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Schiff Bases as CNS Active Agents: A Review

Nikhil Batra[1]*, Shikha Batra[1], Navneet Aggarwal[1], Badri Prakash Nagori[1]

1. Lachoo Memorial College of Science & Technology (Autonomous), Affiliated to Jai Narain Vyas University, Jodhpur, Sector 'A', Shastri Nagar, Rajasthan, India

ABSTRACT

Schiff bases represent an important class of organic compounds owing to their wide range of biological activities and industrial applications. They are characterized by the presence of azomethine group and formed by the condensation of primary amines with aldehydes or ketones. They also serve as a back bone for the synthesis of various heterocyclic compounds. Since last few decades, a variety of Schiff bases and their derivatives have been synthesized and reported to possess a wide variety of biological activities *i.e.* anticancer, antioxidant, antiglycation, antimicrobial, antimalarial, antiviral and CNS activities. This review highlights the synthetic strategies of novel Schiff bases of different heterocycles and their evaluation for different CNS activities.

Keywords: Schiff bases, azomethines, imines, CNS activity, anticonvulsant

*Corresponding Author Email: nikhilpharmacy@yahoo.com

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INTRODUCTION

Schiff bases were first reported by Schiff Hugo in 1864 and they are the condensation products of primary amines with carbonyl compounds[1]. Schiff bases are characterized by the presence of imine group (- N = CH-) with a general formula $R_1HC=N-R_2$, where R_1 and R_2 are alkyl, aryl, cyclo alkyl or heterocyclic groups which may be variously substituted. These compounds are also known as imines, azomethines or anils. Azomethine group is responsible for elucidating the mechanism of transamination and rasemination reactions in biological system. Several studies showed that the presence of a lone pair of electrons in a sp2 hybridized orbital of nitrogen atom of the azomethine group is of considerable chemical and biological importance[2].

Development of new chemotherapeutic Schiff bases is now attracting the attention of medicinal Chemists. Many studies have been reported regarding the biological activities of Schiff bases. Schiff bases derived from various heterocycles have been reported to possess anticancer[3-5], antioxidant[6-8], antiglycation[9], antimicrobial[10-14], antimalarial[15] and antiviral activities[16, 17]. Apart from these pharmacological activities, they also exhibit significant CNS activities and this paper presents a review on Schiff bases of various heterocycles having CNS activities.

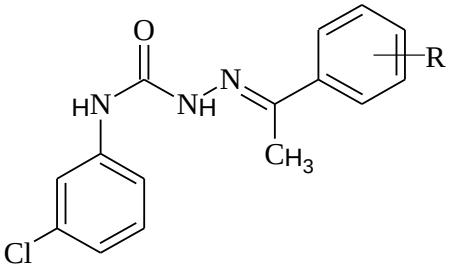
SCHIFF BASES HAVING MONOCYCLIC RING SYSTEMS

Schiff bases having monocyclic ring system with no hetero atom

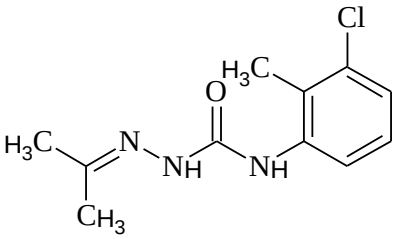
A series of 4-(3-chlorophenyl)-1-(substituted acetophenone) semicarbazones was synthesized by starting with 3-chloroaniline which on reaction with sodium cyanate yielded 1-(3'-chlorophenyl) urea followed by reaction with hydrazine hydrate in the presence of ethanol to give 4-(3'-chlorophenyl) semicarbazide. This compound on condensation with substituted acetophenones gave the final compounds. Compounds were evaluated for anticonvulsant activity by Maximal Electro Shock (MES) method using phenytoin as standard drug. This activity was assessed by absence or reduction of Hind Limb Extensor (HLE) phase. Out of all the synthesized compounds, two compounds (Compounds 1 and 2; Figure 1) having 4-fluoro and 2-chloro substitution were found to be the most potent in the series[18].

A series of 3-chloro-2-methylphenyl substituted semicarbazones was synthesized and evaluated for anticonvulsant and CNS activities. These compounds were synthesized by treating 3-chloro-2-methyl aniline with sodium cyanate in the presence of glacial acetic acid to yield 3-chloro-2-methyl phenyl urea. This urea derivative gave the semicarbazide on condensation with hydrazine hydrate in ethanol in presence of sodium hydroxide. The semicarbazone derivatives were prepared by reaction of the appropriate aryl/ alkyl aldehyde or ketone or isatin derivatives.

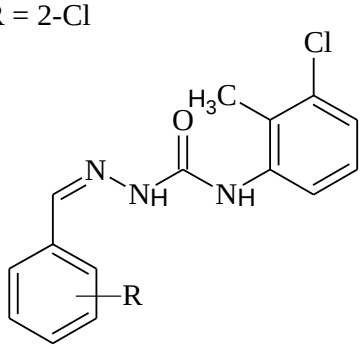
Anticonvulsant activity was evaluated by MES, subcutaneous pentylenetetrazole (scPTZ) and subcutaneous strychnine (scSTY) models. The acetone semicarbazone derivative (Compound 3; Figure 1) exhibited anticonvulsant activity in all the three screens and emerged as the most active compound in this series. In the behavioral study using actophotometer, two compounds (Compounds 4 and 5; Figure 1) showed decreased locomotor activity but did not show any significant behaviour despair effect[19].



Compound 1: R = 4-F
Compound 2: R = 2-Cl



Compound 3



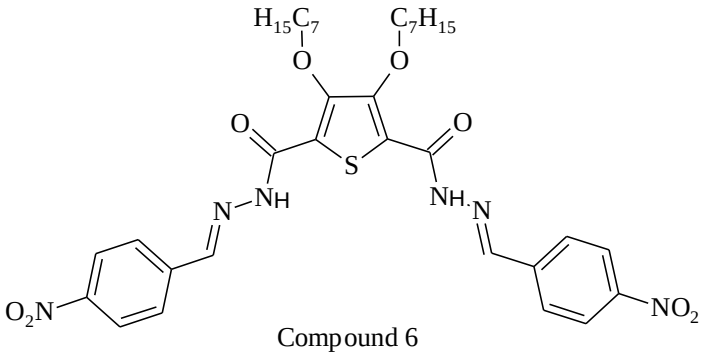
Compound 4: R = 2-OH
Compound 5: R = 2-NO_2

Figure 1: Schiff bases having no heterocyclic nucleus

Schiff bases having monocyclic ring system with one hetero atom

Schiff bases having thiophene nucleus

Thirty nine new 3,4-di(substituted)oxy-N^2, N^5-bis(substituted)thiophene-2,5-dicarbohydrazides were synthesized starting from ethyl thiodiglycolate through multi-step reactions. In the synthetic sequence, 3,4-dihydroxythiophene-2,5-diester was obtained by condensing the ethyl thiodiglycolate with diethyl oxalate. It was derivatized using different alkyl halides to give disubstituted thiophene esters which were then converted to corresponding hydrazides. These hydrazides, on treatment with various substituted carbonyl compounds underwent smooth condensation to yield target hydrazones. The anticonvulsant activity of the title compounds was established by MES test, scPTZ test and 6 Hz screens. One compound (Compound 6; Figure 2) had emerged as an active compound with no neurotoxicity in this series[20].



