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Research Article

Synthesis and biological evaluation of some new Schiff base 1,2,4-triazole derivatives

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Abstract

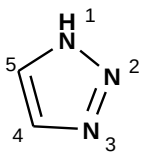
A series of substituted 1,2,4-Triazole derivatives were synthesized, and their anticonvulsant activity and antimicrobial activity were evaluated which include the MES model and by Cup-plate method. However, further studies need to be carried out to ascertain the precise mechanism of action of anticonvulsant activity of these molecules. The compounds 4-[1-(2-Bromo-phenyl)-ethylideneamino]-5-pyridin-3-yl-2,4-dihydro[1, 2, 4] triazole-3-thione (SB-1) and 4-[1-(4-Fluoro-phenyl)-ethylideneamino]-5-pyridin-3-yl-2,4-dihydro[1, 2, 4] triazole-3-thione (SB-2) showed significant anticonvulsant activity and antibacterial activity against ***Escherichia coli.***

Keywords: 1,2,4-Triazole derivatives, Anticonvulsant activity and antibacterial activity.

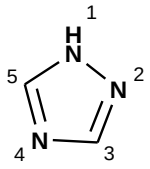
1. Introduction

1, 2, 4-Triazole

There is significant and continuous concern in the chemistry of five-member N-heterocycle compounds, mainly tetrazole (CH_2N_4), triazoles ($C_2H_3N_3$), and their substituted derivatives. Triazole exists as two isomers, 1,2,3-triazoles and 1,2,4- triazoles, as shown in (Fig. 1).[1]



1,2,3-Triazole



1,2,4-Triazole

Figure 1: Isomers of Triazole

A large number of 1,2,4-triazole, a heterocyclic derivative exhibits important structural fragments and considered as biologically active compounds such as antifungal, anticonvulsant anti-tubercular, antioxidant, anti-inflammatory inhibition, anticancer, and antimicrobial activity,[2-7] corrosion inhibitors,[8] pesticides,[9] dyes,[10] acid-base indicator,[11] and other industrial chemicals[12]. At 1885, Bladin was the first scientist who gave the name of (triazole) to the carbon nitrogen ring system ($C_2N_3H_3$) and described triazoles derivatives.[13]

2. Experimental protocols

2.1 Chemistry

All the chemicals and solvents, purchased from Merck (India), Spectrochem (India), Sigma-Aldrich (India), CDH (India) and S.D. Fine were used without further purification. Thin layer chromatographic analysis of compounds was performed on silica gel G coated glass plates. The adsorbent silica gel G was coated to a thickness of about 0.25 mm on previously cleaned TLC plates of 20x5 cm using conventional spreader. The plates were placed in hot air oven at 105^0C for 30 min. The solutions of compounds were applied as a spot on the activated plate about 2 cm above from the lower edge. The mobile phases were selected according to the polarity of compounds. Melting points were determined by using open capillary melting point apparatus and are reported uncorrected.

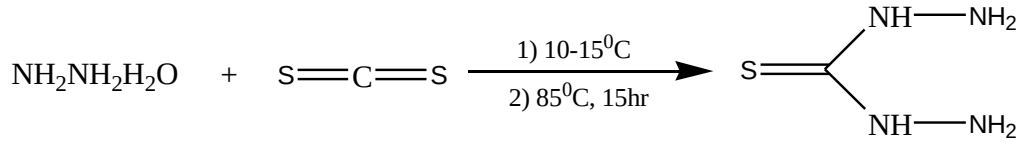
Compounds were placed in one end of the sealed capillary and placed in the caves made for the capillary. Thermometer was placed in the cave. The temperature at which compound starts melting and the temperature at which it completely melts was recorded as a melting point range.

FT-IR spectra (KBr) were recorded on a Perkin-Elmer Spectrometer BX-II spectrophotometer. The ^{1}H-NMR and spectra were recorded on Bruker 400 MHz High Resolution NMR spectrometer using TMS as an internal standard. Chemical shifts were reported in ppm (δ) and signals were described as singlet (s), doublet (d), triplet (t) and multiplet (m).

