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Original Research Article

Synthesis and Anticonvulsant Activity (*Chemo-Shock*) of some Novel Schiff Bases of substituted 4-amino-5-phenyl-2, 4-dihydro-[1, 2, 4]-triazole-3-thione

Meena K Yadav*[1], Laxmi Tripathi[2], Diptendu Goswami[3]
[1]Department of Pharmaceutical chemistry, Mahatma Gandhi Institute of Pharmacy, Lucknow- Kanpur Road, Lucknow, Uttar Pradesh, India-227101
[2]Moradabad Educational Trust, Group of Institutions, Faculty of Pharmacy, Moradabad, Uttar Pradesh India-244001
[3]Faculty of Pharmacy, Naraina Vidya Peeth Group of Institutions, Panki, Kanpur, Uttar Pradesh India-208020.

***Corresponding Author:**
Meena K Yadav
Email: meenayadav82@gmail.com

Abstract: In the present investigation, a series of Schiff bases of substituted 4-Amino- 5 –Phenyl-2, 4- dihydro - [1, 2, 4] - triazole -3 –thione were synthesized and evaluated for their anticonvulsant activity and neurotoxicity study. The structures of the synthesized Schiff bases were confirmed by IR, ^{1}H-NMR, and elemental analysis. In anticonvulsant chemo shock method, all the compounds were tested against three chemical stimulants strychnine, thiosemicarbazide and Isonicotinic acid hydrazide (INH) at a dose of 30,100,300 mg/kg at 0.5h to 2hrs time slot and also successfully passed the rotarod test without any sign of neurological defects. The compounds 4A-i, 4A-j, 4A-k, and 4B-i were observed to be most active for anticonvulsant activity while compounds 4A-b, 4A-f, 4A-g, and 4A-h were showing moderate activity. Results indicated that compounds with menthone, camphor derivatives and having chloro-substituted aldehydes/ ketones showed good anticonvulsant activity. Therefore, these derivatives may possible to use as lead compounds for other biological activities also. Overall, the synthesized compounds emerged as more active and less neurotoxic derivatives.
Keywords: Triazolethione, Anticonvulsants, strychnine, INH, Thiosemicarbazide, Schiff bases

INTRODUCTION

Epilepsy is not a single disease it is a chronic and often progressive disorder characterized by recurrent transient attacks which are caused by an abnormal discharge of cerebral neurons and a set of symptoms that may have different causes in different people. [1, 2] The common thread is an imbalance in the brain's electrical activity [3, 4], causes seizures that may affect part or all of the body and may or may not cause a loss of consciousness. [5].The current therapy of epilepsy with antiepileptic drugs is associated with side effects, dose-related and chronic toxicity and teratogenic effects [6]. Therefore, this is continuing demand for new anticonvulsant agents. Different chemical classes such as hydantoins, barbiturates, benzodiazepines, gamma-aminobutyric acid (GABA) analogs, dibenzazepines, and carbamates are known to be part of anti-epileptic scaffolds. Several of these drugs are known to act through modulating the GABAergic and glutamate/aspartate systems. Gamma-Aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the cerebral cortex, maintains the inhibitory tone that counterbalances neuronal excitation [7-12].When this balance is perturbed, seizures may ensue. GABA is formed within GABAergic axon terminals and released into the synapse, where it acts at one of two types of receptor: $GABA_A$, which controls chloride entry into the cell, and $GABA_B$, which increases potassium conductance, decreases calcium entry, and inhibits the presynaptic release of other transmitters. $GABA_A$-receptor binding influences the early portion of the GABA-mediated inhibitory postsynaptic potential, whereas $GABA_B$ binding influences the late portion. GABA is rapidly removed by uptake into both glia and presynaptic nerve terminals and then catabolized by GABA transaminase. The use of a multidisciplinary approach--laboratory and clinical pharmacology and experimental and human neurochemistry--has demonstrated that GABA neurons and receptors play a variety of functional roles in the mammalian brain. GABA receptor activation can be used to control seizures of diverse etiology and at least one GABA agonist, progabide, is effective in human epilepsy [13, 14]. Hence enhancers of GABAergic transmission comprise a large group of classical and new generation antiepileptic drugs. A new series of GABAergic neurotransmission by N-(substituted)-2-[4-(substituted) benzylidene] hydrazine carbothioamides were reported by Tripathi and Kumar as potential anticonvulsant agents [15]. There is considerable evidence for alterations in glutamatergic and GABAergic synaptic transmission in the origin of the paroxysmal depolarization shifts that initiate epileptic activity. However, recent studies suggest that

extrasynaptic GABA and glutamate receptors may play an important role in seizure initiation, maintenance and arrest hence several GABA analogs have been designed and synthesized in an attempt to synthesize effective anticonvulsants [16-18].Currently, drugs used to treat epilepsy under GABA for anticonvulsant therapy are Gabapentin, Nefiracetam, and Zolpidem. Azoles (aryl alkyl) are one of the structurally distinct classes of antiepileptic drugs. In recently, loreclezole has emerged as a structurally novel 1, 2, 4-triazole anticonvulsant with broad-spectrum activity, which potentiates $GABA_A$ receptor-mediated Cl^- currents through a site present on the β2 and β3 (but not β1) subunits of $GABA_A$ receptors[19].Many numbers of drugs are available currently containing triazole nucleus Figure-2 representing the structure of some selected 1, 2, 4-triazole drugs such as estazolam, anastrozole, ribavirin, and triazolam.[20-24].A sensitive and selective method were elaborated for the determination of the anticonvulsant activity by Plech et al. they synthesized some 4-alkyl-1, 2, 4-triazole derivatives and also observed the effect of the size of the alkyl fragment on anticonvulsant activity[25].In the pharmaceutical industry, Schiff bases are widely used and have compelling pharmacological activities. They are derived from the condensation of aromatic aldehydes/ketones and aromatic amines form an important group of compounds in synthetic chemistry.Triazolethione analogs, due to the importance of triazolethione backbone have shown a variety of biological activities such as anticonvulsant, anti-migraine [26-29]. We report herein the synthesis, anticonvulsant activity and neurotoxicity of a new series of Schiff bases derived from substituted 4-amino -5-phenyl-2, 4-dihydro-[1, 2, and 4] triazole-3-thione with the purpose of considering their possible anticonvulsant activity by chemo shock method. These agents are inflicted in modulating various neurotransmitters and receptors.

