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Synthesis and preliminary pharmacological evaluation of *N*-2-(4-(4-(2-substitutedthiazol-4-yl) piperazin-1-yl)-2-oxoethyl)acetamides as novel atypical antipsychotic agents

K. V. G. Chandra Sekhar [a,*], V. S. Rao [a], D. Ravi Kumar Vyas [b], M. Murali Krishna Kumar [a]

[a] Chemistry Group, Birla Institute of Technology & Science, FDIII, Vidya Vihar, Pilani, Rajasthan 333 031, India
[b] Pharmacy Group, Birla Institute of Technology & Science, FDIII, Vidya Vihar, Pilani, Rajasthan 333 031, India

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ABSTRACT

A series of *N*-2-(4-(4-(2-substitutedthiazol-4-yl) piperazin-1-yl)-2-oxoethyl)acetamides were synthesized in an effort to prepare novel atypical antipsychotic agents. The compounds were synthesized by either microwave irradiation technique or by conventional synthesis and were characterized by spectral data (IR, ^{1}H NMR, and MS) and the purity was ascertained by microanalysis. All the synthesized compounds were screened for their in vivo pharmacological activity in *Swiss albino* mice. D_2 antagonism studies were performed using climbing mouse assay model and 5-HT_{2A} antagonism studies were performed using quipazine induced head twitches in mice. It was observed that none of the new chemical entities exhibited catalepsy. **AG 3** was found to be the most active compound.

Conventional neuroleptics or typical antipsychotics such as chlorpromazine, haloperidol, and fluphenazine are recognized as effective agents in the treatment of positive symptoms of schizophrenia, namely hallucinations and delusions. However, they show poor or no efficacy against negative symptoms[1] (apathy, social withdrawal), and their use is frequently associated with serious side effects, such as extrapyramidal syndrome[2] (EPS), tardive dyskinesia[3] (TD), and hyperprolactinemia.[4] All these compounds were found to be antagonists at dopamine D_2 receptors.[5]

The introduction of clozapine for the pharmacotherapy of schizophrenia represented a significant advance in the treatment of this devastating mental illness. Clozapine is superior to typical neuroleptics in treating positive and negative symptoms, and is effective in many patients who are refractory to typical antipsychotics.[6,7] In addition, clozapine does not induce the EPS commonly caused by the typical agents. Because of these properties, clozapine was termed 'atypical' and represents the prototype drug of this class. Although clozapine is the most efficacious antipsychotic currently available, serious side effects induced by the drug, including agranulocytosis, impose substantial limitations on its use.

Over the past two decades, much attention regarding the treatment for schizophrenia has focused on this new class of antipsychotic medications and led to the proliferation of 'atypical' antipsychotics, including risperidone, olanzapine, quetiapine, ziprasidone, sertindole, iloperidone, aripiprazole, amisulpride, and zotepine.[8] In fact, there is growing evidence that, most of the new medications can offer some advantages over 'typical' or first generation antipsychotics (FGAs) such as greater improvement in negative symptoms, cognitive impairment, relapse prevention and quality of life with fewer EPS and less TD.[9] However, these advantages have been regarded as incremental and not substantial. In addition, concerns about side effects such as EPS have been replaced by other distressing side effects, such as weight gain, hyperglycemia, postural hypotention, seizures, cardiac ventricular arrhythmias, and dyslipidemia.[10,11]

The rationale for development of the antipsychotic drugs recently introduced, and currently under development is predominantly based on dopamine and serotonin hypotheses of schizophrenia. Since this strategy has apparently not yielded an antipsychotic as efficacious as clozapine, it is absolutely necessary to consider other hypotheses of schizophrenia to guide alternative strategies for the discovery of novel antipsychotic agents. In this regard, the NMDA receptor hypofunction hypothesis of schizophrenia provides an alternative strategy for the drug development.

In the etiology of schizophrenia NMDA receptors hypofunction is also reported.[12] It is also reported that agonists at this site will alleviate the negative and cognitive symptoms.[13] Hence in this work compounds are designed incorporating NMDA agonism and D_2 antagonism so that both negative symptoms (including cognitive) and positive symptoms can be cured. This way of targeting/designing we attempt for the first time.

