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SYNTHESIS AND ANTI CONVULSANT ACTIVITY OF SOME TRAIZOLE DERIVATIVES

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ABSTRACT

Compounds with 1, 2, 4-triazole moiety found to display a wide range of potent biological activities such as antifungal, anti-inflammatory, anticonvulsant, antimicrobial and anti tumor activity. In the present scheme, we have made an attempt to synthesize some novel triazole derivatives by reacting 3, 5-diphenyl, 4-amino triazole with various aromatic aldehydes to get Schiff's bases (comp I). Compound I is further reduced with $NaBH_4$ to get the reduced intermediate (comp II), which was later treated with chloroacetyl chloride to get corresponding chloro acetyl derivatives (comp III). The resulting compound is further reacted with hydrazine hydrate. The hydrazine hydrate derivatives were then reacted with 4-nitrobenzaldehyde to get titled compounds. The synthesized compounds were characterized and confirmed by IR and NMR spectroscopy.

KEYWORDS: 4-Amino Triazole, Schiff's base, $NaBH_4$, Hydrazine Hydrate.

INTRODUCTION[1]

The triazole family constitutes most widely used antifungal agents today. The drugs in this class offer activity against many fungal pathogens without the serious nephrotoxic effects observed with amphotericin B administration. Although amphotericin B has been the gold standard for the treatment of many severe, life-threatening systemic fungal infections, newer azole agents are emerging as first-line therapies for severe fungal disease, including invasive aspergillosis. The initial systemic use of earlier azoles, such as ketoconazole, has generally

been replaced by the triazoles because of superior pharmacokinetics, improved safety profiles and better studies on clinical efficacy in the treatment of systemic mycoses.

1,2,4-Triazole:[2] is one of a pair of isomeric chemical compounds with molecular formula $C_2H_3N_3$, called triazoles, which have a five-membered ring comprising of two carbon atoms and three nitrogen atoms. 1, 2, 4-Triazole is a basic aromatic heterocycle. 1, 2, 4-Triazole derivatives find use in a variety of applications, most notably as antifungal such as fluconazole and itraconazole.1, 2, 4-Triazoles can be prepared using the Einhorn-Brunner reaction or the Pellizzari reaction.

The 1,2,4-triazole moiety has featured in the structure of several medicinal agents whose synthesis was reported over the years.

Numerous references have appeared within the last few years that highlight 1,2,4-triazole-based structures. Typically the 1,2,4-triazole is usually an appended or occasionally a fused ring which has been designed and synthesized to impart a particular medicinal or agriculturally useful compound.

MATERIALS AND METHOD

The chemicals used in the present project work were of AR grade and LR grade, purchased from SD-fine, Loba Chemie, Qualigens, sigma, Ranchem, and Merck.

ANALYTICAL TECHNIQUES

Physical data

Melting points of the synthesized compounds were taken in open capillary tubes and Theil`s melting point apparatus.

Thin Layer Chromatography (TLC)

Purity of the synthesized compounds and progress of reaction were monitored by thin layer chromatography using silica gel G as stationary phase and suitable mobile phases. The spots resolved were visualized using UV and iodine chamber.

Instrumentation

The compounds were synthesized by both Microwave irradiation and conventional methods. The techniques employed for the characterization of the synthesized compounds were IR spectra and ^{1}H-NMR spectra.

Infrared spectra: The IR spectra of the synthesized compounds were recorded on a Fourier Transform IR spectrometer (model Shimadzu 8400S) in the range of 400-4000 by KBr pellet method and the values of ν_{max} are reported in cm^{-1}.