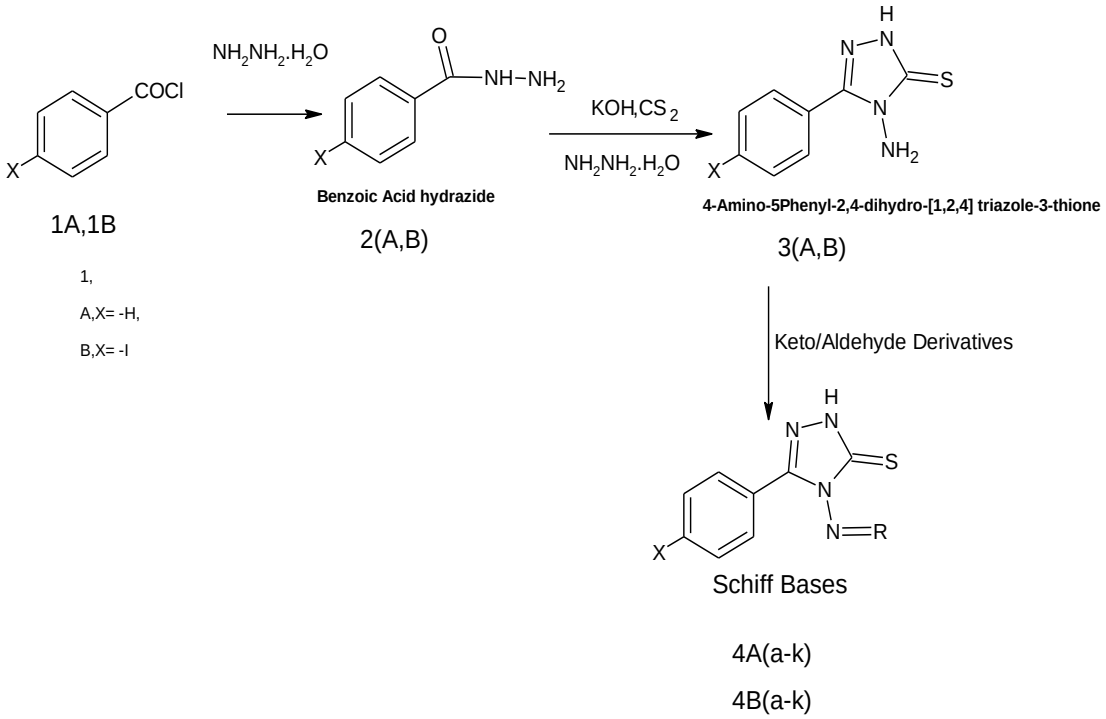
MATERIAL AND METHODS

Experimental

Melting points were determined in open capillary tubes and are uncorrected. The purity of compounds was checked routinely by TLC (0.5 mm thickness) using silica gel–G coated Al-plates (Merck) and spots were visualized by exposing the dry plates to iodine vapors. Microanalysis of the compounds was done on Perkin-Elmer model 240 analyzer and the values found within ±0.4% of the theoretical values. 1H- NMR spectra were recorded on DPX-300 NMR spectrometer, using CDCl3 or DMSO–d6 as solvent and TMS as the internal reference (chemical shifts in δ, ppm). The IR spectra were recorded in KBr pellets on BIO-RAD FTS, IR spectrophotometer. All the chemicals and solvents used were procured from Merck (India), S.D.Fine Chemicals (India) & Rankem (India).

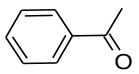
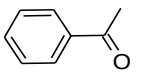
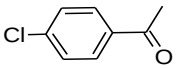
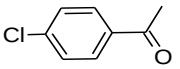
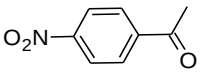
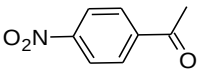
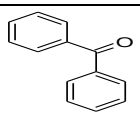
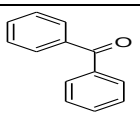
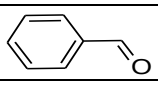
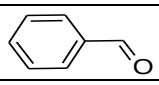
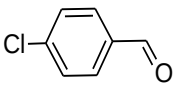
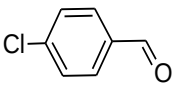
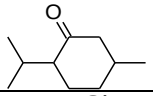
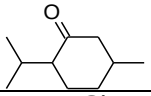
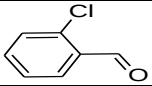
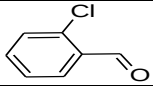
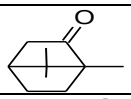
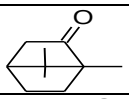
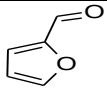
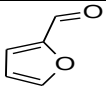
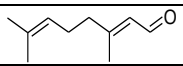
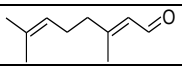
General method for the synthesis of Schiff bases 4A (a-k), 4B (a-k)