2.2 General

2.2.1 Synthesis of Thiocarbohydrazide (1)

In a round bottom flask hydrazine hydrate (1.0 mol) was placed, which was equipped with thermometer, efficient agitator, and reflux condenser. The temperature was lowered to 10°C and 0.2 mol of carbon disulfide (15.2 g, 12.1 mL) was added dropwise into the flask while maintaining the temperature below 15°C and the temperature was raised gradually to 85°C for 1.5 hr. reaction mixture was cooled to 10°C, precipitate was filtered and washed with water. The physico-chemical data was calculated: R_f value 0.48, % yield 65.61, melting point 95-97°C, Cream color solid.



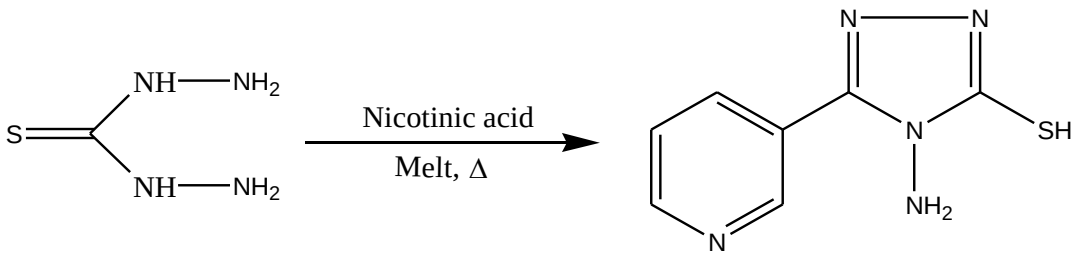
Hydrazine hydrate Carbon Disulphide

Thiocarbohydrazide

(1)

2.2.2 Synthesis of 4-Amino-5-(substituted-phenyl)-4H-[1,2,4]-triazole-3-thiol (2)

A mixture of substituted benzoic acid (0.01mol) and thiocarbohydrazide (0.015mol) were taken in a round bottomed flask and heated on a mantle until the content of the flask was melted. The product obtained on cooling was treated with sodium bicarbonate solution to neutralize the unreacted carboxylic acid, if any. It was then washed with water and collected by filtration. The product was recrystallized with ethanol to afford the title compounds. The physico-chemical data was calculated: R_f value 0.44, % yield 56.21, melting point 83-85°C, Cream color solid.



Thiocarbohydrazide

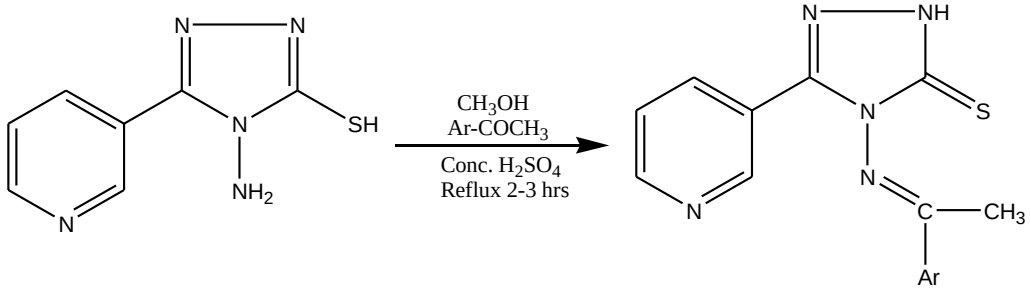
(1)

4-Amino-5-pyridin-3-yl-4*H*-[1,2,4]triazole-3-thiol

(2)

2.2.3 Procedure for 1,2,3-Triazole Derivative Preparation Containing Schiff base. (3)

To a suspension of substituted amino mercapto triazole (0.2 mol) in methanol, an equimolar amount of the corresponding substituted acetophenone with 3 to 4 drops of sulphuric acid was added. The reaction mixture was refluxed for 2-3 h at 80-90°C. The precipitate was obtained which was washed with water, filtered and dried.