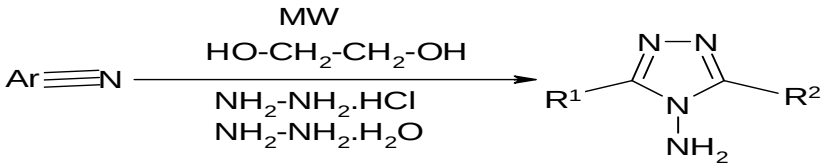
^{1}H-NMR magnetic resonance spectra

^{1}HNMR spectra were recorded on DMM X - 200 MHz NMR, Brookfield Astra zeneca pharma India Ltd. using $CDCl_3$ and DMSO. The chemical shifts (δ) are reported in parts per million downfield from internal reference Tetramethylsilane (TMS).

EXPERIMENTAL

Preparation of 3, 5-Di phenyl 4-Amino triazole[3]

A mixture of the Benzyl nitrile (0.02mol), Hydrazine Dihydrochloride(0.02mol) and Hydrazine Hydrate(0.06mol) in ethylene glycol (10ml) were introduced into a two neck flask and placed in a microwave oven under a reflux condenser and irradiated for 12mins at 490 watt. After irradiation the reaction mixture was cooled and added to ice-cold water of about 100ml. The precipitate formed was collected, dried and recrystallized with using ethanol.



Step I.

General method for synthesis of arylidene triazole derivatives(1a-5a)[4]

The corresponding aldehyde(0.005mol) was added to a solution of compound 1(0.005mol) in 20 ml of glacial acetic acid and the mixture was refluxed for 4hrs. After cooling, The mixture was poured into a beaker containing 100ml of ice-cold water. The precipitate formed was filtered. After drying in vacuo, the product was recrystallized from an appropriate solvent to get desired product.

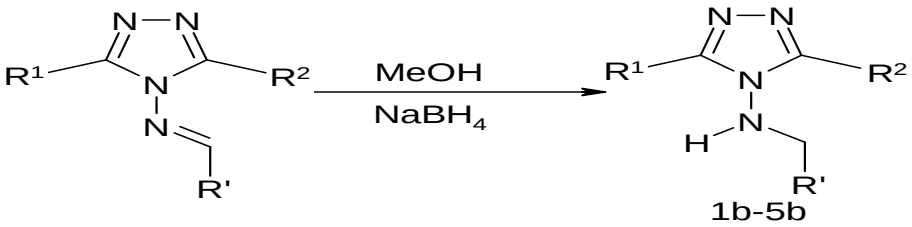
IR KBr: 1569cm^{-1}(C=N), 1471(C=C) Aromatic stretching.

^{1}H NMR(DMSO-d_6) δ 8.6 (S, 1H, N=CH), 7.67 (m, Ar-H).

Step II.

General method for the reduction of arylidene triazoles (1b-5b)[5]

The corresponding arylidene triazole (1a-5a,0.005mol) was dissolved in 50ml of dried methanol and $NaBH_4$(0.01mol) was added in small portions to this solution. The mixture was refluxed for 20mins and then allowed to cool. After concentrating at 25^0C-30^0C under reduced pressure, the solid residue obtained was washed with cold water. After drying, the solid product was recrystallized from an appropriate solvent to get the desired compound.



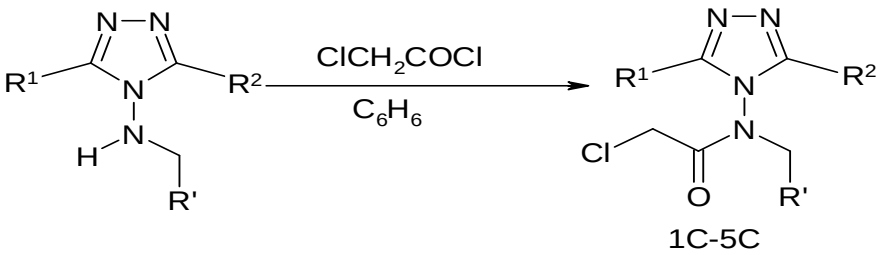
IR KBr: 3221cm^{-1}(-NH), 1604(C=N), 1489(C=C) Aromatic stretching.