A mixture of benzoyl chloride A /4-iodobenzoyl chloride B (0.01 mole) 1 in benzene (50 ml) and hydrazine hydrate (0.02 mole) were refluxed for 5-6 hrs. The excess solvent was distilled off and the solid products 2(A, B) were filtered, dried and crystallized from ethanol. Further a mixture of potassium hydroxide (0.015 moles) in absolute ethanol (50 ml), benzoic acid hydrazide 2A /4-iodobenzoic acid hydrazide 2B (0.01 mole) and carbon disulfide (0.015 moles) were stirred for 8-10 hrs. The mixtures were cooled to room temperature and then treated with dilute sodium bicarbonate to remove unreacted starting materials. Further, these products 3(A, B) were refluxed with stirring for 8 hrs with hydrazine hydrate (0.03 mole) in methanol. The crudes were washed with water filtered, dried and crystallized from ethanol. Schiff bases 4A (a-k), 4B (a-k) were synthesized when an equimolar amount of 3(A, B) were refluxed with different aldehydes/ketones (Table 1) in presence of glacial acetic acid and methanol for about 3-4 hrs. The reaction mixtures were cooled and poured onto crushed ice. The solids thus obtained were filtered, washed with brine and recrystallized from methanol. The physical constants data of the synthesized compounds were presented in Table 2 and the formation of the title compounds was confirmed by its IR and ^{1}HNMR spectral studies. The new derivatives were prepared through following the reaction sequences depicted in Scheme-1.



Scheme-1: Synthesis of Schiff bases 4A (a-k), 4B (a-k)

Table 1: Different aldehydes/ketones (R) used in the preparation of Schiff bases 4A (a-k), 4B (a-k)

Sr.no.	Compound ID	X	R	Sr.no.	Compound ID	X	R
1	4A- a	-H		12	4B- a	-I	
2	4A- b	-H		13	4B- b	-I	
3	4A- c	-H		14	4B- c	-I	
4	4A- d	-H		15	4B- d	-I	
5	4A- e	-H		16	4B- e	-I	
6	4A- f	-H		17	4B- f	-I	
7	4A- g	-H		18	4B- g	-I	
8	4A- h	-H		19	4B- h	-I	
9	4A- i	-H		20	4B- i	-I	
10	4A- j	-H		21	4B- j	-I	
11	4A- k	-H		22	4B- k	-I	

Characterization of synthesized compounds

4-amino-5-phenyl-2, 4-dihydro-3H-1, 2, 4-triazole-3-thione 3A

IR (KBr, cm^{-1}) 3130 (Ar. C-H), 3235 (NH), 1622 (C=N), 1323 (C=S), 1510 (Ar. C=C) 3450 (NH2), NMR (300 MHz, $CDCl_3$, ppm, δ): 7.31(m, 5H, ArH), 14.01 (s 1H, NH), 5.55 (2H, s, NH_2) anal.calcd.for; $C_8H_8N_4S$(192.24)(%): found = C (49.98) H (4.19) N (29.14)Calculated = C (49.68) H (4.09) N (29.04)

4-amino-5-(4-iodophenyl)-2, 4-dihydro-3*H*-1, 2, 4-triazole-3-thione 3B

IR (KBr, cm^{-1}) 3130 (Ar. C-H), 3235 (NH), 1622 (C=N), 1323 (C=S), 1510 (Ar. C=C) 3450 (NH2), NMR (300 MHz, $CDCl_3$, ppm, δ): 7.31(m, 5H, ArH), 14.01 (s 1H, NH), 5.56 (2H, s, NH_2) anal.calcd.for; $C_8H_7IN_4S$(318.13)(%): found = C (30.15) H (2.19) N (17.58) Calculated = C (30.20) H (2.22) N (17.61)

5-phenyl-4-{[(1*E*)-1-phenylethylidene] amino}-2, 4-dihydro-3*H*-1, 2, 4-triazole-3-thione 4A-a

IR (KBr, cm^{-1}) 3150 (Ar. C-H), 3155 (NH), 1625 (C=N), 1330 (C=S), 1515 (Ar. C=C), NMR(300MHz,$CDCl_3$,ppm,δ):7.29(m,5H,ArH),7.51(m, 5H,ArH),13.80(s,1H,NH),2.9(s,3H,CH_3),anal.calcd.for; $C_{16}H_{14}N_4S$(328.05)(%):found=C(65.28)H(4.79)N(19. 03)calculated = C(65.08) H (4.67) N (19.43)

4-{[(1*E*)-1-(4-chlorophenyl) ethylidene] amino}-5-phenyl-2, 4-dihydro-3*H*-1, 2, 4-triazole-3-thione 4A-b

IR (KBr, cm^{-1}) 3152 (Ar. C-H), 3252 (NH), 1621 (C=N), 1332 (C=S), 1509 (Ar. C=C), NMR(300MHz,$CDCl_3$,ppm,δ):7.45(m,5H,ArH),7.35(m, 2H,ArH),7.28(m,2H,ArH),14.10(s,1H,NH),2.5(s,3H,C H_3),anal.calcd.for; $C_{16}H_{13}ClN_4S$ (328.05)(%):found= C (58.44) H (3.98) N (17.04) calculated = C (58.24) H (3.78) N (17.34)

4-{[(1*E*)-1-(4-nitrophenyl) ethylidene] amino}-5-phenyl-2, 4-dihydro-3*H*-1, 2, 4-triazole-3-thione 4A-c

