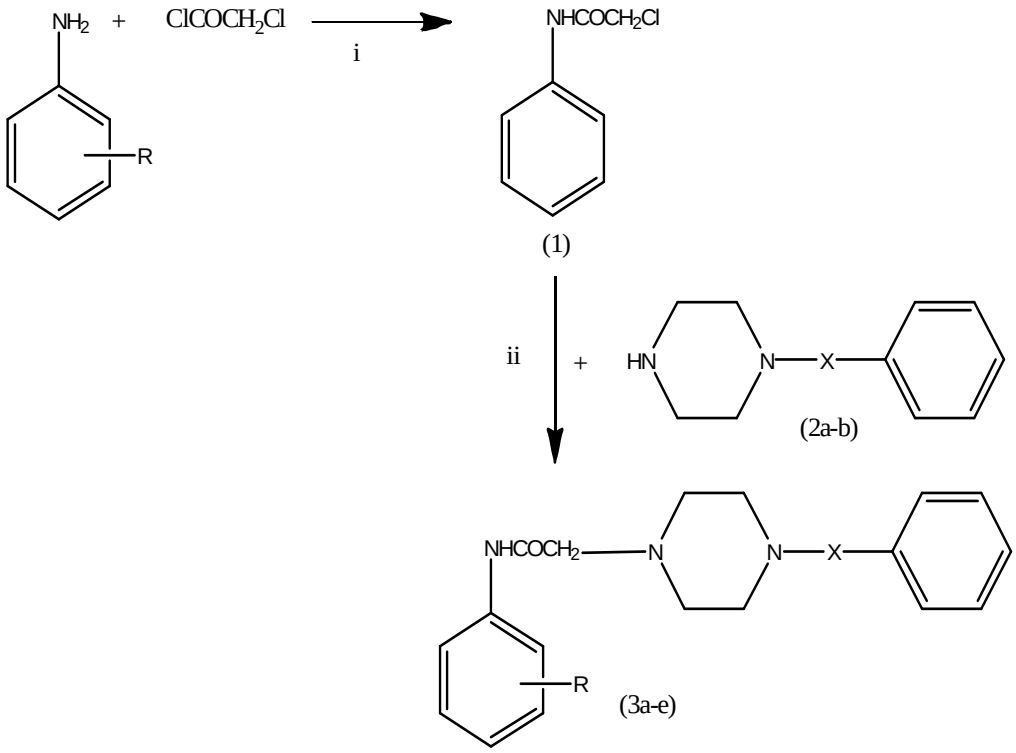
2-Chloro-N- (substituted phenyl) acetamide (0.005 mol) was dissolve in (100 ml) acetonitrile in a round bottom flask. Anhydrous K_2CO_3 (0.005 mol) catalytic amount of potassium iodide and appropriate benzyl / benzoyl piperazines (0.005mol) were added in to above solution. The mixture was allowed to 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.

Table 2 Substituent of compounds (3a-e)

Compound no.	Compound codes	R	X
1	3a	H	CH_2
2	3b	H	CO
3	3c	3-Cl	CH_2
4	3d	3-Cl	CO
5	3e	2-F	CH_2

Table 3 Physical parameters of synthesized compounds

Compound codes	Molecular formula	Melting point (°C)	Percentage yield (%)	Rf value
3a	$C_{19}H_{23}N_3O$	108-110	65	0.68
3b	$C_{19}H_{21}N_3O_2$	198-200	65.89	0.58
3c	$C_{19}H_{22}\ ClN_3O$	73-76	58.39	0.66
3d	$C_{19}H_{20}\ ClN_3O_2$	124-126	53.22	0.55
3e	$C_{19}H_{22}\ FN_3O$	180-182	70.49	0.70



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

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 Table 4. 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 and shown in Table 5. 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 [6].

Table 4 Calculation of molecular properties of synthesized compounds and standard drugs

Cpd Codes	Log P	MW[a]	MR[b]	SAS[c]	MSA[d]	SEV[e]	TPSA[f]	MTI[g]	WI[h]	Ova[i]
3a	2.24	309.41	93.23	579.24	311.22	275.04	35.58	11284	1456	1.52
3b	1.68	323.39	93.06	589.01	309.30	277.83	52.65	12069	1591	1.54
3c	2.80	343.85	98.03	603.61	326.31	289.52	35.58	12151	1635	1.53
3d	2.24	357.83	97.86	601.22	325.12	281.93	52.65	12972	1782	1.53
3e	2.40	327.14	93.44	597.42	311.93	276.32	35.58	12071	1618	1.52
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 5 Similarity values of synthesized compounds with respect to standard drugs

Compound Codes	Similarity [a,b] (in %) to		
	Clozapine	Ketanserin	Risperidone
3a	77	71.26	69.01
3b	62.95	77.49	74.21
3c	69.37	80.93	72.86
3d	57.12	81.04	78.22
3e	71.42	73.51	62.48

[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 atypical 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]. An observer made all observations unaware of the specific drug treatments.