Compound 6

Figure 2: Schiff bases having thiophene nucleus

Schiff bases having pyridine nucleus

A series of *N'*-[substituted] pyridine-4-carbohydrazides were designed and synthesized keeping in view the structural requirements of pharmacophore for anticonvulsant activity *i.e.* hydrophobic unit, an electron donor group and a hydrogen donor/ acceptor unit. For the synthesis of title compounds, 4-substituted benzaldehydes were prepared by refluxing various substituted phenol with 4-fluorobenzaldehyde in *N,N'*-DMF in presence of potassium carbonate. The pyridine-4-carbohydrazide was refluxed with various 4-substituted benzaldehyde and isatin in the presence of catalytic amount of glacial acetic acid to yield the titled compounds. The anticonvulsant activity of these compounds was established in three seizure models, which include MES, subcutaneous Metrazole (scMET) and psychomotor seizure (6 Hz) tests in mice. Computational study was carried out to highlight the pharmacophore distance mapping, miLog P calculation and prediction of pharmacokinetic parameters. Docking study was performed with six established epilepsy molecular targets namely GABA (A) alpha-1 receptor, GABA (A) delta receptor, glutamate receptor, Na/H exchanger, Na channel receptor, T-type calcium channel receptor by using AutoDock 4.0 along with its LGA algorithm for automated flexible ligand docking and affinity (Kcal/mol) and count of probable hydrogen bonds were evaluated. *N'*-[4-(4-fluorophenoxy)benzylidene] pyridine-4-carbohydrazide (Compound 7; Figure 3) was found to be the most active compound of this series which displayed significant protection and emerged as a lead in this series. *N'*-[4-(4-methylphenoxy)benzylidene]pyridine-4-carbohydrazide (Compound 8; Figure 3) also came out as a potential candidate for further investigation[21].

A series of Schiff bases and 2-azetidinones of isonocotinyl hydrazone was prepared by novel methods of stirring and sonication involving cyclocondensation reaction of the appropriate Schiff bases with chloroacetyl chloride, followed by the addition of triethyl amine in the presence of molecular sieves. These compounds were investigated for antidepressant activity by Forced Swim Test and Tail Suspension Test and for nootropic activity by Elevated Plus Maze Test and

Passive Avoidance Test in mice. All the synthesized Schiff bases and azetidinone analogues exhibited antidepressant and nootropic activities in a dose dependant manner. However, *N*'-[(1*Z*)-(2,5-dimethoxyphenyl)methylidene]pyridine-4-carbohydrazide (Compound 9; Figure 3) and *N*-[3-chloro-2-(2,5-dimethoxyphenyl)-4-oxoazetidin-1-yl]pyridine-4-carboxamide (Compound 11; Figure 3) having 2,5-dimethoxy substitution on aryl ring exhibited the highest antidepressant activity and *N*'-[(1*Z*)-(4-nitrophenyl)methylidene]pyridine-4-carbohydrazide (Compound 10; Figure 3) and *N*-[3-chloro-2-(4-nitrophenyl)-4-oxoazetidin-1-yl]pyridine-4-carboxamide (Compound 12; Figure 3) having para nitro substitution on aryl ring exhibited the highest nootropic activity[22].

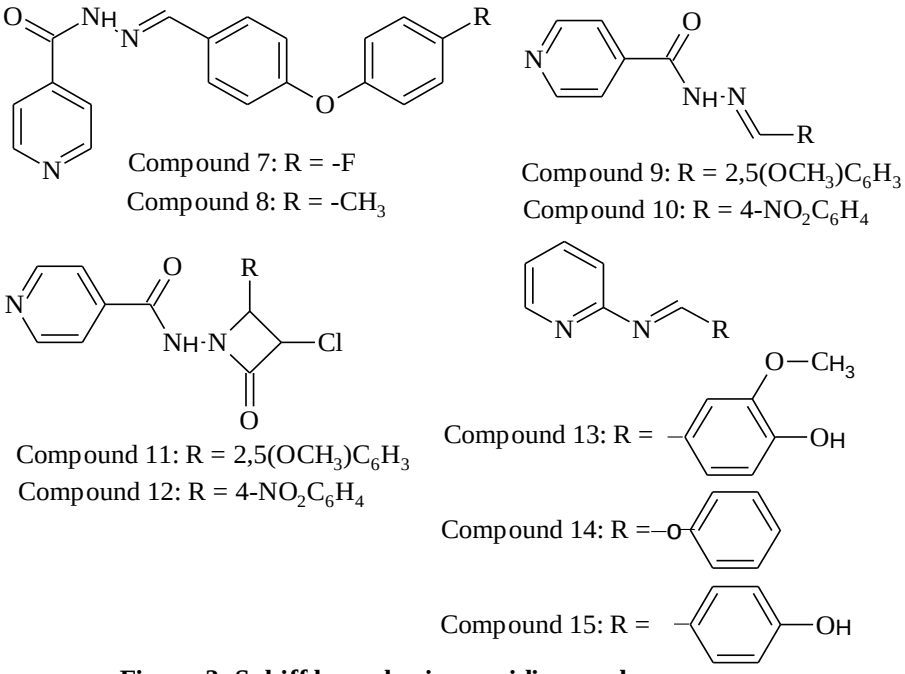


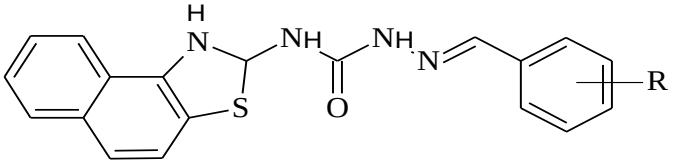
Figure 3: Schiff bases having pyridine nucleus

A series of new Schiff bases of 2-aminopyridine was synthesized through the condensation reaction between 2-aminopyridine with different aldehydes/ ketones and cyclic ketones. These compounds were evaluated for anticonvulsant activity by MES, subcutaneous scPTZ and scSTY models in mice. Schiff bases showed better anticonvulsant potency against MES and scPTZ induced seizures while found moderately active against scSTY induced seizures. Compound having R = 4-hydroxy-3-methoxy phenyl (Compound 13; Figure 3) and compound having R = phenoxy group (Compound 14; Figure 3) and the Schiff bases prepared from cyclic ketones showed better ED_{50} values with Protective Index (PI) >10 against MES induced seizures than that of standard drugs - Phenytoin and Phenobarbital. While in scSTY induced seizures, one compound having R = 2-hydroxy phenyl group (Compound 15; Figure 3) showed good ED_{50} value[23].