IR (KBr, cm^{-1}) 3155 (Ar. C-H), 3257 (NH), 1625 (C=N), 1330 (C=S), 1501 (Ar. C=C), NMR (300MHz,$CDCl_3$,ppm,δ):7.42(m,5H,ArH),7.28(m,2H,A rH),7.18(m,2H,ArH),14.12(s,1H,NH),2.4(s,3H,CH_3),an al.calcd.for; $C_{16}H_{13}N_5O_2$ (339.07)(%):found= C (56.63) H (3.86) N (20.64) calculated = C (56.43) H (3.66) N (20.84)

4-[(diphenylmethylidene) amino]-5-phenyl-2, 4-dihydro-3*H*-1, 2, 4-triazole-3-thione 4A-d

IR (KBr, cm^{-1}) 3153 (Ar. C-H), 3254 (NH), 1622 (C=N), 1335 (C=S), 1512 (Ar. C=C), NMR (300MHz,$CDCl_3$,ppm,δ):7.51(m,5H,ArH),7.42(m,10H, ArH),14.09(s,1H,NH),anal.calcd.for;$C_{21}H_{16}N_4S$ (356.10)(%):found= C (70.76) H (4.52) N (15.72) calculated = C (70.36) H (4.42) N (15.92)

5-phenyl-4-{[(*E*)-phenylmethylidene] amino}-2, 4-dihydro-3*H*-1, 2, 4-triazole-3-thione 4A-e

IR (KBr, cm^{-1}) 3156 (Ar. C-H), 3258 (NH), 1620 (C=N), 1338 (C=S), 1515 (Ar. C=C), NMR (300MHz,$CDCl_3$,ppm,δ):7.31(m,5H,ArH),7.40(m,5H,A rH),13.80(s,1H,NH),10.45(s,1H,N=CH)anal.calcd.for; $C_{15}H_{12}N_4S$ (280.07)(%):found= C (64.26) H (4.31) N (19.98) calculated = C (64.46) H (4.53) N (19.74)

4-{[(*E*)-(4-chlorophenyl) methylidene] amino}-5-phenyl-2, 4-dihydro-3*H*-1, 2, 4-triazole-3-thione 4A-f

IR (KBr, cm^{-1}) 3152 (Ar. C-H), 3253 (NH), 1625 (C=N), 1331 (C=S), 1517 (Ar. C=C), NMR (300MHz,$CDCl_3$,ppm,δ):7.38(m,5H,ArH),7.20(m,2H,A rH),7.10(m,2H,ArH),10.35(s,1H,N=CH)13.90(s,1H,NH),anal.calcd.for; $C_{15}H_{11}ClN_4S$ (314.03)(%):found= C (57.23) H (3.52) N (17.80)calculated = C (57.03) H (3.62) N (17.55)

4-{[(1*E*)-5-methyl-2-(propan-2-yl) cyclohexylidene] amino}-5-phenyl-2, 4-dihydro-3*H*-1, 2, 4-triazole-3-thione 4A-g

IR (KBr, cm^{-1}) 3156 (Ar. C-H), 3257 (NH), 1628 (C=N), 1335 (C=S), 1515 (Ar. C=C), NMR (300MHz,$CDCl_3$,ppm,δ):7.31(m,5H,ArH),7.34(m,5H,A rH),13.95(s,1H,NH), 1.35(s, 3H,CH_3), 1.10(s, 3H,CH_3), 1.20(s, 3H,CH_3)anal.calcd.for; $C_{18}H_{24}N_4S$ (314.03)(%):found= C (65.82) H (7.36) N (17.06) calculated = C (65.64) H (7.36) N (17.46)

4-{[(*E*)-(2-chlorophenyl) methylidene] amino}-5-phenyl-2, 4-dihydro-3*H*-1, 2, 4-triazole-3-thione 4A-h

IR (KBr, cm^{-1}) 3150 (Ar. C-H), 3256 (NH), 1628 (C=N), 1335 (C=S), 1520 (Ar. C=C), NMR (300MHz,$CDCl_3$,ppm,δ):7.35(m,5H,ArH),6.95(m,2H,A rH),7.05(m,2H,ArH)14.01(s,1H,NH),10.40(s,1H,N=CH)anal.calcd.for; $C_{15}H_{11}ClN_4S$ (314.03)(%):found= C (57.23) H (3.52) N (17.80) calculated = C (57.43) H (3.72) N (17.40)

4-(cyclohexylideneamino)-5-phenyl-2, 4-dihydro-3*H*-1, 2, 4-triazole-3-thione 4A-i

IR (KBr, cm^{-1}) 3146 (Ar. C-H), 3247 (NH), 1638 (C=N), 1337 (C=S), 1512 (Ar. C=C), NMR (300MHz,$CDCl_3$,ppm,δ):7.27(m,5H,ArH), 13.85(s,1H,NH), 6.35(m,8H,camphor), 1.39(s, 3H,CH_3), 1.15(s, 3H,CH_3), 1.28(s, 3H,CH_3)anal.calcd.for; $C_{16}H_{14}N_4S$ (272.10)(%):found= C (69.32) H (4.92) N (18.66) calculated = C (69.52) H (4.72) N (18.46)

4-{[(*E*)-furan-2-ylmethylidene] amino}-5-phenyl-2, 4-dihydro-3*H*-1, 2, 4-triazole-3-thione 4A-j

IR (KBr, cm^{-1}) 3155 (Ar. C-H), 3266 (NH), 1622 (C=N), 1330 (C=S), 1525 (Ar. C=C), NMR (300MHz,$CDCl_3$,ppm,δ):7.21(m,5H,ArH),6.75(m,3H,A rH),14.11(s,1H,NH), 10.41 (s, 1H, N=CH);anal. calcd.

for; $C_{13}H_{14}N_4OS$ (274.08)(%):found= C (56.91) H (5.14) N (20.42) calculated = C (56.71) H (5.44) N (20.22)