^{1}HNMR(DMSO-d_6) δ 7.39 (m,Ar-H), 3.73 (d,2H,CH2), 2.5 (s,1H. NH).

Step III.

General method for the synthesis of Chloroacetyl derivatives(1c-5c)[6]

The compound(1b-5b,0.005mol) was taken in a beaker containing 20ml dry Benzene, In another beaker chloroacetyl chloride(0.005mol) in 50 ml dry Benzene was taken. The chloroacetyl chloride was added drop wise to the beaker having reduced product in dry Benzene slowly and under continous stirring, for about 1hr. Then the reaction mixture was refluxed for about 3 hrs in a round bottom flask fitted with a condenser, just above room temperature. After refluxation, the reaction mixture was cooled and added to the crushed ice taken in a beaker and kept overnight. The precipitate was later collected and washed with water, dried and recrystallized using methanol.



IR KBr: 1602(C=O), 1492(C=N), 1471(C=C) Aromatic stretching, 704cm^{-1}(R-Cl).

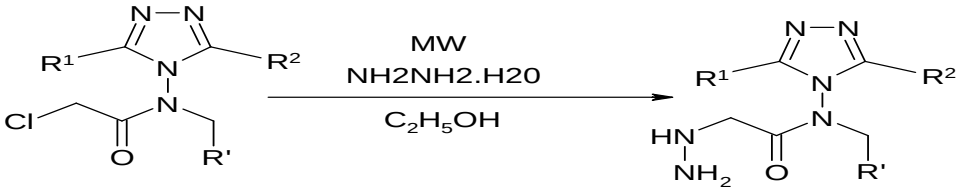
^{1}HNMR ($CDCl_3$) δ7.21 (m, Ar-H), 5.1 (s, 2H, CH_2Cl), 3.84 (d,2H, CH_2).

Step IV.

Microwave method

General method for synthesis of Hydrazine derivatives (1d-5d)[7]

Chloroacetyl derivatives (1c-5c, 0.005mol) were taken in 10ml of Ethanol in a beaker to which Hydrazine hydrate (0.005mol) was added. The reaction mixture was refluxed for 10mins at 690watt by taking in a two neck flask fitted with a condenser. After irradiation the reaction mixture was cooled and added to the ice-cold water. The precipitate formed was collected, dried and recrystallized using methanol.



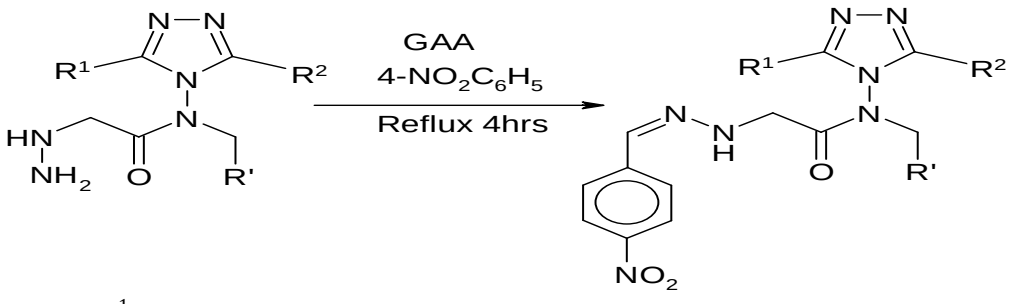
IR KBr 3298cm^{-1}(NH), 1625(C=O), 1492(C=N), 1471(C=C) Aromatic stretching.

^{1}HNMR(CDCl3) δ 7.7 (m, Ar-H), 6.8 (d, 2H, CH_2NH), 3.74 (d, 2H,-CH_2), 1.8 (s, 1H, NH) 1.7 (s, 2H, NH_2).

Step V.