* Corresponding author.
E-mail address: kvgcs@yahoo.com (K.V.G.C. Sekhar).

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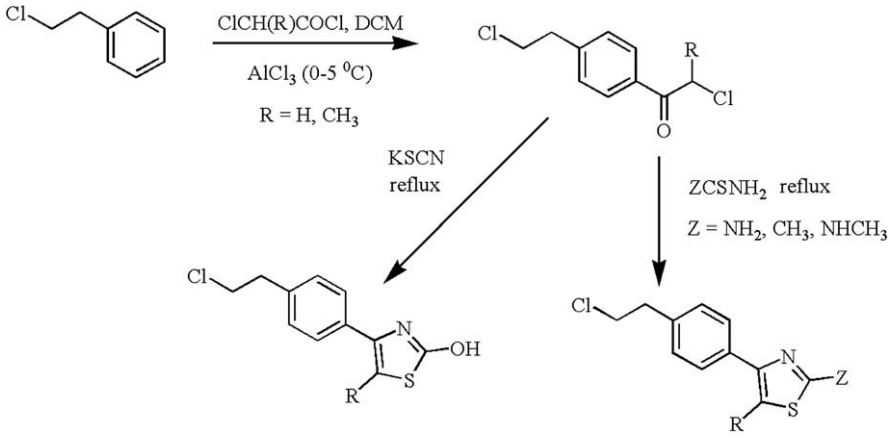
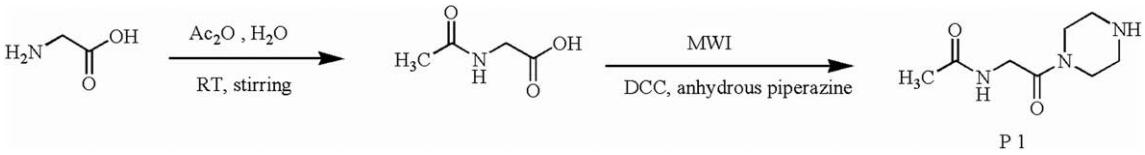
The strategy of Ariens, which was promulgated few years ago, has been employed for the design of potential atypical antipsychotic agents.[14] Ariens strategy in brief, involves modification of the structure of a receptor agonist, in this case dopamine, with a large lipophilic group on the amino position, which binds to the accessory binding site adjacent to the agonist binding site and transforms the agonist into an antagonist. Using this strategy the current marketed drug ziprasidone was developed.[15] We adopted this strategy and employed glycine, a co-agonist, at the NMDA receptor[16] as one portion of the molecule.

We synthesised compounds in which 2- and 5-substituted chloroethylphenylthiazoles (**CEP**: **1–7**) have been incorporated at the piperazinyl nitrogen atom of acetamido glycine piperazine looking for NMDA agonism and D_2 antagonism. Seven new compounds have been synthesized and the synthetic schemes are illustrated in Schemes 1–3. Scheme 1 illustrates synthesis of 2- and 5-substituted chloroethylphenylthiazoles (**CEP**:**1–7**) whereas Scheme 2 illustrates synthesis of acetamido glycine piperazine (**P1**) while Scheme 3 illustrates coupling of these two fragments to yield the title compounds.