4-{[(1*E*, 2Z)-3, 7-dimethylocta-2, 6-dien-1-ylidene] amino}-5-phenyl-2, 4-dihydro-3*H*-1, 2, 4-triazole-3-thione 4A-k

IR (KBr, cm^{-1}) 3156 (Ar. C-H), 3258 (NH), 1620 (C=N), 1338 (C=S), 1515 (Ar. C=C), NMR (300MHz,$CDCl_3$,ppm,δ):7.28(m,5H,ArH), 13.01(s,1H,NH), 1.75 (m,6H,CH_3)2.08 (s, 4H, CH_2),5.2(m,3H,methylene),10.31(s,1H,N=CH),; anal. calcd. for;$C_{18}H_{22}N_4S$(326.15)(%):found= C (66.22) H (6.79) N (17.16) calculated = C (66.45) H (6.55) N (17.36)

5-(4-iodophenyl)-4-{[(1*E*)-1-phenylethylidene] amino}-2, 4-dihydro-3*H*-1,2,4-triazole-3-thione 4B-a

IR (KBr, cm^{-1}) 3152 (Ar. C-H), 3245 (NH), 1620 (C=N), 1335 (C=S), 1517 (Ar. C=C), NMR(300MHz,$CDCl_3$,ppm,δ):7.69(m,2H,ArH),7.01(m, 2H,ArH),13.80(s,1H,NH),2.9(s,3H,CH_3),7.25(m,5H,Ar H),anal.calcd.for; $C_{16}H_{13}IN_4S$ (419.99)(%): found= C (45.71) H (3.10) N (13.33) calculated = C (45.73) H (3.12) N (13.33)

4-{[(1*E*)-1-(4-chlorophenyl) ethylidene] amino}-5-(4-iodophenyl)-2, 4-dihydro-3*H*-1, 2, 4-triazole-3-thione 4B-b

IR (KBr, cm^{-1}) 3154 (Ar. C-H), 3254 (NH), 1620 (C=N), 1335 (C=S), 1510 (Ar. C=C), NMR(300MHz,$CDCl_3$,ppm,δ):7.65(m,2H,ArH),7.05(m, 2H,ArH),7.38(m,2H,ArH),7.27(m,2H,ArH),14.12(s,1H, NH),2.3(s,3H,CH_3),anal.calcd.for; $C_{16}H_{12}ClIN_4S$ (453.95)(%): found= C (42.20) H (2.60) N (12.30) calculated = C (42.26) H (2.66) N (12.32)

5-(4-iodophenyl)-4-{[(1*E*)-1-(4-nitrophenyl) ethylidene] amino}-2, 4-dihydro-3*H*-1, 2, 4-triazole-3-thione 4B-c

IR (KBr, cm^{-1}) 3150 (Ar. C-H), 3259 (NH), 1628 (C=N), 1335 (C=S), 1500 (Ar. C=C), NMR (300MHz,$CDCl_3$,ppm,δ):7.65(m,2H,ArH),7.05(m,2H,A rH),7.25(m,2H,ArH),7.20(m,2H,ArH),14.10(s,1H,NH), 2.41(s,3H,CH_3),anal.calcd.for; $C_{16}H_{12}IN_5O_2S$ (464.97)(%): found= C (41.28) H (2.58) N (15.01) calculated = C (41.30) H (2.60) N (15.05)

4-[(diphenylmethylidene) amino]-5-(4-iodophenyl)-2, 4-dihydro-3*H*-1, 2, 4-triazole-3-thione 4B-d

IR (KBr, cm^{-1}) 3150 (Ar. C-H), 3252 (NH), 1620 (C=N), 1330 (C=S), 1515 (Ar. C=C), NMR (300MHz,$CDCl_3$,ppm,δ):7.61(m,2H,ArH),7.06(m,2H,A rH),7.41(m,10H,ArH),14.10(s,1H,NH),anal.calcd.for; $C_{21}H_{15}IN_4S$ (482.00)(%):found= C (52.24) H (3.10) N (11.60) calculated = C (52.29) H (3.13) N (11.62)

5-(4-iodophenyl)-4-{[(*E*)-phenylmethylidene] amino}-2, 4-dihydro-3*H*-1, 2, 4-triazole-3-thione 4B-e

IR (KBr, cm^{-1}) 3150 (Ar. C-H), 3252 (NH), 1625 (C=N), 1333 (C=S), 1511 (Ar. C=C), NMR (300MHz,$CDCl_3$,ppm,δ):7.62(m,2H,ArH),7.08(m,2H,A rH),7.41(m,5H,ArH),13.81(s,1H,NH),10.41(s,1H,N=C H)anal.calcd.for; $C_{15}H_{11}IN_4S$ (405.97)(%): found= C (44.32) H (2.70) N (13.72) calculated = C (44.35) H (2.73) N (13.79)

4-{[(*E*)-(4-chlorophenyl) methylidene] amino}-5-(4-iodophenyl)-2, 4-dihydro-3*H*-1, 2, 4-triazole-3-thione 4B-f

IR (KBr, cm^{-1}) 3156 (Ar. C-H), 3257 (NH), 1628 (C=N), 1330 (C=S), 1512 (Ar. C=C), NMR (300MHz,$CDCl_3$,ppm,δ):7.60(m,2H,ArH),7.00(m,2H,A rH),7.21(m,2H,ArH),7.12(m,2H,ArH),10.32(s,1H,N=C H)13.92(s,1H,NH),anal.calcd.for; $C_{15}H_{10}ClIN_4S$ (439.93)(%): found= C (40.81) H (2.25) N (12.67) calculated = C (40.88) H (2.29) N (12.71)