General method for synthesis of Schiff's bases (1e-5e)[8]

The hydrazide derivative (1d-5d, 0.005mol) of the triazole was taken in 20ml of glacial acetic acid to which p-nitrobenzaldehyde(0.005mol) was added and kept for refluxation in a round bottom flask fitted with a condenser for about 4hrs. The reaction mixture was cooled and then added to the water. It was later heated for about 10mins.The solution was filtered hot and kept overnight to get the shiny yellow crystals.



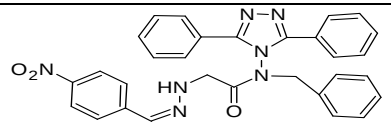
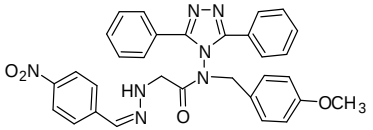
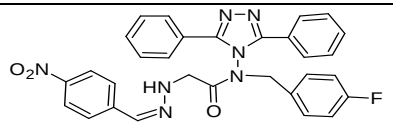
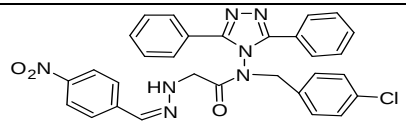
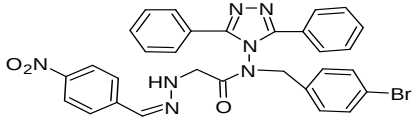
IR KBr 3389cm^{-1}(C=NH), !606(C=N), 1344(C=C).

^{1}HNMR($CDCl_3$) δ 8.4 (d,1H, N=CH), 7.6 (m, Ar-H) 6.84 (d, 2H, CH_2NH),3.7 (d, 2H, CH_2), 1.6 (s, 1H, NH).

Table No. 1: List of substituents.

SL No	R^1&R^2	R'
1	Ar	C_6H_6
2	Ar	p-$C_6H_5OCH_3$
3	Ar	p-C_6H_5F
4	Ar	p-C_6H_5Cl
5	Ar	p-C_6H_5Br

SYNTHESISED 3,5-DIPHENYL 4-AMINO TRIAZOLE DERIVATIVES

Products	Structure	Mol. formula	IUPAC Name	%Yield	Mobile Phase for TLC	Mp in 0C
1		$C_{30}H_{25}N_7O_3$	*N*-benzyl-*N*-(3,5-diphenyl-4*H*-1,2,4-triazol-4-yl)-2-[(2*Z*)-2-(4-nitrobenzylidene)hydrazino]acetamide	47	Hexane:EtoAc:MeOH 3:2:6	118-20
2		$C_{31}H_{27}N_7O_4$	*N*-(3,5-diphenyl-4*H*-1,2,4-triazol-4-yl)-*N*-(p-methoxybenzyl)-2-[(2*Z*)-2-(4-nitrobenzylidene)hydrazino]acetamide	53	Hexane:EtoAc:MeOH 3:2:6	134-36
3		$C_{30}H_{24}FN_7O_3$	*N*-(3,5-diphenyl-4*H*-1,2,4-triazol-4-yl)-*N*-(4-fluorobenzyl)-2-[(2*Z*)-2-(4-nitrobenzylidene)hydrazino]acetamide	60	Hexane:EtoAc:MeOH 3:2:6	164-66
4		$C_{30}H_{24}ClN_7O_3$	*N*-(4-chlorobenzyl)-*N*-(3,5-diphenyl-4*H*-1,2,4-triazol-4-yl)-2-[(2*Z*)-2-(4-nitrobenzylidene)hydrazino]acetamide	60	Hexane:EtoAc:MeOH 3:2:6	227-29
5		$C_{30}H_{24}BrN_7O_3$	*N*-(4-bromobenzyl)-*N*-(3,5-diphenyL-4*H*-1,2,4-triazol-4-yl)-2-[(2*Z*)-2-(4-nitrobenzylidene)hydrazino]acetamide	57	Hexane:EtoAc:MeOH 3:2:6	122-24

ANTICONVULSANT ACTIVITY OF 3, 5-DIPHENYL 4-AMINO, 1,2,4-TRIAZOLE DERIVATIVES

Study of anticonvulsant activity of 3, 5-Diphenyl 4-Amino, 1, 2,4-Triazole derivatives against PTZ-induced convulsion

OBSERVATIONS

Table no: 4: Anticonvulsant activity of 3,5 Diphenyl, 4-Amino 1,2,4-Triazole derivatives by PTZ-induced convulsion.