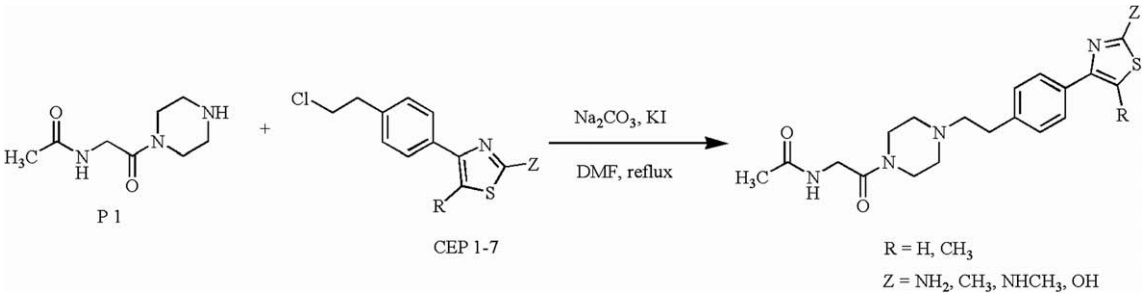
Substituted chloroethylphenylthiazoles (fragment 1) were prepared as per the literature protocol with modifications in some steps.[17] Acetyl glycine required as starting material for fragment 2 was prepared by acetylating glycine at room temperature using the literature protocol.[18] Microwave irradiation of acetyl glycine with anhydrous piperazine in the presence of DCC in DMF for about 5 min gave acetamido glycine piperazine[19] (**P1**). Equimolar amounts of acetamido glycine piperazine (**P1**) and 2- and 5-substituted chloroethylphenylthiazoles (**CEP**: **1–7**) along with 2.125 equivalents of anhydrous Na_2CO_3 and catalytic amount of KI (2 mg) in DMF as solvent when refluxed for 48 h afforded the title compounds.[20] All the synthesized compounds were characterized by spectral (IR, ^{1}H NMR, and mass) and elemental analysis data. Infrared spectral analysis of the final compounds (**AG: 1–7**) showed strong peaks at ~3440 cm^{-1} (NH stretch); ~3050 cm^{-1} (aromatic C–H stretch); ~2870 cm^{-1} (aliphatic C–H stretch); ~1645 cm^{-1} (CO stretch); ~700 cm^{-1} (C–S–C stretch); ~1620 cm^{-1} (aromatic C=C stretch); ~1640 cm^{-1} (C=N ring stretch); ~1255 cm^{-1} (aliphatic C–N stretch); ~810 cm^{-1} (para disubstituted benzene). In ^{1}H NMR spectra, methylene protons (cyclic) adjacent to N^1 nitrogen of piperazine showed triplet in the range of δ 3.11–3.36 whereas methylene protons (cyclic) adjacent to N^4 nitrogen of piperazine showed triplet in the range of δ *2.46–2.69*. Methyl protons of the amide functionality appeared as singlet at δ 2.12. The labile proton on amide functionality appeared as a singlet at δ 8.10. Methylene protons of glycine were seen as singlet at δ 4.20. The final compounds showed signals corresponding to four protons



Scheme 1.



Scheme 2.



Scheme 3.

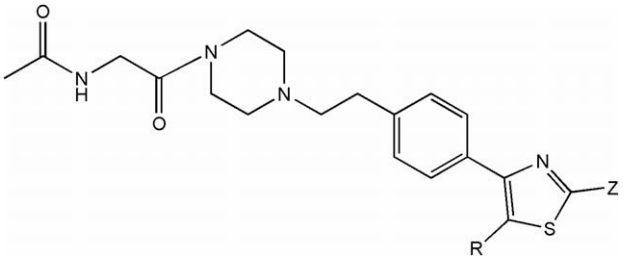
around δ 7.10–7.49 for the aromatic protons as a multiplet. PMR signal corresponding to four protons of the ethyl linker was observed at δ 2.60–2.70 as multiplet. Elemental (CHNS) analysis indicated that the calculated and observed values were within the acceptable limits (±0.4%). Physical data of final compounds is represented in Table 1.

The Institutional Animal Ethics Committee of the Birla Institute of Technology and Science, Pilani, India, approved experimentation on animals (Protocol No. IAEC/RES/11/2, 17.09.07). *Swiss albino* mice (25–30 g) of either sex obtained from Hissar Agricultural University, Hissar, Haryana, India were used for the pharmacological studies. Inhibition or reversal of Apomorphine induced cage-climbing behavior in mice by a test compound is an indication of mesolimbic dopaminergic D_2 receptor antagonism.[21]