5-(4-iodophenyl)-4-{[(1*E*)-5-methyl-2-(propan-2-yl) cyclohexylidene] amino}-2, 4-dihydro-3*H*-1, 2, 4-triazole-3-thione 4B-g

IR (KBr, cm^{-1}) 3153 (Ar. C-H), 3251 (NH), 1625 (C=N), 1337 (C=S), 1517 (Ar. C=C), NMR (300MHz,$CDCl_3$,ppm,δ): 7.66(m,2H,ArH),7.01(m,2H,ArH),7.30(m,5H,ArH),13. 90(s,1H,NH), 1.37(s, 3H,CH_3), 1.12(s, 3H,CH_3), 1.21(s, 3H,CH_3)anal. calcd. for; $C_{18}H_{23}IN_4S$ (454.06)(%): found= C (47.55) H (5.09) N (12.30) calculated = C (47.58) H (5.10) N (12.33)

4-{[(*E*)-(2-chlorophenyl) methylidene] amino}-5-(4-iodophenyl)-2, 4-dihydro-3*H*-1, 2, 4-triazole-3-thione 4B-h

IR (KBr, cm^{-1}) 3152 (Ar. C-H), 3255 (NH), 1625 (C=N), 1333 (C=S), 1525 (Ar. C=C), NMR (300MHz,$CDCl_3$,ppm,δ):7.61(m,2H,ArH),7.02(m,2H,A rH),6.91(m,2H,ArH),7.05(m,2H,ArH)14.05(s,1H,NH),1 0.42(s,1H,N=CH)anal.calcd.for; $C_{15}H_{10}ClIN_4S$ (439.93)(%): found= C (40.82) H (2.22) N (12.70) calculated = C (40.88) H (2.29) N (12.71)

4-(cyclohexylideneamino)-5-(4-iodophenyl)-2, 4-dihydro-3*H*-1, 2, 4-triazole-3-thione 4B-i

IR (KBr, cm^{-1}) 3148 (Ar. C-H), 3243 (NH), 1632 (C=N), 1335 (C=S), 1510 (Ar. C=C), NMR (300MHz,$CDCl_3$,ppm,δ):7.64(m,2H,ArH),7.03(m,2H,A rH),13.88(s,1H,NH), 6.33(m,8H,camphor), 1.38(s, 3H,CH_3), 1.17(s, 3H,CH_3), 1.26(s, 3H,CH_3)anal. calcd. for; $C_{14}H_{15}IN_4S$ (398.00)(%): found= C (42.20) H (3.68) N (14.01) calculated = C (42.22) H (3.80) N (14.07)

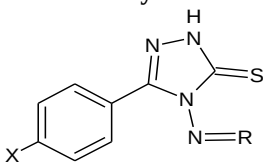
4-{[(*E*)-furan-2-ylmethylidene] amino}-5-(4-iodophenyl)-2, 4-dihydro-3*H*-1, 2, 4-triazole-3-thione 4B-j

IR (KBr, cm^{-1}) 3150 (Ar. C-H), 3262 (NH), 1625 (C=N), 1334 (C=S), 1521 (Ar. C=C), NMR (300MHz,$CDCl_3$,ppm,δ): 7.66(m,2H,ArH),7.08 (m,2H,ArH),6.71(m,3H,ArH),14.10(s,1H,NH), 10.40 (s, 1H, N=CH);anal.calcd.for; $C_{13}H_9IN_4OS$ (399.98)(%): found= C (39.40) H (2.25) N (14.10) calculated = C (39.41) H (2.29) N (14.14)

4-{[(1*E*, 2Z)-3, 7-dimethylocta-2, 6-dien-1-ylidene] amino}-5-(4-iodophenyl)-2, 4-dihydro-3*H*-1, 2, 4-triazole-3-thione 4B-k

IR (KBr, cm^{-1}) 3152 (Ar. C-H), 3256 (NH), 1622 (C=N), 1335 (C=S), 1510 (Ar. C=C), NMR (300MHz,$CDCl_3$,ppm,δ):7.60(m,2H,ArH),7.07(m,2H,ArH),13.07(s,1H,NH), 1.74 (m,6H,CH_3)2.05 (s, 4H, CH_2),5.21(m,3H,methylene),10.30(s,1H,N=CH),;anal.calcd.for; $C_{18}H_{21}IN_4S$ (452.05)(%):found= C (47.75) H (4.66) N (12.35) calculated = C (47.79) H (4.68) N (12.39)

Table-2: Physical properties of the final synthesized Schiff bases 4A (a-k) 4B (a-k)