Schiff bases having monocyclic ring system with two hetero atoms

Schiff bases having thiazole nucleus

A series of N^4-(naphtha[1,2-*d*]thiazol-2-yl)semicarbazides were designed and synthesized by following one of the main trends of current investigations *i.e.* search for novel antiepileptic drugs with neuroprotective properties. Anticonvulsant activity of title compounds was determined by MES and scPTZ models in mice and minimal motor impairment was determined by rotorod test. A majority of the compounds exhibited significant activity against tonic convulsions induced by electrical and chemical stimuli in mice and rats. Some of the selected compounds were evaluated orally in rats for activity in scPTZ test at several time points (50 mg/kg). The most active compounds **(**Compounds 16 to 19; Figure 4) possessed bromo, fluoro and nitro substituents at 4-position in the phenyl ring. Biochemical estimations of malondialdehyde (MDA), superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) from brain homogenate clearly implicated the role of free radicals in PTZ-induced convulsions and also explained the possible mechanism of protective effect of semicarbazides, through the reduced formation of MDA and increased formation of SOD and GSH-Px[24].

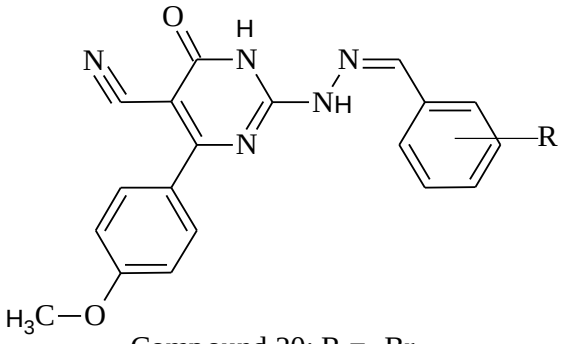


Compound 16: R = 4-Br
Compound 17: R = 4-F
Compound 18: R = 2-NO_2
Compound 19: R = 4-NO_2

Figure 4: Schiff bases having thiazole nucleus

Schiff bases having pyrimidine nucleus

A series of 2-[2-(substituted benzylidene) hydrazinyl]-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile was synthesized by refluxing 2-hydrazino-4-(4-methoxy-phenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile with different substituted aromatic aldehydes in glacial acetic acid and absolute alcohol mixture (8:2). The compounds were evaluated for their anticonvulsant activity by MES model. Results indicated that increase in the number of functional groups on arylidene moiety caused a decrease in anticonvulsant activity. Compounds having R = 4-Br, 4-OH and 3-F (Compounds 20 to 22; Figure 4) were found to be highly active at a dose level of 30 mg/kg at 0.5 h time interval, indicating their ability to prevent seizure spread at a relatively low dose. These compounds also showed the absence of neurotoxicity at maximum administered dose *i.e.* 300 mg/kg[25].



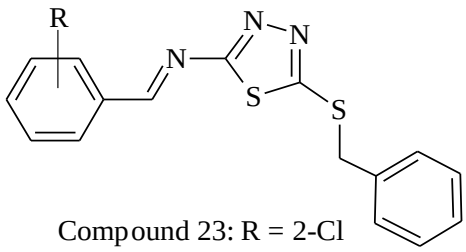
Compound 20: R = -Br
Compound 21: R = -OH
Compound 22: R = 3-F

Figure 4: Schiff bases having pyrimidine nucleu

Schiff bases having monocyclic ring system with three hetero atoms

Schiff bases having thiadiazole nucleus

Benzyl and chlorobenzyl substituted 1,3,4-thiadiazole imine derivatives were prepared by refluxing aromatic aldehyde imine derivatives and benzyl chloride/ 4-chloro benzyl chloride in ethanolic potassium hydroxide. The synthesized compounds were evaluated for anticonvulsant activity by MES model in mice. Neurotoxicity of the compounds was screened through Rota Rod and Ethanol Potentiation Tests. Chlorobenzyl substituted compounds (Compounds 23 to 27; Figure 5) showed potent activity same as like as the standard drug – phenytoin, while the normal benzyl derivatives have also showed good activity, but not much as the chlorobenzyl substituted compounds which indicated that chlorine or other electronegative groups increased the activity[26].



Compound 23: R = 2-Cl
Compound 24: R = 4-Cl
Compound 25: R = 2-NO_2
Compound 26: R = 4-NO_2
Compound 27: R = 4-F

Figure 5: Schiff bases having thiadiazole nucleu

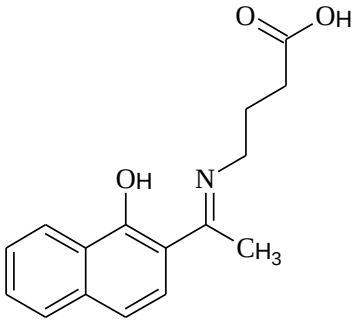
SCHIFF BASES HAVING BICYCLIC RING SYSTEMS

Schiff bases having bicyclic ring system with no hetero atom

Schiff bases having naphthalene nucleus

A series of 2-acetylnaphthalene derivatives was designed, synthesized and evaluated for anticonvulsant/ antimicrobial activities. Molecular design of the compounds was based on the

modification of nafimidone [1-(2-naphthyl)-2-(imidazol-1-yl)ethanone], which is a representative of the (arylalkyl)imidazole anticonvulsant compounds. Along with these derivatives, a Schiff base derivative (Compound 28; Figure 6) was also synthesized through Schiff reaction between the ketone group of 1-hydroxy-2-acetylnaphthalene and amino group of GABA sodium salt prepared from the reaction of GABA and sodium ethoxide. This derivative was designed as brain targeted molecules of valproic, valeric, isovaleric acids and GABA. The anticonvulsant activity profile of all the synthesized compounds was determined by MES and scMET models. Schiff base derivative did not show any significant efficacy or toxicity in these models probably because of the high effective dose level of these acids and also metabolic decomposition (hydrolysis or reduction) problems of ester and azomethine groups. Lipophilicity was not the cause of drop in the activity since clog P was found to be 2.55 for this compound. Therefore, formation of hydrogen bond between hydroxyl group on the naphthalene ring and carbonyl group which is also important for the receptor interaction was speculated as the cause of drop[27].