4-Amino-5-pyridin-3-yl-4*H*-[1,2,4]triazole-3-thiol

(2)

1,2,4-Triazole derivatives

(3)

Synthesis 1:

4-[1-(2-Bromo-phenyl)-ethylideneamino]-5-pyridin-3-yl-2,4-dihydro-[1,2,4]triazole-3-thioe from 2-Bromoacetophenone. 3a (SB-1)

To a suspension of 4-Amino-5-pyridin-3-yl-4H-[1,2,4]triazole-3-thiol (0.2 mol) in methanol, an equimolar amount of the corresponding 2-Bromoacetophenone with 3 to 4 drops of sulphuric acid was added. The reaction mixture was refluxed for 2-3 h at 80-90 °C. The precipitate was obtained which was washed with water, filtered and dried. The physico-chemical data was calculated: R_f value 0.42, % yield 54.44, melting point 150-152^{0}C, Cream color solid.

Synthesis 2:

4-[1-(4-Fluoro-phenyl)-ethylideneamino]-5-pyridin-3-yl-2,4-dihydro-[1,2,4]triazole-3-thione from 4-Flouroacetophenone. 3b (SB-2)

To a suspension of 4-Amino-5-pyridin-3-yl-4H-[1,2,4]triazole-3-thiol (0.2 mol) in methanol, an equimolar amount of the corresponding 4-Fluoroacetophenone with 3 to 4 drops of sulphuric acid was added. The reaction mixture was refluxed for 2-3 h at 80-90 °C. The precipitate was obtained which was washed with water, filtered and dried. The physico-chemical data was calculated: R_f value 0.64, % yield 50.21, melting point 110-112^{0}C, Cream color solid.

