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SYNTHESIS AND ANTI INFLAMMATORY ACTIVITY OF 3,5-DIPHENYL 4-AMINO 1,2,4 -TRIAZOLE 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been replaced by the triazoles because of superior pharmacokinetics, improved safety profiles and better studies on clinical efficacy in the treatment of systemic mycoses.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}.

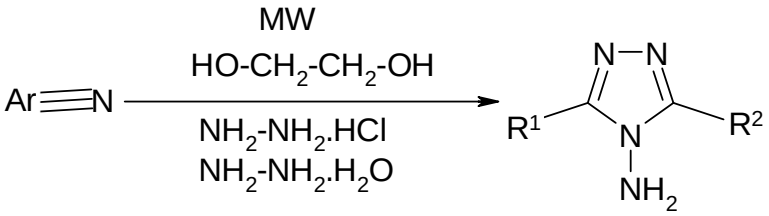
^{1}H-NMR magnetic resonance spectra

^{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

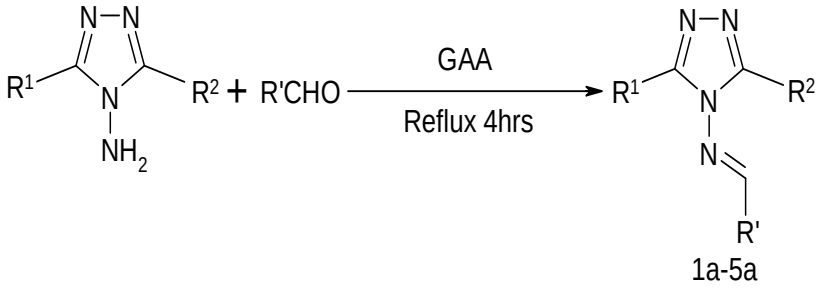
Preparation of 3, 5-Di phenyl 4-Amino triazole[3]

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.

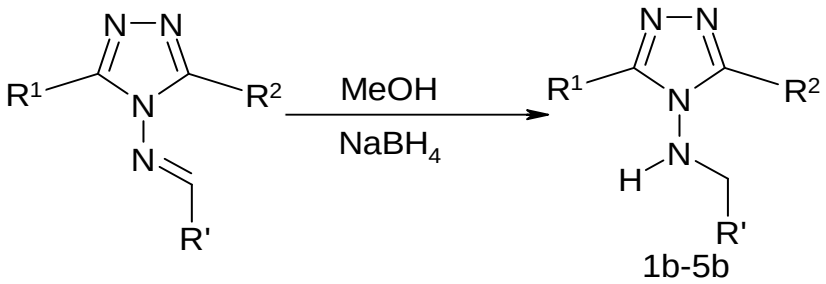


IR KBr: 1569cm^{-1}(C=N), 1471(C=C) Aromatic stretching.

^{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^{0}C-30^{0}C 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.

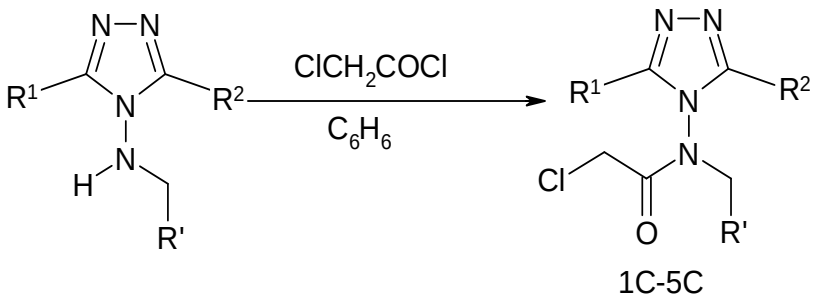


IR KBr: 3221cm^{-1}(-NH), 1604(C=N), 1489(C=C) Aromatic stretching.

^{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.