Compound 28

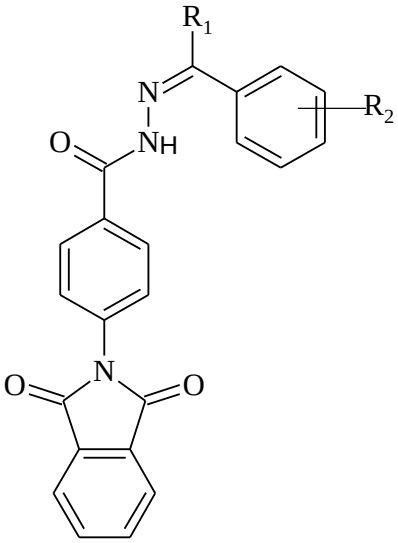
Figure 6: Schiff base having naphthalene nucleu

Schiff bases having bicyclic ring system with one hetero atom

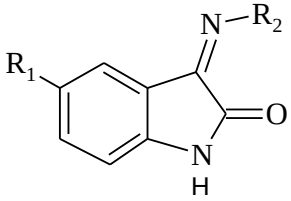
Schiff bases having indole nucleus

A series of Schiff bases of phthalimide was prepared by refluxing 4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)benzohydrazide with equivalent amount of carbonyl compounds in methanol in presence of glacial acetic acid. All the synthesized compounds were evaluated for anticonvulsant and neurotoxicity activities. Anticonvulsant screening was performed using MES test at three doses (30, 100 and 300 mg/kg). All the Schiff bases of phthalimides were found to be active in MES test at a dose of 300 mg/kg, indicative of their ability to prevent seizure spread. At a dose of 100 mg/kg, three compounds **(**Compounds 29 to 31; Figure 7) showed protection in half or more of the tested mice. Compound 31 having nitro substitution at ortho position of the distal

aryl ring emerged as most promising anticonvulsant agent with low neurotoxicity profile. Results indicated the importance of the size of the group at the carbimino carbon atom. Replacement of the hydrogen atom on the carbimino carbon atom by methyl group increased the anticonvulsant activity because of additional van der Walls bonding or alternately steric impedance to alignment at the binding site causing lower activity or its loss. The attachment of distal aryl ring to the proximal aryl ring increased the van der Walls bonding at the binding site and increases potency. The distal aryl ring at carbimino terminal (benzylidene ring) was found to be essential for the pharmacokinetic properties of compounds since the variation in the substitution at the distal aryl ring was found to affect the biological activity[28].



Compound 29: R_1 = -H, R_2 = 3-NO_2
Compound 30: R_1 = -CH_3, R_2 = 4-NO_2
Compound 31: R_1 = -CH_3, R_2 = 2-NO_2



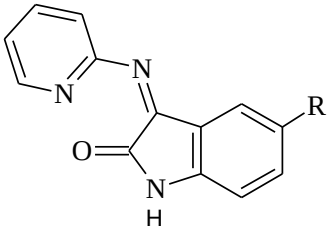
Compound 32: R_1 = -CH_3, R_2 = 1-naphthyl
Compound 33: R_1 = -CH_3, R_2 = 4-chloro phenyl
Compound 34: R_1 = -CH_3, R_2 = 4-methyl phenyl
Compound 35: R_1 = -CH_3, R_2 = thiosemicarbazino
Compound 36: R_1 = -CH_3, R_2 = 2,4-dinitro phenylhydrazin

Figure 7: Schiff bases having indole nucleus

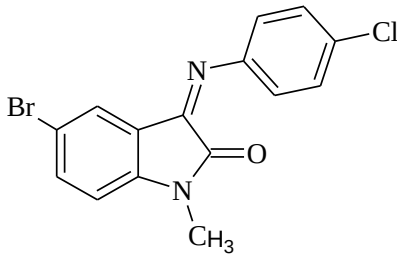
Anticonvulsant activity of hydrazones, Schiff and Mannich bases of isatin were evaluated by MES and scMET models at 30, 100 and 300 mg/kg dose levels. Neurotoxicity of the compounds was also assessed at the same dose levels. Five compounds of the series (Compounds 32 to 36; Figure 7) exhibited significant anticonvulsant activity at 30 mg/kg dose level. 3-(4-chloro-phenylimino)-5-methyl-1,3-dihydro-indol-2-one (Compound 33) was found to be the most potent compound of the series with 87% protection at 100 mg/kg and an ED_{50} of 53.61 mg/kg in scMET model. All the compounds exhibited lesser neurotoxicity compared to phenytoin. All the active compounds showed greater protection than sodium valproate. A pharmacophore model was also established with the essential structural features *i.e.* presence of hydrophobic unit (R), hydrogen bonding domain (HBD) and electron donor (D) responsible for interaction with receptor site[29].

Schiff bases having isatin nucleus

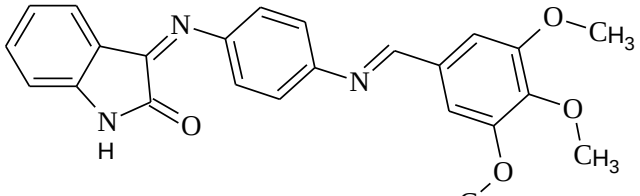
A series of N-substituted Schiff bases of (3*Z*)-3-(pyridin-2-ylimino)-1,3-dihydro-2*H*-indol-2-one was synthesized by reacting 2-amino pyridine with isatin. Further, Mannich bases were also synthesized by reaction of Schiff bases with formaldehyde along with various secondary amines *i.e.* dimethylamine, diethylamine, piperazine, isopropyle amine, morpholine in the presence of glacial acetic acid. All the synthesized compounds were screened for anticonvulsant activity using different chemical induced convulsion models *i.e.* isoniazid induced convulsion test, thiosemicarbazide induced convulsion test and 4-aminopyridine induced convulsion in mice at the dose of 30 mg/kg body weight. Two Schiff bases (Compounds 37 and 38; Figure 8) were found to be the most active amongst all the screened compounds using isoniazid induced model and thiosemicarbazide induced model[30].