Synthetic scheme

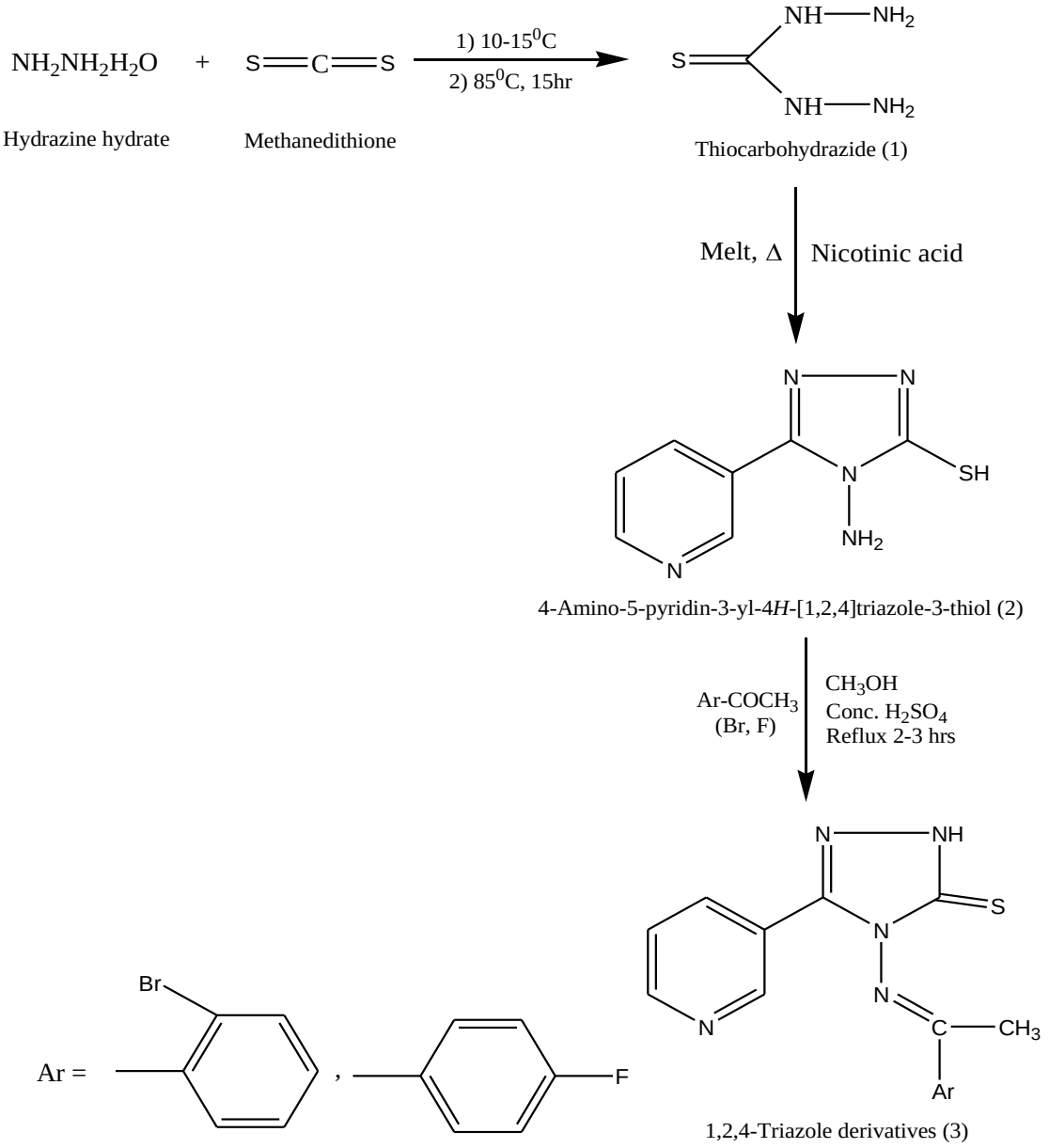


Figure 2: Synthesized compound is: SB-1 and SB-2

2.3 Characterization of the synthesized compounds

4-[1-(2-Bromo-phenyl)-ethylideneamino]-5-pyridin-3-yl-2,4-dihydro[1,2,4]triazole-3-thione. (SB-1)

Cream colored flakes, M.F. $C_{15}H_{12}BrN_5S$, M.P. 150-152 ^{0}C, R_f 0.42, % yield 54.44, IR (KBr, cm^{-1}, υ): 2913.9(-NH-); 1687.8(-C=N); 1226.1(-C=S); 1152.6(-C-N); 647.3(-C-Br).^{1}H NMR (500 MHz, DMSO-*d*), δ 10.214 (s, 1H, -NH), 7.352-8.143 (m, 8H, Ar-H), 1.312 (s, 3H, $-CH_3$).

4-[1-(4-Fluoro-phenyl)-ethylideneamino]-5-pyridin-3-yl-2,4-dihydro[1,2,4]triazole-3-thione. (SB-2)

Cream colored flakes, M.F. $C_{15}H_{12}FN_5S$, M.P. 110-112 ^{0}C, R_f 0.64, % yield 50.21, IR (KBr, cm^{-1}, υ): 3276.6(-NH-); 1606.5(-C=N); 1302.5(-C=S); 1132.5(-C-N); 1028(-C-F).^{1}H NMR (500 MHz, DMSO-*d*), δ 10.014 (s, 1H, -NH), 7.214-7.623 (m, 8H, Ar-H), 1.231 (s, 3H, $-CH_3$), MS (m/z+) [M+1] 313.02

3. Result and discussion

3.1 Pharmacological evaluation

3.1.1 Anticonvulsant Activity

The compounds were primarily subjected for evaluating their anticonvulsant activity and then screened compounds were subjected to study various phases of MES. The results are shown in Table 1. The compounds 4-[1-(2-Bromo-phenyl)-ethylideneamino]-5-pyridin-3-yl-2,4-dihydro [1,2,4]triazole-3-thione(SB-1)and4-[1-(4-Fluoro-phenyl)-ethylideneamino]-5-pyridin-3-yl-2,4-dihydro[1,2,4]triazole-3-thione (SB-2) i.e. 66.33% protection.