The effect of pretreatment with 10 mg/kg dose of the test compounds on apomorphine (0.5 mg/kg sc) induced cage climbing behavior was studied by the literature method.[21] Haloperidol (1.0 mg/kg ip) was used as control as it completely inhibited the climbing induced by apomorphine. Inhibition or reversal of quipazine induced head-twitches in mice by the test molecule (10 mg/kg dose) is an indication of central serotonergic 5-HT_{2A} receptor antagonism and this behavior was studied by the literature method.[22] Risperidone (0.6 mg/kg ip) was used as control as it completely inhibits quipazine induced head twitches in mice. Cataleptic effect of new chemical entities (NCEs) was evaluated by the literature method [23] and scoring was done as per literature.[24]

In this study, we have demonstrated the synthesis and pharmacological activity of novel *N*-2-(4-(4-(2-substitutedthiazol-4-yl)

Table 1
Physical constants of *N*-2-{4-[4-(2-substitutedthiazol-4-yl)piperazin-1-yl]-2-oxoethyl} acetamides (**AG**: **1**–**7**)



Compound	R	Z	Mp (°C)	% Yield	Recryst. solvent	Mol. formula[a] (Mol. weight)[b]
AG 1	NH_2	H	146–147	61	DMF–H_2O	$C_{19}H_{25}N_5O_2S$ (387)
AG 2	$NHCH_3$	H	182–183	67	EtOH	$C_{20}H_{27}N_5O_2S$ (401)
AG 3	NH_2	CH_3	200–202	83	Acetone	$C_{20}H_{27}N_5O_2S$ (401)
AG 4	OH	H	189–200	84	MeOH	$C_{19}H_{24}N_4O_3S$ (388)
AG 5	CH_3	CH_3	192–194	48	MeOH	$C_{21}H_{28}N_4O_2S$ (400)
AG 6	$NHCH_3$	CH_3	208–209	50	DMF–H_2O	$C_{21}H_{29}N_5O_2S$ (415)
AG 7	CH_3	H	182–184	48	DMF–H_2O	$C_{20}H_{26}N_4O_2S$ (386)

[a] Elemental (CHNS) analysis indicated that the calculated and observed values were within the acceptable limits (±0.4%).
[b] Molecular weight determination by mass spectral analysis.

Table 2
Results of D_2, 5-HT_{2A} antagonism, and catalepsy test of compounds **AG 1**–**7**

Compound	% D_2 inhibition (Mean ± SEM)			% 5-HT_{2A} inhibition (Mean ± SEM)	Max. avg. cataleptic time (s)	Max. avg. cataleptic score
	10th min	20th min	30th min			
AG 1	85 ± 10	65 ± 6.12	90 ± 6.12	22 ± 5.5	16.74	0
AG 2	60 ± 10	50 ± 10	60 ± 10	54 ± 5.29	16.54	0
AG 3	70 ± 12.25	65 ± 6.12	60 ± 10	79 ± 2.78	8.71	0
AG 4	75 ± 9.35	65 ± 6.12	65 ± 6.12	80 ± 6.90	3.67	0
AG 5	65 ± 6.12	65 ± 6.12	80 ± 9.35	71 ± 6.26	5.12	0
AG 6	70 ± 12.25	70 ± 12.25	85 ± 6.12	67 ± 2.78	3.89	0
AG 7	70 ± 12.25	65 ± 6.12	70 ± 12.25	20 ± 6.43	4.62	0
Risperidone	91 ± 5	91 ± 5	90 ± 5	100 ± 0	2.54	0

Table 3
Summary of results of in vivo pharmacological studies of **AG 1**–**7**

Compound	% 5-HT_{2A} inhibition	% Max. D_2 inhibition	5-HT_{2A}/D_2 ratio	Max. avg. cataleptic score
AG 1	22 ± 5.55	90 ± 6.12	0.24444	0
AG 2	54 ± 5.29	60 ± 10	0.90000	0
AG 3	79 ± 2.78	70 ± 12.25	1.12857	0
AG 4	80 ± 6.90	75 ± 9.35	1.06667	0
AG 5	71 ± 6.26	80 ± 9.35	0.8875	0
AG 6	67 ± 2.78	85 ± 11.12	0.78883	0
AG 7	20 ± 6.43	70 ± 12.25	0.28572	0
Risperidone	100 ± 0	91 ± 5	1.09890	0