The inhibition of 5-HTP induced head twitches behavior study showed that benzoyl analogues **(3b and 3d)** produced higher activity than benzyl analogues (3a, 3c and 3e) Fig. 1

Table 6 Inhibition of 5-hydtoxytryptophan (5-HTP) induced head twitches behavior

S. No.	Compounds	Total Head Twitches
1	3a	4.7 ± 0.21
2	3b	3.4± 0.15
3	3c	5.5± 0.19
4	3d	4.2±0.22
5	3e	5.1±0.16
6	Control	6.2±0.17
7	Clozapine	0.84±0.14

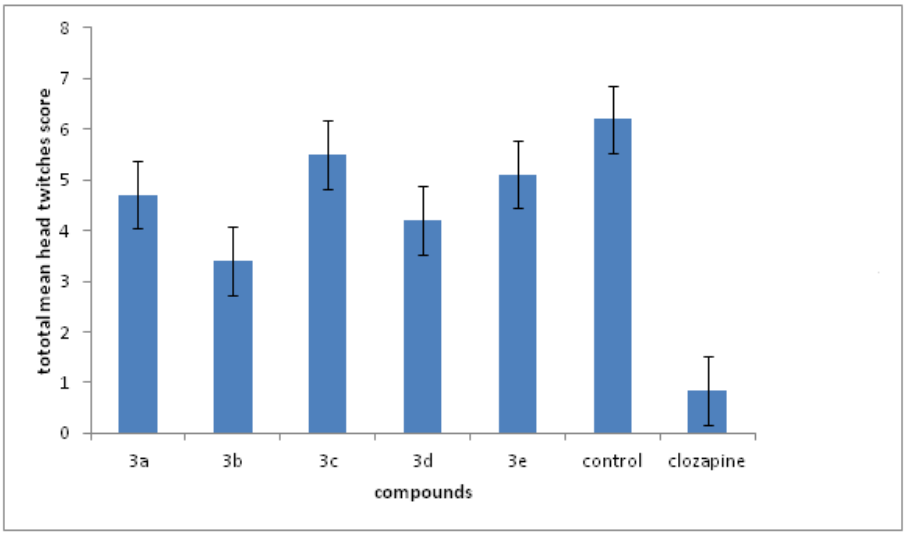


Fig 1 The effect of synthesized compounds (3a-e) on the 5-HTP induced head twitches behavior
Each column represents the mean ± SEM of total head twitches score for group of six mice assessed at 10-min intervals for 30 min, starting 20 after the 5-HTP treatment. A score of 8 is maximum possible. All values statistically significant with respect to control at p<0.05.

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. All observations were made between 10.00 and 16.00 hrs in a quiet room at 23-25ºC [9, 10]. 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. The Catalepsy results showed all new compounds (3a-e) were less cataletogenic than haloperidol. Among them benzoyl analogues (3band 3d) exhibit the lowest propensity to produce catalepsy (Fig. 2)

Table 7 Induction of catalepsy

S. No.	Compound code	Mean Catalepsy Score				
		30 min	60 min	90 min	120 min	240 min
1	3a	3.15±0.12	5.43±0.24	6.93±0.22	9.18±0.28	3.81±0.17
2	3b	2.73±0.14	4.21±0.25	5.9±0.19	7.91± 0.18	3.26±0.24
3	3c	3.71±0.17	6.45±0.17	8.45±0.14	10.36±0.22	4.18±0.19
4	3d	2.84±0.27	4.5±0.19	6.0±0.17	7.5±0.12	3.5±0.24
5	3e	3.41±0.23	6.01±0.22	7.35±0.25	9.40±0.23	3.71± 0.15
6	Haloperidol	4.4±0.21	7.5±0.23	10.4±0.24	12.5±0.15	6.6±0.14

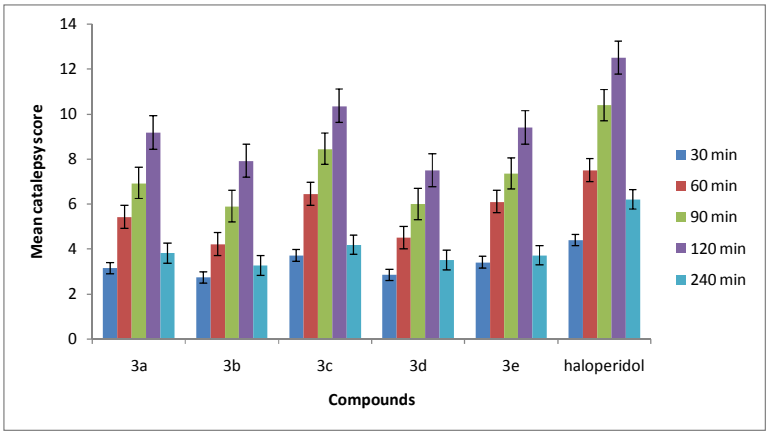


Figure 2: The effect of synthesized compounds on induction of catalepsy in mice
Results are expressed as the mean ±SEM (n =6) p<0.05.