Compound ID	Molecular Formula	Molecular wt.	Log p	M.P.	Yield (%)	Rf values
4A-a	$C_{16}H_{14}N_4S$	294.0939	2.67	220-222	65	0.48
4A-b	$C_{16}H_{13}ClN_4S$	328.0549	2.56	190-192	57	0.52
4A-c	$C_{16}H_{13}N_5O_2$	339.079	2.34	108-110	80	0.61
4A-d	$C_{21}H_{16}N_4S$	356.1096	3.22	213-215	85	`0.44
4A-e	$C_{15}H_{12}N_4S$	280.0783	2.56	100-102	73	0.79
4A-f	$C_{15}H_{11}ClN_4S$	314.0393	2.45	140-142	88	0.72
4A-g	$C_{18}H_{24}N_4S$	314.0393	2.45	240-242	63	0.81
4A-h	$C_{15}H_{11}ClN_4S$	314.0393	2.45	128-130	75	0.74
4A-i	$C_{16}H_{14}N_4S$	272.1096	2.45	198-200	61	0.50
4A-j	$C_{13}H_{14}N_4OS$	274.0888	2.23	218-220	65	0.52
4A-k	$C_{18}H_{22}N_4S$	326.1565	2.89	155-157	76	0.57
4B-a	$C_{16}H_{13}IN_4S$	419.9906	2.56	227-229	55	0.54
4B-b	$C_{16}H_{12}ClIN_4S$	453.9516	2.45	200-202	70	0.66
4B-c	$C_{16}H_{12}IN_5O_2S$	464.9756	2.23	125-127	65	0.63
4B-d	$C_{21}H_{15}IN_4S$	482.0062	3.11	230-232	85	0.49
4B-e	$C_{15}H_{11}IN_4S$	405.9749	2.45	105-107	68	0.56
4B-f	$C_{15}H_{10}ClIN_4S$	439.9359	2.34	145-147	80	0.76
4B-g	$C_{18}H_{23}IN_4S$	454.0688	2.78	247-249	72	0.78
4B-h	$C_{15}H_{10}ClIN_4S$	439.9359	2.34	170-172	77	0.69
4B-i	$C_{14}H_{15}IN_4S$	398.0062	2.34	275-277	85	0.45
4B-j	$C_{13}H_9IN_4OS$	399.9855	2.12	248-250	67	0.53
4B-k	$C_{18}H_{21}IN_4S$	452.0532	2.78	165-167	70	0.50

Biological Evaluation

Anticonvulsant screening

Animals

Albino mice of either sex weighing between 20- 25 g, were used in the present study. All albino mice employed in this study is approved by Institutional Animal Ethics Committee of NBRI, Lucknow and carried out as per CPCSEA guidelines. The animals were kept in large spacious hygienic cages during the course of the experimental period. The animals had free access to standard commercial diet and water ad libitum and were kept in rooms maintained at 22± 10C with 12 h light dark cycle. The animals were divided into three groups of 10 animals each: Group I: Control group (distilled water treated). Group II: Test group (were dissolved in polyethylene glycol (PEG-400) and 30, 100, 300 mg/kg i.p. doses), Group III: Standard group, on reference drug (Diazepam, 10 mg/kg i.p. phenytoin 30 mg/kg i.p., Diazepam, 30 mg/kg i.p.). All the drugs were administered 30 min prior to the administration of strychnine (1 mg/kg, i.p.) thiosemicarbazide (20 mg/kg, s.c.) and isoniazid (INH) (300 mg/kg, s.c.). The anticonvulsant screening of the final compounds was done according to the protocols of the anticonvulsant drug development (ADD) program [30].

Procedure

Strychnine induced model

Mice of either sex with a weight of 25-30 g were treated with the test compounds or the standard (diazepam 10 mg/kg i.p.) by an oral or intraperitoneal administration. Controls received the vehicle only.30-minute prior treatment with a subcutaneous dose of 1mg/kg strychnine, test compounds in doses 30, 100; 300 mg/kg i.p. was injected. The occurrence of clonic seizures, tonic seizures, and death or recovery was recorded after 0.5 hr, 1hr, 2hr, & 4hr respectively [31].

Thiosemicarbazide induced model

Mice of either sex with a weight of 25-30 g were treated with the test compounds or the standard (diazepam 10 mg/kg i.p.) by the oral or intraperitoneal administration. Controls received the vehicle only. 30-minute prior treatment with a subcutaneous dose of 20 mg/kg thiosemicarbazide, test compounds in doses 30, 100, 300 mg/kg i.p. was injected. The occurrence of clonic seizures, tonic seizures, and death or recovery was recorded after 0.5 hr, 1hr, 2hr, & 4hr respectively [32,33]. Not protected means death of the rats occurs at the mentioned time.

Isonicotinic Acid Hydrazide (INH) induced model

Mice of either sex with a weight of 25-30 g were treated with the test compounds or the standard (diazepam 30 mg/kg i.p.) by the oral or intraperitoneal administration. Controls received the vehicle only.30 minute after i.p. treatment the animals were injected with a subcutaneous dose of 300 mg/kg isoniazid (INH). The occurrence of clonic seizures, tonic seizures, and death or recovery was recorded after 0.5 hr, 1hr & 2hr respectively [34].

Neurotoxicity screening:

The activity of the drugs interfering with motor coordination was checked by the rotarod test. The mice will train to stay on an accelerating rotarod that rotates at 6 revolutions per minute. Trained animals were given ip injection of the test compounds in doses of 30, 100, 300 mg/kg. The rod diameter was 3.2cm. Neurotoxicity indicated by the inability of the animal to maintain equilibrium on the rotarod for at least 1 min in each of three trials. The dose, at which the animals were unable to grasp the rotarod, will determine. All the results were reported in **Table 3.**