piperazin-1-yl)-2-oxoethyl)acetamides (**AG 1–7**) as atypical antipsychotic agents. The results (Table 2) clearly indicate that all the NCEs have the capability of antagonizing mesolimbic dopaminergic D_2 receptors with% inhibition varying between 50% and 90% at the dose level studied (10 mg/kg). A maximum of 90% inhibition was observed in **AG 1**, while a minimum of 50% inhibition was observed in **AG 2**. The capability of antagonizing central serotonergic 5-HT_{2A} receptors varied between 20% and 80% at the dose level studied (10 mg/kg). A maximum of 80% inhibition was observed in **AG 4**, while a minimum of 20% inhibition was observed in **AG 7**. The results tabulated in Table 2 clearly indicate that the maximum average cataleptic score observed is 0 for the NCEs at dose level studied (10 mg/kg) indicating that all compounds are noncataleptic. The overall results of title compounds are summarized in Table 3. Compound **AG 3** is the most active one among the synthesized compounds with 5-HT_{2A}/D_2 ratio of 1.1286 and an average cataleptic score of zero (risperidone's 5-HT_{2A}/D_2 ratio is 1.0989). Hence this compound, better than risperidone, satisfies all the criteria required for a molecule to be atypical antipsychotic according to Meltzer's classification.[25] Further studies in transforming these agents into clinically useful agents are in progress in our laboratory.

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19. *N*-(2-oxo-2-piperazin-1-ylethyl)acetamide **(P1)**: % Yield: 86% (1.35 g); melting point: 192 °C. IR (KBr) cm^{-1}: 3360 (N–H stretch); 2850, 2735 (aliphatic C–H stretch); 1642 (C=O stretch); 1250 (aliphatic C–N stretch). ^{1}H NMR ($CDCl_3$) (δ) ppm: 2.12 (s, 3H, $COCH_3$); 2.45–2.63 (t, 4H, $N^4(CH_2)_2$); 3.10–3.21 (t, 4H, $N^1(CH_2)_2$); 4.62(s, 2H, $COCH_2NH$); 5.35 (s, 1H, NH); 6.35 (s, 1H, $COCH_2NH$). Mass (FAB, M^+): Calcd: 185.112. Found: 185.1. Anal. ($C_8H_{15}N_3O_2$): Calcd C, 51.88; H, 8.16; N, 22.69. Found C, 51.62; H, 8.04; N, 22.47.
20. *N*-{2-[4-(4-(2-aminothiazol-4-yl)phenethyl) piperazin-1-yl]-2-oxoethyl} acetamide (**AG 1**): % Yield: 61% (0.117 g); melting point: 146–147 °C. IR (KBr) cm^{-1}: 3428 & 3400 (NH_2 stretch); 3330 (NH stretch); 3037, 3018 (aromatic C–H stretch); 2980, 2955 (aliphatic C–H stretch); 1645 (C=O stretch); 1641 (C=N ring stretch); 1620, 1592 (aromatic C=C stretch); 1257 (aliphatic C–N stretch); 808 (para disubstituted benzene); 700 (C–S–C stretch). ^{1}H NMR ($CDCl_3$) (δ) ppm: 2.12 (s, 3H, $COCH_3$); 2.55–2.62 (t, 4H, $N^4(CH_2)_2$); 2.67–2.72 (m, 4H, $(CH_2)_2$); 3.16–3.19 (t, 4H, $N^1(CH_2)_2$); 3.84 (s, 2H, NH_2); 4.25 (s, 2H, $COCH_2NH$); 8.11 (s, 1H, $COCH_2NH$); 6.92 (s, 1H, thiazole); 7.15–7.49 (m, 4H, Ar-H). Mass (FAB, M^+): Calcd: 387.197. Found: 387.21. Anal. ($C_{19}H_{25}N_5O_2S$): Calcd C, 58.89; H, 6.50; N, 18.07; S, 8.27. Found C, 58.62; H, 6.26; N, 17.97; S, 7.99.
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