Compound 37: R = -H
Compound 38: R = -Br



Compound 39



Compound 40

Figure 8: Schiff bases having isatin nucleus

Schiff bases were synthesized by refluxing equimolar quantities of 5-substituted *N*-methyl/*N*-acetyl isatin and different aryl amines into absolute ethanol containing a few drops of glacial acetic acid. Schiff bases of aromatic amines have been prepared because they contain a two electron donor system and *N*-methyl and *N*-acetyl groups were incorporated to increase the lipophilicity of the compounds. All the compounds were screened by MES and ScMET tests for anticonvulsant activity. *N*-methyl-5-bromo-3-(*p*-chlorophenylimino) isatin (Compound 39; Figure 8) exhibited significant anticonvulsant activity in MES and ScMET models with LD_{50} > 600 mg/kg, showed better activity than the standard drugs - phenytoin, carbamazepine and valproic acid. Thus, this compound may be chosen as a prototype for development of new anticonvulsant drugs[31].

A series of novel Schiff bases of isatin was prepared by condensation of equimolar quantities of imesatins with different aromatic aldehydes in ethanol. After standing for one to two days at room temperature, the product of different substituted derivatives of isatin separated out as a mixture of E and Z isomers were filtered, dried and recrystallised from absolute ethanol. The above mentioned imesatins were synthesized by reacting equimolar quantities of isatin and *p*-phenylenediamine dissolved in sufficient quantity of methanol in the presence of acetic acid and refluxed for 1 hr, then kept for 2 hr at room temperature. All the synthesized compounds were screened for anticonvulsant activity by MES and ScMET models. Among the synthesized compounds, 3-(4-(3,4,5-trimethoxy benzylideneamino) phenylimino) indoline-2-one (Compound 40; Figure 8) showed excellent anticonvulsant activity with lower dose in MES as well as in ScMET methods. Thus, this compound may be chosen as a prototype for development of new anticonvulsant drugs[32].

Schiff bases having bicyclic ring system with two hetero atoms

Schiff bases having benzimidazole nucleus

Schiff bases of benzimidazole were synthesized by reacting 2-(1*H*-benzimidazol-2-yl sulfanyl) acetohydrazide with different carbonyl compounds. Schiff bases were further reacted with thioglycolic acid in presence of DMF and zinc chlorides to synthesize 4-thiazolidinone derivatives of Schiff bases. All the compounds were screened for anticonvulsant activity by MES model. The existence of a hydrophobic unit in benzimidazole ring, an electron donor group and hydrogen bonding domain was found to be essential for anticonvulsant activity that is also evidenced by active drugs - phenytoin and carbamazepine. SAR studies revealed that the four compounds (Compounds 41 to 44; Figure 9) exhibited significant ability to diminish tonic-extensor seizures.

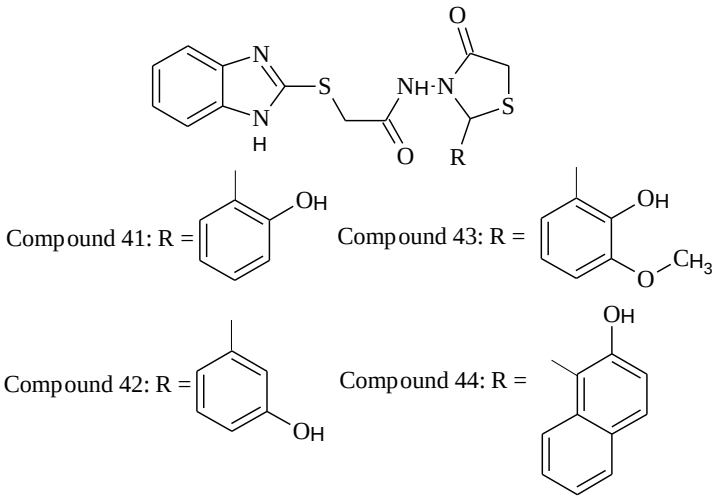
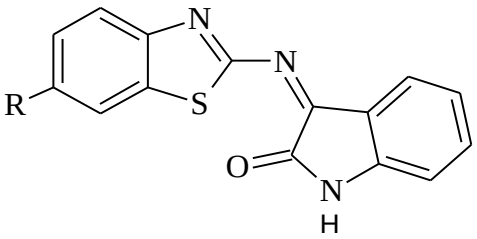


Figure 9: Schiff bases having benzimidazole nucleus

The presence of a hydroxyl function at 2 and 4 position of the phenyl ring were found to be the main structural requirement for maintaining activity. The extensor phase time was remarkably reduced for these compounds. This requirement was further evidenced by compounds where hydroxyl function was replaced by chloro and methyl function which resulted the complete loss of activity. This study revealed the emergence of four compounds as lead moieties[33].

Schiff bases having benzothiazole nucleus

A series of Schiff bases of isatin nucleus was synthesized by reacting equimolar quantities of 1,3-benzothiazol-2-amine and indole-2,3-dione in presence of few drops of glacial acetic acid and screened for anticonvulsant activity by MES and scMET models. Unsubstituted derivative (R = -H) had shown 100% protection at 300 mg/kg of dose administered in MES test and 60% promising protection in scMET test up to 0.5 hrs. However, this compound had also shown 87.5% non-toxic effect. When various 6-substituted 2-amino benzothiazole were introduced in the 3rd position of isatin, in the majority of the cases, there had been no significant change in activity profile. However, introduction of chloro group (Compound 45; Figure 10) and methoxy group (Compound 46; Figure 10) had shown potential results. Dimethyl amino substituted derivative (Compound 47; Figure 10) had shown 33.33% protection at a dose of 100 mg/kg after half an hour, which prolonged after 4 hours without any toxicity but it was found to be toxic at 300 mg/kg of doses. In the scMET test, all the compounds were found inactive except the unsubstituted derivative[34].