RESULTS AND DISCUSSIONS

The preparation of Schiff bases 4A (a-k) 4B (a-k) were depicted in scheme 1. All the synthesized compounds from Scheme 1 were characterized by the IR, ^{1}H-NMR, and elemental analysis. IR-spectra (cm-1) of final compounds 4A (a-k) 4B (a-k) showed stretching frequency range between 3155, 3256 (NH), 1620, 1625 (C=N), 1323, 1333 (C=S).^{1}H-NMR spectra give a characteristic proton resonance shifts for all the synthesized triazolethione Schiff bases 4A (a-k) 4B (a-k) derivatives, which ensured the existence of aromatic, amine and imine protons. In the ^{1}H NMR spectra for 3A and 3B, the characteristic NH_2 protons of compound 3A and 3B were observed at d 5.55ppmand 5.56 ppm. The compounds 4A (a-k) 4B (a-k) were not shown a characteristic signal of NH_2 protons, it concludes that, the formation of –N=C/ bond between triazole moiety and different aldehydes and ketones for the Schiff bases formation. The triazolethione Schiff bases 4A (a-k) 4B (a-k) indicated the NH protons at 13.90–14.05 ppm. In all the cases of the TLC of the products showed the single spot confirming the chromatogram for only one product. The physical constants of synthesized compounds 4A (a-k) 4B (a-k) were shown in the Table 2.Almost all the synthesized Schiff bases showed potent anticonvulsant activity. All the synthesized compounds comprise essential pharmacophoric requirements that are important for good anticonvulsant activity as proposed by Dimmock *et al.*, [35]. In the pharmacological study, we have investigated anticonvulsant activity as well as the neurotoxicity. All the synthesized compounds were screened for their anticonvulsant activity using various chemical induced convulsion models using strychnine, thiosemicarbazide and 4-aminopyridine to induced convulsion, diazepam and phenytoin were used as the standard drug at the dose of 30, 100, 300 mg/kg b.w. anticonvulsant activity and neurotoxicity (NT) data for the triazolethione Schiff bases 4A (a-k) 4B (a-k) were given in Table 3 and most of the compounds showed mild to moderate anticonvulsant activity.The chemo stimulants used were strychnine, isonicotinic acid hydrazide (INH) and thiosemicarbazide. Strychnine acts on the glycine receptors, whereas INH and thiosemicarbazide modulate GABA levels. All the compounds protected mice in Strychnine, thiosemicarbazide and isonicotinic acid hydrazide (INH) induced seizures at 30mg/kg at 0.5h except 4A-a. The majority of the compounds are protected at 1hr. time interval only 4A-i, 4A-j, 4A-k, 4B-i, were protected mice in all the tests at 2hr.The compounds 4A-i, 4A-j, 4A-k, and 4B-i were observed to be most active for anticonvulsant activity and compounds 4A-b, 4A-f, 4A-g and 4A-h were showing moderate activity. Thus these compounds could be considered most potent. Further, all the compounds exhibited no neurotoxicity in rotarod test up to a dose of 300mg/kg. All the compounds showed activity against chemo shock method pinpointing their capability to prevent seizure spread.

Table-3: Anticonvulsant evaluation and neurotoxicity screenings of new triazolethione Schiff bases 4A (a-k) 4B (a-k) in the strychnine, thiosemicarbazide, and isonicotinic acid hydrazide (INH) induce models after intraperitoneal injection in mice.

Strychnine induced convulsion				Thiosemicarbazide induced convulsion			Isonicotinic acid hydrazide (INH) induced convulsion			Neurotoxicity screen	
Time to peak effect	**0.5 h**	**1 h**	**2 h**	**0.5 h**	**1 h**	**2 h**	**0.5 h**	**1 h**	**2 h**	**0.5h**	**4h**
Controls	-	-	-	-	-	-	-	-	-	-	-
Compound ID											
4A-a	-	-	-	30	-	-	30	-		30	-
4A-b	300	30	-	300	30	-	300	100	-	300	100
4A-c	30	-	-	30	-	-	-	-	-	100	-
4A-d	30	30	-	30	30	-	30	30	-	100	-
4A-e	30	30	-	30	30	-	30	30	-	30	-
4A-f	300	100	-	300	-	-	100	30	-	300	-
4A-g	300	100	-	300	-	-	100	30	-	300	-
4A-h	300	100	-	300	-	-	300	30	-	300	-
4A-i	300	300	100	300	100	30	300	100	30	300	30
4A-j	300	100	100	300	30	30	300	100	30	300	30
4A-k	300	300	100	300	100	30	300	100	30	300	300
4B-a	30	30	-	100	30	-	30	30	-	100	-
4B-b	30	-	-	30	-	-	-	-	-	30	-
4B-c	30	-	-	-	-	-	-	-	-	100	-
4B-d	30	-	-	30	-	-	30	-	-	100	-
4B-e	30	-	-	30	-	-	30	-	-	30	-
4B-f	30	-	-	30	-	-	-	-	-	100	-
4B-g	300	100	100	300	100	30	100	30	-	100	-
4B-h	100	30	-	100	100	-	30	30	-	30	-
4B-i	300	300	30	30	-	30	300	100	30	300	100
4B-j	30	-	-	-	-	-	-	-	-	30	-
4B-k	30	-	-	-	-	-	-	-	-	30	-
Diazepam(mg/kg)	10	10	10	10	10	10	30	30	30		

Test compounds were suspended in polyethylene glycol (PEG) and doses of 30, 100,300 mg/kg were administered through intraperitoneal (i.p.) injection in mice. The figures in the table indicate the dose in mg/kg at which bioactivity was observed in a majority of the animals. The dash (-) indicates an absence of activity at maximum dose administered (300 mg/kg)

CONCLUSION

We have attempted to design and synthesize novel triazolethione Schiff bases 4A (a-k) 4B (a-k) to exhibit anticonvulsant activity. The results obtained revealed that numbers of novel triazolethione derivatives effective in chemical induce (chemo shock) model, compounds 4A-i, 4A-j, 4A-k, and 4B-i were observed to be most active for anticonvulsant activity while 4A-b, 4A-f, 4A-g and 4A-h showing moderate activity and remaining compounds showed mild anticonvulsant activity. Results indicated that compounds with menthone, camphor derivatives and having chloro-substituted aldehydes/ ketones showed good anticonvulsant activity. Therefore, these derivatives may possible to use as lead compounds for other biological activities also. Overall, the synthesized compounds emerged as more active and less neurotoxic derivatives.

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