1C-5C

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

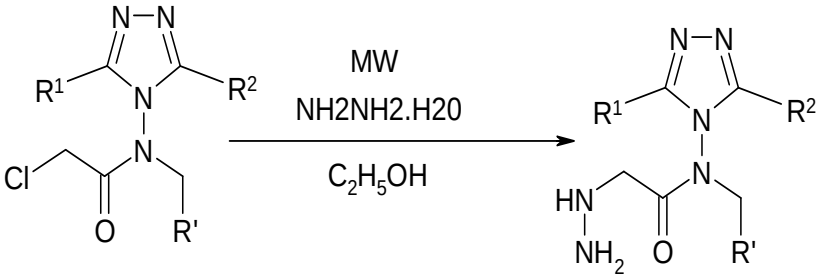
^{1}HNMR ($CDCl_3$) δ7.21 (m, Ar-H), 5.1 (s, 2H, CH_2Cl), 3.84 (d,2H, CH_2).

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.

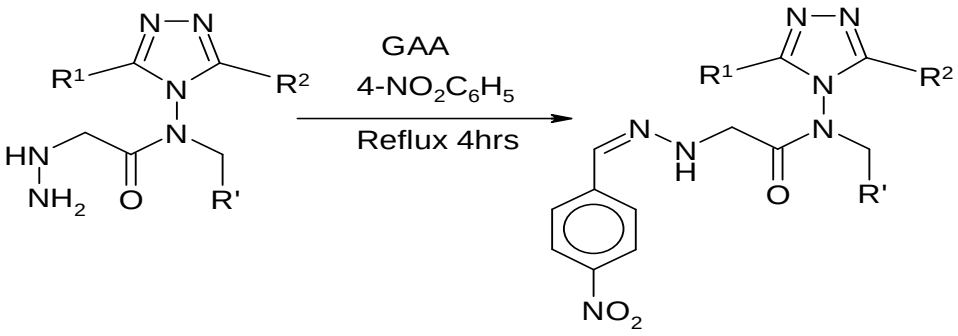


IR KBr 3298cm^{-1}(NH), 1625(C=O), 1492(C=N), 1471(C=C) Aromatic stretching.

^{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.



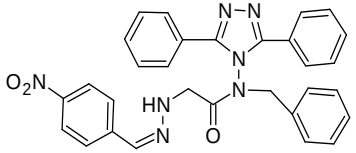
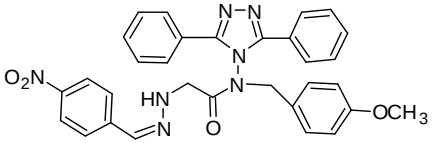
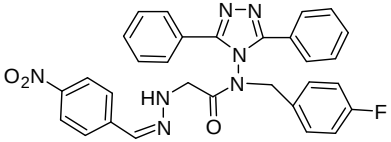
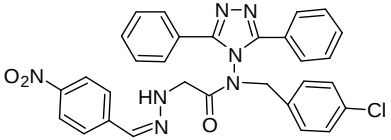
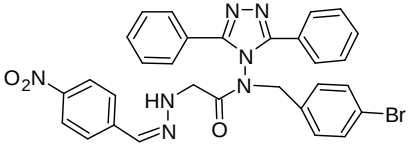
IR KBr 3389cm^{-1}(C=NH), !606(C=N), 1344(C=C).

^{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 substituent groups 1a-5e.

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

TABLE NO:2 SYNTHESISED 3,5-DIPHENYL 4-AMINO TRIAZOLE DERIVATIVES

PRODUCTS	STRUCTURE	MOL. FORMULA	IUPAC NAME	%YIELD	MOBILE PHASE FOR TLC	MP IN 0C
1		C30H25N7O3	*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		C31H27N7O4	*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		C30H24FN7O3	*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		C30H24CLN7O3	*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		C30H24BRN7O3	*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

ANTI INFLAMMATORY STUDIES[9,10.11]

The anti-inflammatory activity of the newly synthesized triazole derivatives were carried out using carrageenan induced rat hind paw edema method. The adult Wistar albino rats of either sex weighing 120-25 g were selected and were assigned into seven groups of 6 animals each. They were marked with picric acid for individual animal identification. The animals were deprived of food overnight. (Water ab libitum) and the synthetic compounds were administred once before the injection of carrageenan. First five groups received the synthetic compounds (1-5) suspended in 0.5%w/v carboxy methyl cellulose sod. salt and administred at dose level of 50mg/kg in a volume not exceeding 0.1ml/100gms orally. The positive control Indomethacin (10mg/kg) was also administered in a similar manner. The seventh group served as solvent control.