Compound 45: R = -Cl

Compound 46: R = -OCH_3

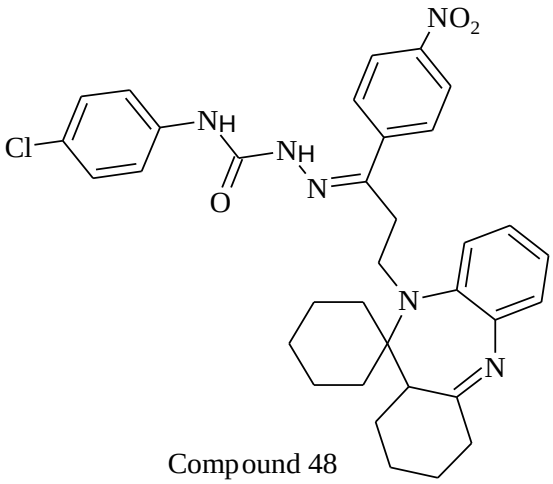
Compound 47: R = -$N(CH_3)_2$

Figure 10: Schiff bases having benzothiazole nucle

Schiff bases having benzodiazepine nucleus

1,5-Benzodiazepines were synthesized by condensation of 1 : 2.5 mole ratio mixture of *o*-phenylenediamine and ketones in presence of sulfated zirconia. Further Mannich bases were synthesized by using equimolar quantities of fused ring benzodiazepine and formaldehyde & various acetophenones (*i.e.* acetophenone, *p*-nitroacetophenone, and *p*-chloroacetophenone).

Schiff bases were synthesized using Mannich base of 1,5-benzodiazepines with *p*-chloroaniline and *p*-chlorophenylsemicarbazide in the presence of glacial acetic acid. All the synthesized compounds were evaluated at the dose of 30 mg/kg for anticonvulsant activity by Isoniazid Induced Convulsion Model. Among all the synthesized compounds, Schiff base (Compound 48; Figure 11) had shown good anticonvulsant activity and had an advantage of non-sedative nature[35].



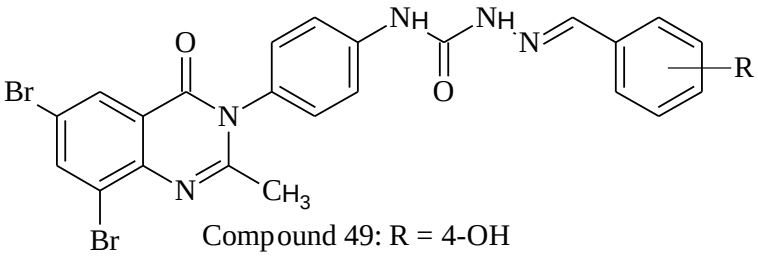
Compound 48

Figure 11: Schiff bases having benzodiazepine nucle

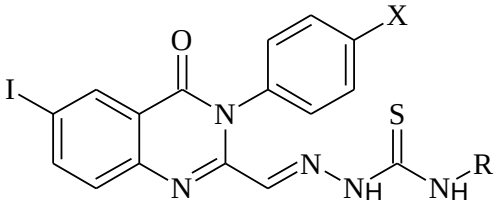
Schiff bases having quinazolin-4-one nucleus

A series of novel 6,8-dibromo quinazolin-4(3*H*)-one derivatives was synthesized by substituting different 1-(substituted/ unsubstituted benzylidene) -4-phenyl semicarbazide at the 3rd position and methyl/ phenyl group at 2nd position of the quinazolin-4(3*H*)-one nucleus. 3,5-dibromanthranilic acid and acetic anhydride/ benzoyl chloride were used as starting materials to produce 6,8-dibromo-2-(methyl/phenyl)-4*H*-benzo-(1,3)-oxazin-4-one by acetylation/ benzoylation followed by ring closure reaction. Title compounds were synthesized by Schiff base reaction in which different aromatic aldehydes (carbonyl compound) and amino derivatives (Quinazolin-4(3*H*)-one analog) undergo nucleophilic addition, forming a hemiaminal. This reaction was followed by a dehydration to generate title compounds by forming a stable imine. The synthesized compounds were screened for antiepileptic activity using MES and scPTZ seizures tests. Three compounds (Compounds 49 to 51; Figure 12) were found to be active in both MES and scPTZ tests. These compounds contain electron donating substituent at the hydrophobic domain (distal aryl ring). The nature of substituted group at hydrophobic domain appeared to greatly influence the antiepileptic activity; compounds with electron releasing groups exhibited higher antiepileptic activity than the compounds containing electron

withdrawing groups. Among electron donating groups, *p*-OH substituted compound exhibited better activity than *p*-$N(CH_3)_2$ and *p*-OH-*m*-OCH_3 substituted compounds[36].



Compound 49: R = 4-OH
Compound 50: R = 4-$N(CH_3)_2$
Compound 51: R_1 = 4-OH-3-OCH_3



Compound 52: R = -H; X = -H
Compound 53: R = -H; X = -F
Compound 54: R = -CH_3, X = -F
Compound 55: R = -C_2H_5, X = -F

Figure 12: Schiff bases having quinazolin-4-one nucleus

Novel 3-aryl-4(3*H*)-quinazolinone-2-carboxaldehydes, their corresponding Schiff bases and thiosemicarbazone derivatives were synthesized starting from 5-iodo anthranilic acid. Copper (II), zinc (II) complexes of some thiosemicarbazone derivatives were also synthesized. Screening for some selected compounds was carried out to probe their potential anticonvulsant, analgesic, cytotoxic as well as their antimicrobial activities. Anticonvulsant activity was carried out by scPTZ model. Four compounds **(**Compounds 52 to 55; Figure 12) showed protection for the animals from developing seizure in comparison with control group. Narcotic analgesic activity was carried out hot-plate model and two compounds (Compounds 52 and 53; Figure 12) showed remarkable activity[37].

Schiff bases having quinoxalin-2-one nucleus

A series of 1, 2, 4-triazolo (4,3-a)quinoxalin-4-5*H*-one derivatives was synthesized with the expectation to have AMPA receptor antagonistic activity. In the synthesis of this series, 1-ethyl-2-oxoquinoxalin-3-yl hydrazine was taken as the key intermediate for the synthesis of the new compounds. All the compounds were subjected to docking study to explore their binding mode to AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor, since AMPA is a target for a remarkable variety of anticonvulsant agents. From the results of docking study and

biological evaluation, it was concluded that the presence of another aromatic system attached to quinoxaline nucleus like 1,2,4-triazolo nucleus increased the binding affinity with AMPA receptor due to the formation of favourable kind of interaction with the active site. It established a strong correlation between the results of molecular modeling and the anticonvulsant activity of the synthesized compounds. The highest fitting value was noticed for two compounds (Compounds 56 and 57; Figure 13) which also showed the highest anticonvulsant activity[38].