Drug	Dose (mg/kg)	Latency of clonic convulsion (s)	Latency of tonic convulsion (s)	Convulsion %	Mortality %
Control (normal saline)	0.2ml	1.34 ± 0.08	4.78 ± 0.48	100	100
Compound 1	1.2ml	4.95 ± 0.48[a]	6.96 ± 0.73	100	100
Compound 2	1.2ml	6.08 ± 0.30[a]	11.72 ± 0.92[a]	100	100
Compound 3	1.2ml	6.71 ± 0.41[a]	11.71 ± 0.73[a]	100	100
Compound 4	1.2ml	4.93 ± 0.48[a]	6.96 ± 0.73	100	100
Compound 5	1.2ml	6.07 ± 0.30[a]	11.71 ± 0.92[a]	100	100
Phenytoin	0.42ml	3.17 ± 0.27[a]	7.27± 0.68 [a]	100	100
Phenytoin + *compound 1*	1.2+0.42=1.62ml	3.40 ± 0.33[a]	6.82 ± 2.49	100	100

Data are represented as mean ± SEM. Significant at aP < 0.01 when compared to control (n=6).

Anticonvulsant activity

Pentylene tetrazole-induced convulsion

The results of the effect of 3,5 Diphenyl, 4-Amino 1,2,4-Triazole derivatives on pentylene tetrazole (PTZ)-induced convulsion in mice is shown on table 4. The 3,5 Diphenyl, 4-Amino 1,2,4-Triazole derivatives significantly (P<0.01-0.001) delayed the onset of clonicn and tonic convulsion caused by PTZ when compared to control. The delay caused by the 3,5 Diphenyl, 4-Amino 1,2,4-Triazole derivatives was higher than that of the standard, phenytoin(40mg/kg). However, the extract could not prevent convulsion and mortality due to PTZ-induced seizure. Phenytoin also could not protect the animals

DISCUSSION

Results of this study shows that the extract significantly delayed the onset of clonic/tonic convulsion produced by PTZ and picrotoxin. This was observed also for phenytoin the standard drug used.According to De Sarro *et al.* (1999), PTZ may be exerting its anticonvulsant effect by inhibiting the activity of gamma aminobutyric acid (GABA) at GABAA receptors. Gamma aminobutyric acid is the major inhibitory neurotransmitter which is implicated in epilepsy. The enhancement and inhibition of the neurotransmission of GABA

will attenuate and enhance convulsion respectively (Gale, 1992; Westmoreland *et al.*, 1994). Phenobarbitone and diazepam, standard epileptic drugs, have been shown to exert their antiepileptic effects by enhancing GABA-mediated inhibition in the brain(Porter and Meldrum,2001; Rang *et al*., 2003). These drugs are reported to antagonise PTZinduced convulsion (Amabeoku *et al*., 2007) by enhancing GABA neurotransmission. Phenytoin was unable to prevent PTZ-induced seizure because it is thought to exert its antiepileptic effect by blocking sodium ions into brain cells thus inhibiting generation of repitative action potential (Porter and Meldrum, 2001). Since the 3, 5-Diphenyl 4-Amino, 1, 2,4-Triazole derivatives was able to delay PTZ-induced convulsion it is probable that it may be interfering with gabaergic mechanism(s) to exert its effect.

From the results above, the 3, 5-Diphenyl 4-Amino, 1, 2,4-Triazole derivatives has a considerable anticonvulsant activity.

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