After 30mins of test compound administration, 0.1ml of 1% w/v of carrageenan in normal saline was injected into the sub plantar region of the left hind paw of the rat. Immediately after the carrageenan injection, the volume of its displacement was measured using plethesmometer.

The reading was recorded at the end of 180 mins. The % inhibition of edema was calculated by using the formula

$$\% \text{ Inhibition} = 100 \times (1 - Vt/Vc)$$

Vt/Vc ⟶ edema volume in the rat treated with test drug and control respectively.

Table no: 3 Effect of 3, 5- diphenyl Triazole Derivatives On Carrageenan Induced hind Paw Edema In Rats.

Compound	Dose (mg/kg)	Increased paw volume after 30 min	%decrease in paw volume
Control	2ml/kg	0.64 ± 0.04	
Indomethacin	10	0.44 ± 0.01a	35.29
1	50	0.52 ± 0.06b	23.53
2	50	0.58 ± 0.04	14.71
3	50	0.46 ± 0.02a	32.35
4	50	0.51 ± 0.05b	25.00
5	50	0.48 ± 0.04a	29.41

No. of animals in each group = 6, values are expressed as mean ± sem

ap<0.01; bp<0.05; vs control.

Values were analysed one way anova followed by tukey multiple comparison test.

RESULTS AND DISCUSSION

Triazole derivatives are a class of heterocyclic compounds, widely used as antifungal, anti-inflammatory, antipyretic, analgesic, anticonvulsant, anticancer and antibacterial agents. These interesting pharmacological properties exhibited by triazole derivatives have prompted us to synthesize some novel triazole derivatives and so synthesized compounds were further screened for their anti-inflammatory and anticonvulsant property.

The titled compounds were synthesized according to the procedures as given in the methodology. The reactions were monitored by TLC. The physical constants like melting point and solubility were determined for all the intermediate and final products. The compounds were further characterized by IR and ^{1}H NMR. All the titled compounds were evaluated for their anti-inflammatory and anti-convulsant activities.

Table 3: Indicates the anti- inflammatory activity of the synthesized compounds.

The test compounds were screened for anti- inflammatory activity by carrageenan induced hind paw edema method using Indomethacin as standard. And the following activity was observed.

Derivatives 3 and 5 showed significant activity of all the compounds tested, where as 1 and 4 has moderate activity and 2 does not shown any anti-inflammatory activity.

CONCLUSION

- The main focus of this research work was to synthesize, purify, characterize and evaluate anti-inflammatory and anti-convulsant activities of novel Diphenyl triazole derivatives.
- A series of titled compounds, i.e.,[1-5] have been synthesized using appropriate synthetic procedures, as per the scheme given in the methodology.
- The yield of the synthesized compounds was found to be in range from 47%- 60%.
- Structures of synthesized compounds were characterized and confirmed with the help of analytical data's such as IR and ^{1}H NMR.
- Anti-inflammatory activity was carried out using carrageenan induced hind paw edema method in rats.
- Among the synthesized compounds screened for anti-inflammatory activity, the compounds 3 and 5 showed significant activity while compounds 1 and 4 exhibited

moderate activity and compound 2 did not show any activity in comparison with the standard drug Indomethacin.

- However none of the test compounds showed better anti-inflammatory activity than the standard.
- Hence, we can conclude that the newly synthesized Diphenyl triazole derivatives do possess considerable Antiinflammatory activity and further lead optimization could be carried out for the better-expected anti-inflammatory activity.

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