Table 1: Anticonvulsant activity of compounds

Treatment	Dose (mg/kg)	Various phase of convulsions (time in sec)				
		Flexion	Extension	Stupor	Recovery	%Protection
Control	Tween 80	4.416±0.43	14.88±0.31	80.68±0.19	122.1±0.91	33.33
Std.	25	0.592±0.12**	1.22±0.13**	29.01±0.92**	61.47±0.46**	100
SB-1	50	3.870±0.30	11.96±0.28	65.84±0.24*	109.5±0.50**	66.33
SB-2	50	2.628±0.30*	8.32±0.40**	59.23±0.35**	86.68±0.10*	66.33

Values represent the mean ± SD of six animals each group (n=6), SB-1 and SB-2 test compounds. *indicates p<0.05, **indicates p<0.01 and when compared to the control group.(the mean difference was considered significant at 0.01 level).

3.1.2 Antibacterial activity

A compound 4-[1-(4-Fluoro-phenyl)-ethylideneamino]-5-pyridin-3-yl-2,4-dihydro[1, 2, 4] triazole-3-thione (SB-2) showed stronger antimicrobial activity against MTCC-521 gram (-)ve bacteria were evaluated after Cup-plate method. The results are shown in Table 2. The studied products are still under investigation. Their antibiotic properties have promising applications in the control of infections.

Table 2: Antibacterial activity of compounds

Compound code	Zone of inhibition in mm		
	E. coli (MTCC-521)		
	10 µg/ml	30 µg/ml	50µg/ml
SB-1	2	3	5
SB-2	4	6	7
Ampicillin	**8**	**9**	**11**
Control	-	-	-

4. Conclusion

The compounds 4-[1-(2-Bromo-phenyl)-ethylideneamino]-5-pyridin-3-yl-2,4-dihydro[1, 2, 4] triazole-3-thione(SB-1) and 4-[1-(4-Fluoro-phenyl)-ethylideneamino]-5-pyridin-3-yl-2,4-dihydro [1,2,4] triazole-3-thione (SB-2) showed significant anticonvulsant activity and show sufficient antibacterial activity against *Escherichia coli.* The Compound 4-[1-(4-Fluoro-phenyl)-ethylideneamino]-5-pyridin-3-yl-2,4-dihydro[1, 2, 4] triazole-3-thione (SB-2) showed significant inhibitory characteristics with stronger antimicrobial activity against MTCC-521 gram(-)ve bacteria.

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References

[1]. RM. Balabin, Tautomeric Equilibrium and Hydrogen Shifts in Tetrazole and Triazoles: Focal-Point Analysis and ab-initio Limit, *J. Chem. Phys*., 2009; 131 (154307): 1- 8.

[2]. FA. Hassan, & KW. Younus, "Biological Evaluation of Some Azole Derivatives in Cooling Fluids (Lubricant Oils)," *Res. J. Bio. Sci.*, 2012; 7(1): 48-51.

[3]. SP. Pardeshi, SV. Patil, R. Patil, & VD. Bobade, "Synthesis and Antimicrobial Activities of Some 1,2,4- Triazolo[3,4-b][1,3,4]thiadiazoles and 1,2,4-Triazolo [3,4-b][1,3,4]thiadiazines Bearing Bistrifluoromethyl phenyl Moiety," *J. Chem. Pharma. Res*., 2014; 6 (4): 675-681.

[4]. AJ. Atia, & SS. Al-Mufrgeiy, "Synyhesis and Antibacterial Activities of New 3-Amino-2-Methyl-Quinazolin-4(3H)-One Derivatives," *Am. J. Chem*., 2012; 2 (3): 150-156.

[5]. T. Taj, RR. Kamble, T. Gireesh, & BV. Badami, "An Expeditious Green Synthesis of Schiff Bases and Azetidinones Derivatised with 1,2,4-Triazoles," *J. Chem. Sci*., 2011; 123 (5):, 657–666.