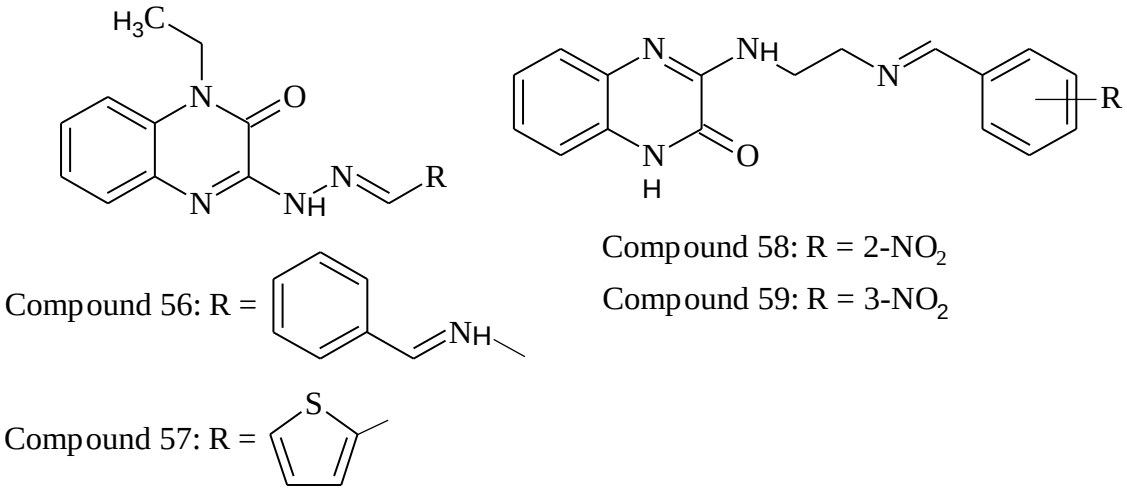


Figure 13: Schiff bases having quinoxalin-2-one nucleus

Some novel Schiff bases of 3-{[2-({(*E*)-[substituted) phenyl] methylidene} amino) ethyl] amino} quinoxalin-2(1*H*)-one were synthesized by reacting with different aromatic aldehydes in ethanol and evaluated for anticonvulsant activity by scPTZ model. Compounds having 2-nitro and 3-nitro groups (Compounds 58 and 59; Figure 13) showed significant activity as compared with standard drug[39].

CONCLUSION

Schiff bases formed from different heterocycles provide a versatile synthetic methodology for incorporating hydrophilic as well as hydrophobic groups in the respective heterocyclic systems. This review highlights the work carried out on Schiff bases having various CNS activities. Some of the Schiff bases having anticonvulsant activity also match with the identifiable structural features like (i) hydrophobic aryl ring; (ii) a hydrogen bonding domain; (iii) an electron-donor group; and (iv) another distal hydrophobic site. Further investigations related to Schiff bases involving docking studies, QSAR and pharmacokinetic parameters are required to develop the novel leads to treat various CNS problems in the new millennium.

REFERENCES

1. Cimerman Z, Miljanic S, Ga lic N. Schiff bases derived from aminopyridines as

spectrofluorimentric analytical reagents. Croat Chem Acta 2000; 73: 81-95.

2. Ashraf MA, Mahmood K, Wajid A. Synthesis, characterization and biological activity of schiff bases. IACSIT Press, Singapore. International Conference on Chemistry and Chemical Process (ICCCP) 2011; 10: 1-7.
3. Singh P, Kaur P, Luxami V, Kaurb S, Kumara S. Syntheses and anti-cancer activities of 2-[1-(indol-3-yl-/ pyrimidin-5-yl-/ pyridine-2-yl-/ quinolin-2-yl)-but-3-enylamino]-2-phenyl-ethanols. Bioorg Med Chem 2007; 15: 2386-2395.
4. Hu G, Wang G, Duan N, Wen X, Cao T, Xie S, Huang W. Design, synthesis and antitumor activities of fluoroquinolone C-3 heterocycles(IV): s-triazole Schiff - Mannich bases derived from ofloxacin. Acta Pharm Sin B 2012; 2(3): 312-317.
5. Hranjec M, Starcevic K, Pavelic SK, Lucin P, Pavelic K, Zamola GK. Synthesis, spectroscopic characterization and antiproliferative evaluation *in vitro* of novel Schiff bases related to benzimidazoles. Eur J Med Chem 2011; 46: 2274-2279.
6. Chinnasamy RP, Theivendran P, Sundararajan R. Synthesis and evaluation of antioxidant activities of some indole-2,3-dione derivatives and analogs. Toxicol Environ Chem 2010; 92(8): 1397-1407.
7. Zhang Y, Fang Y, Liang H, Wang H, Hu K, Liu X, Yi X, Peng Y. Synthesis and antioxidant activities of 2-oxo-quinoline-3-carbaldehyde Schiff-base derivatives. Bioorg Med Chem Lett 2013; 23: 107-111.
8. Zhang Y, Zou B, Chen Z, Pan Y, Wang H, Liang H, Yi X. Synthesis and antioxidant activities of novel 4-Schiff base-7-benzyloxy-coumarin derivatives. Bioorg Med Chem Lett 2011; 21: 6811-6815.
9. Khan KM, Khan M, Ali M, Taha M, Rasheed S, Perveen S, Choudhary MI. Synthesis of bis-Schiff bases of isatins and their antiglycation activity. Bioorg Med Chem 2009; 17: 7795-7801.
10. Mange YJ, Isloor AM, Malladi S, Isloor S, Fun H. Synthesis and antimicrobial activities of some novel 1,2,4-triazole derivatives. Arabian Journal of Chemistry 2013; 6: 177-181.
11. Amin RM, Abdel-Kader NS, El-Ansary AL. Microplate assay for screening the antibacterial activity of Schiff bases derived from substituted benzopyran-4-one. Spectrochim Acta A Mol Biomol Spectrosc 2012; 95: 517-525.
12. Khanmohammadi H, Abnosib MH, Hosseinzadeh A, Erfantalab M. Synthesis, biological and computational study of new Schiff base hydrazones bearing 3-(4-pyridine)-5-mercapto-1,2,4-triazole moiety. Spectrochim Acta A 2008; 71: 1474-1480.