RESULTS

2-(4-Benzylpiperazin-1-yl)-N-phenylacetamide (3a)

Yield: 65%; I R (KBr, cm^{-1}): 3397 (NH str.), 3023 (CH str. Aromatic) , 2937 (CH str. Aliphatic), 1682 (C=O str. Amide), 1533(C=C str. Aromatic), 1345 (C-N str. Aromatic), 1217(C-N str. Aliphatic) ; ^{1}H NMR (300MHz; $CDCl_3$ □): 2.52-3.44 (m, 8H, pip. ring), 4.21(d, 2H, -NCH_2), 4.57 (d, 2H, -$COCH_2$), 6.71-8.60 (m, 10H, -Ar H), 9.88 (s, 1H, -NH) , Anal. Calcd for $C_{19}H_{23}N_3O$ – C. 73.76: H. 7.49: N.13.58: O.5.17;

2-(4-Benzoylpiperazin-1-yl)-N-phenylacetamide (3b)

Yield: 65.89%; I R (KBr, cm^{-1}): 3229(NH str.), 3054 (CH str. Aromatic) , 2956 (CH str. Aliphatic), 1618(C=O str. Amide), 1575(C=C str. Aromatic), 1365 (C-N str. Aromatic), 1247(C-N str. Aliphatic) ; ^{1}H NMR (300MHz; $CDCl_3$ □): 2.57-3.87 (m, 8H, pip. ring), 4.55 (d, 2H, -$COCH_2$), 6.56-8.19 (m, 10H, -Ar H), 9.85 (s, 1H, -NH), Anal. Calcd for $C_{19}H_{21}N_3O_2$ – C. 70.57: H. 6.55: N. 12.99: O. 9.89;

2-(4-(2-Chlorobenzyl) piperazin-1-yl)-N-phenylacetamide (3c)
Yield: 58.39 %; I R (KBr, cm^{-1}): 3307 (NH str.), 3060 (CH str. Aromatic) , 2948 (CH str. Aliphatic), 1659 (C=O str. Amide), 1588(C=C str. Aromatic), 1368 (C-N str. Aromatic), 1255(C-N str. Aliphatic) ; ^{1}H NMR (300MHz; $CDCl_3$ □): 2.41-3.46 (m, 8H, pip. ring), 4.24(d, 2H, -NCH_2), 4.53 (d, 2H, -$COCH_2$), 7.17- 7.97(m, 10H, -Ar H), 9.87 (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. 4.64;

2-(4-(2-Chlorobenzoyl) piperazin-1-yl)-N-phenylacetamide (3d)
Yield: 53.22%; I R (KBr, cm^{-1}): 3398 (NH str.), 3057 (CH str. Aromatic) , 2956 (CH str. Aliphatic), 1617(C=O str. Amide), 1546(C=C str. Aromatic), 1365(C-N str. Aromatic), 1248(C-N str. Aliphatic) ; ^{1}H NMR (300MHz; $CDCl_3$ □): 2.55-3.87 (m, 8H, pip. ring), 6.52- 8.02 (d, 2H, -$COCH_2$), 4.53 (m, 10H, -Ar H), 9.83(s, 1H, -NH)**,** Anal. Calcd for $C_{19}H_{20}$ Cl N_3O_2 –C. 63.77: H. 5.63: Cl. 9.91: N. 11.74: O. 8.94;

2-(4-Benzylpiperazin-1-yl)-N-(2-fluorophenyl) Acetamides (3e)
Yield: 70.49 %; I R (KBr, cm^{-1}): 3373(NH str.), 3061 (CH str. Aromatic) , 2948(CH str. Aliphatic), 1673 (C=O str. Amide), 1501(C=C str. Aromatic), 1368(C-N str. Aromatic), 1263(C-N str. Aliphatic) ; ^{1}H NMR (300MHz; $CDCl_3$ □): 2.83-3.44 (m, 8H, pip. ring), 4.24(d, 2H, -NCH_2), 4.49 (d, 2H, -$COCH_2$), 7.81-7.49(m, 10H, -Ar H), 9.80 (s, 1H, -NH), Anal. Calcd for $C_{19}H_{22}FN_3O$ – C. 69.70: H.6.77: F.5.80: N.12.83: O.4.89;

DISCUSSION AND CONCLUSION

The target compounds (**3a-e**) were synthesized as outlined in scheme 1. The synthesized compounds were tested for antagonism of 5-HTP induced head twitches at 40 mg/kg. The inhibition of 5-HTP induced head twitches behavior study showed that benzoyl analogues **(3b and 3d)** produced significant activity than benzyl analogues. The synthesized compounds were also tested for catalepsy study at 80 mg/kg. The catalepsy results showed all compounds **(3a-e)** less cataletogenic than haloperidol. Among them benzoyl analogues **(3b and 3d)** exhibited the lowest propensity to produce catalepsy. Computational studies of target compounds **(3a-e)** were carried out by using software programs. The target compounds showed good similarity with respect to standard drugs.

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