[6]. O. Bekircan, E. Menteşe, S. Ülker, & C. Kucuk, "Synthesis of Some New 1,2,4-Triazole Derivatives Starting from 3-(4-Chlorophenyl)-5-(4-methoxybenzyl)-4H-1,2,4-triazol with Anti-Lipase and Anti-Urease Activities," *Arch. Pharm. Chem. Life Sci*., 2014; 347: 387–397.

[7]. HM. Abdullah, IK. Jassim, & MN. Safi, "Synthesis and Characterization of New Heterocyclic Compounds with Studying Its Biological Activity," *Kerbala J. Pharm. Sci.*, 2012; 4: 115-135.

[8]. S. Sripriya1, C. Subha, & A. Selvaraj, The Inhibition Chemistry of 2-Amino, 5-Phenyl 1, 3, 4-Triazole forAluminium in Hydrochloric Acid Solution, *IOSR-JAC*, 2013; 6 (2): 25-29.

[9]. AK. Sengupta, & M. Garg, "Studies on Potential Pestisides-Part XIV Synthesis and Biological Activities of Some New Thiosemicarbazide and Triazole Derivatives," *Def. Sci*., 1988; 31 (2): 91-96.

[10]. JC. Er, MK. Tang, CG. Chia, H. Liew, M. Vendrell, & YT. Chang, "Megastockes BODIPY-triazoles as Environmentally Sensitive Turn-on Fluorescent Dyes," *J. Chem. Sci*., 2014; 4: 2168-2176.

[11]. VN. Bulut, C. Duran, A. Gundogdu, M. Soylak, N. Yildirim, & M. Tufekci, "A Triazole Derivatives as A New Acid-Base Indicator," *Bull. Chem. Soc. Ethiop*. 2010; 24 (3): 457-460.

[12]. S. Cassani, S. Kovarich, PP. Roy, L. Van der Wal, & P. Gramatica, "Daphnia and Fish Toxicity of (Benzo)triazoles: Validated QSAR Models, and Interspecies Quantitative Activity-Activity Modeling, " *J. Haz. Mat*., 2013; 258-259: 50-60.

[13]. AK. Singh, & KR. Kandel, "Synthesis of Triazole Derivative: [4-(Benzylideneamino)-5-phenyl-4H-1,2,4- triazole-3-thiol], " *J. Nepal Chem. Soc*., 2012; 30: 174-177.

[14]. SI. Koteleviskii, & OV. Prezhdo, "Aromaticity Indices revisited: Refinement and Application to Certain Five-Membered Ring Heterocycles, " *Tetrahedron*, 2001; 57: 5715-5729.

[15]. IB. Obot, & AS. Johnson, "Ab initio, DFT and TD-DFT Electronic Absorption Spectra Investigations on 3,5-Diamino-1,2,4-triazole, *Elixir Comp. Chem.*, 2012; 43: 6658-6661.

[16]. WP. Ozimin´ski, JCz. Dobrowolski, & AP. Mazurek, DFT Studies on Tautomerism of C5-Substituted 1,2,3-Triazoles, " *J. Mol. Str.*, 2003; 651-653, 697-704.

[17]. A. Chawla, & P. Kaur, A Systematic "Review: Microwave Synthesis as A Part of Green Chemistry for the Synthesis of Novel 1,2,4-Triazole Derivatives, " *IRJP*., 2013; 4 (1): 49-72.

[18]. DC. Pinto, CM. Santos, & AM. Silva, "Advanced NMR Techniques for Structural Characterization of Heterocyclic Structures," *Recent Res. Dev. Heter. Chem.*, 2007; 37/661 (2): 397-475.

[19]. VB. Feshin, & EV. Feshin, "Ab initio Calculation of the Structure of 5-Chloro-1,2,4-triazole" *Chem. Heter. Comp*. 2001; 37 (1): 95-99.

[20]. G. Guimon, G. Pfister-Guillouzo, A. Bernardini, & P. Viallefont, "A Photoelectron Study (Hel, Hell) of the Tautomeric Equilibrium Chloro- and Bromo-1,2,4-triazole, " *Tetrahedron*, 1980; 36 (8): 1071-1078.