13. Karthikeyan MS, Prasad DJ, Poojary B, Bhat KS, Holla BS, Kumari NS. Synthesis and biological activity of Schiff and Mannich bases bearing 2,4-dichloro-5-fluorophenyl moiety. Bioorg Med Chem 2006; 14: 7482-7489.
14. Raparti V, Chitre T, Bothara K, Kumar V, Dangre S, Khachane C, Gore S, Deshmane B. Novel 4-(morpholin-4-yl)-N0-(arylidene)benzohydrazides: Synthesis, antimycobacterial activity and QSAR investigations. Eur J Med Chem 2009; 44: 3954-3960.
15. Kalkanidis M, Klonis N, Tilley L, Deady LW. Novel phenothiazine antimalarials: Synthesis, antimalarial activity, and inhibition of the formation of β-haematin. Biochem Pharmacol 2002; 63: 833-842.
16. Krishnan SK, Ganguly S, Veerasamy R, Clercq ED. Synthesis, antiviral activity and cytotoxicity evaluation of Schiff bases of some 2-phenyl quinazoline-4(3)*H*-ones. Eur J Med Chem 2010; 45: 5474-5479.
17. Sriram D, Yogeeswari P, Myneedu S, Saraswat V. Abacavir prodrugs: Microwave-assisted synthesis and their evaluation of anti-HIV activities. Bioorg Med Chem Lett 2006; 16: 2127-2129.
18. Sameem S, Kumar N, Pathak D. Synthesis and anticonvulsant activity of some newer semicarbazone derivatives. International Journal of Pharmaceutical Sciences and Drug Research 2012; 4(3): 195-198.
19. Yogeeswari P, Thirumurugan R, Kavya R, Samuel JS, Stables J, Sriram D. 3-Chloro-2-methylphenyl-substituted semicarbazones: synthesis and anticonvulsant activity. Eur J Med Chem 2004; 39: 729-734.
20. Kulandasamy R, Adhikari AV, Stables JP. A new class of anticonvulsants possessing 6 Hz activity: 3,4-Dialkyloxy thiophene bishydrazones. Eur J Med Chem 2009; 44: 4376-4384.
21. Tripathi L, Singh R, Stables JP. Design & synthesis of *N*'-[substituted] pyridine-4-carbohydrazides as potential anticonvulsant agents. Eur J Med Chem 2011; 46: 509-518.
22. Thomas AB, Nanda R., Kothapalli LP, Hamane SC. Synthesis and biological evaluation of Schiff's bases and 2-azetidinones of isonocotinyl hydrazone as potential antidepressant and nootropic agents. Arabian Journal of Chemistry 2011 doi:10.1016/j.arabjc.2011.02.015.
23. Pandey S, Srivastava RS. Anticonvulsant activity of some Schiff bases synthesized from 2- aminopyridine. Pharmacologyonline 2009; 2: 1048-1074.

24. Azam F, Alkskas IA, Khokra SL, Prakash O. Synthesis of some novel N^4-(naphtha[1,2-*d*]thiazol-2-yl)semicarbazides as potential anticonvulsants. Eur J Med Chem 2009; 44: 203-211.
25. Shaquiquzzaman M, Khan SA, Amir M, Alam MM. Synthesis, anticonvulsant and neurotoxicity evaluation of some new pyrimidine-5-carbonitrile derivatives. Saudi Pharm J 2012; 20: 149-154.
26. Bahar A, Yusuf M. Syntheses of aromatic aldehyde imine derivatives of 2-thiobenzyl-1,3,4-thiadiazole and evaluation of their anticonvulsant activity. Indian J Chem 2010; 49 B: 241-246.
27. Karakurt A, Ozalp M, Isik S, Stables JP, Dalkara S. Synthesis, anticonvulsant and antimicrobial activities of some new 2-acetylnaphthalene derivatives. Bioorg Med Chem 2010; 18: 2902-2911.
28. Bhat MA, Al-Omar MA. Synthesis, characterization and *in vivo* anticonvulsant and neurotoxicity screening of Schiff bases of phthalimide. Acta Pol Pharm 2011; 68(3): 375-380.
29. Sridhar SK, Pandeya SN, Stables JP. Atmakuru R. Anticonvulsant activity of hydrazones, Schiff and Mannich bases of isatin derivatives. Eur J Pharm Sci 2002; 16: 129-132.
30. Chaubey AK, Pandeya SN. Synthesis & anticonvulsant activity (chemo shock) of Schiff and Mannich bases of isatin derivatives with 2-amino pyridine (mechanism of Action). International Journal of PharmTech Research 2012; 4(2): 590-598.
31. Verma M, Pandeya SN, Singh KN, Stables JP. Anticonvulsant activity of Schiff bases of isatin derivatives. Acta Pharm 2004; 54: 49-56.
32. Chinnasamy RP, Sundararajan R, Saravanan G. Synthesis, characterization and anticonvulsant activity of novel Schiff base of isatin derivatives. Int J Pharm Pharm Sci 2010; 2(4): 177-181.
33. Shingalapur RV, Hosamani KM, Keri RS, Hugar MH. Derivatives of benzimidazole pharmacophore: Synthesis, anticonvulsant, antidiabetic and DNA cleavage studies. Eur J Med Chem 2010; 45: 1753-1759.
34. Sharma PP, Pandeya SN, Roy RK, Verma AK. Gupta S. Synthesis and anticonvulsant activity of some novel isatin Schiff's bases. International Journal of ChemTech Research 2009; 1(3): 758-763.
35. Pandeya SN. Rajput N. Synthesis and anticonvulsant activity of various Mannich and Schiff Bases of 1,5-benzodiazepines. International Journal of Medicinal Chemistry.

doi:10.1155/2012/237965.

36. Saravanan G, Alagarsamy V, Chinnasamy RP. Design, synthesis and anticonvulsant activities of novel 1-(substituted/ unsubstituted benzylidene)-4-(4-(6,8-dibromo-2-(methyl/phenyl)-4-oxoquinazolin-3(4*H*)-yl)phenyl) semicarbazide derivatives. Bioorg Med Chem Lett 2012; 22: 3072-3078.
37. Aly MM, Mohamed YA, El-Bayouki KAM, Basyouni WM, Abbas SY. Synthesis of some new 4(3*H*)-quinazolinone-2-carboxaldehyde thiosemicarbazones and their metal complexes and a study on their anticonvulsant, analgesic, cytotoxic and antimicrobial activities Part-1. Eur J Med Chem 2010; 45: 3365-3373.
38. Bayoumi A, Ghiaty A, El-Morsy A, Khair HA, Hassan MH, Elmeligie S. Synthesis and evaluation of some new 1,2,4-triazolo(4,3-a) quinoxalin-4-5*H*-one derivatives as AMPA receptor antagonists. Bulletin of Faculty of Pharmacy, Cairo University 2012; 50: 141–146.
39. Ghadage RV, Shirote PJ. Synthesis and anticonvulsant activity of Schiff's bases of 3-{[2-({(*E*)-[(substituted) phenyl] methylidene} amino) ethyl] amino} quinoxalin-2(1*H*)-one. Bangladesh J Pharmacol 2011; 6: 92-99.