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Synthesis, Antibactrial Activity And Carcinogenicity Study Of 1, 4 – disubsubstituted 1, 2, 3- Bistriazoles Via Click Chemistry

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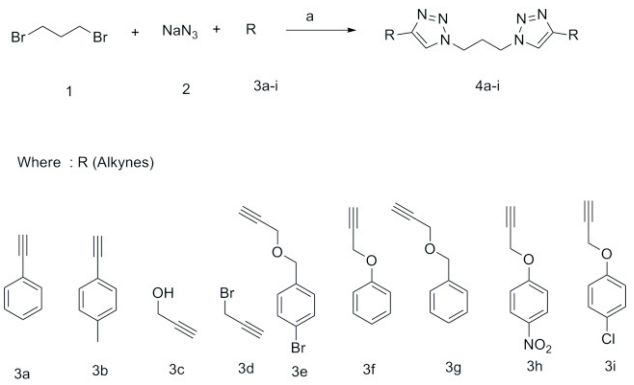
Abstract:- A series of bistriazole derivatives 4a-i was prepared by the treatment of 1, 3 dibromopropane with sodium azide, sodium carbonate, ascorbic acid and substituted alkynes, respectively. The title compounds bistriazole derivatives shown good yields and high purity. All the synthesized compounds were characterized by IR, 1H NMR, and Mass spectroscopy and these molecules were evaluated in vitro for their antibacterial activity and carcinogenicity study.

Keywords:1,2,3-Bistriazoles, Antibacterial activity and Carcinogenicity study.

INTRODUCTION

Bis-heterocyclic compounds are gaining increased interest in the recent past as the dimeric analogues have proven to be having better and potent biological activity than the corresponding monomer[1,3].Most of the nitrogen containing molecules are pharmacologically very active which can be attributed to the fact that nitrogenous compounds are part and parcel of the biomolecular diversity[4,10]. The 'click chemistry' approach has been the most widely used method for the synthesis of libraries of a large number of biologically active molecular frame works particularly for the regioselective synthesis of 1, 2, 3-triazoles , which involves the copper (1)-catalyzed cycloaddition reaction between azides and terminal alkynes (CuAAC). This reaction has been termed as the 'cream of the crop' of click reactions and has found application in various facts of drug discovery as it enables a modular approach to generate novel pharmacophores utilizing a collection of reliable chemical reactions[11,12] . Thus, the development of the copper (1)-catalyzed 'triazole click chemistry' has led to many interesting applications including the synthesis, medicinal chemistry, molecular biology, and material science. The bioorthogonality of azide and alkynes[13] has allowed the use of their [3 + 2] cycloaddition in various biological applications including target guided synthesis[14] and activity-based protein profiling of particular interest would be the dimeric heterocycle based ligands which are designed for specific target interactions[15].Various approaches reported for the synthesis of biologically relevant bis-triazoles include Cu (1)-catalyzed 1, 3-dipolar cycloaddition of monoazides with diacetylenes or that of monoacetylenes with diazides. Respectively Keeping into consideration the tremendous biological potence of triazoles and bis-triazoles in general and the antimicrobial activity in particular, we have continuous toward the synthesis of pharmacologically active molecules such as bistriazoles and its derivatives are reported as anti-HIV[16] antimicrobial [17] antiallergic [18] antifungal[19] antitumor[20] and selective β3 adrenergic receptor agonist[21].

SYNTHESIS OF 1,2,3-BISTRIAZOLES VIA CLICK CHEMISTRY REACTION



Scheme 1 : Synthesis of 1,2,3-bistriazoles (4a-I)

Reaction reagents and condition: (a) Na_2CO_3, $CuSO_4.5H_2O$, ascorbic acid, DMF: H_2O ,15-20 hrs , RT.

MATERIALS AND METHODS

1,3 dibromopropane , sodium azide , Ascorbic acid , Copper sulphate , sodium carbonate , dimethyl formamide (DMF), were obtained from Aldrich and used as received. All other chemicals were reagent grade and used without additional purification.

Physical Measurements

The IR spectra were recorded as KBr disks of bistriazoles on a PerkinElmer Model 2000 FT-IR spectrophotometer (Kyoto, Japan). The 1H NMR spectra were recorded on a Bruker DPX 400 (400 MHz) superconducting NMR spectrometer using $CDCl_3$ as solvent and TMS as an internal standard; chemical shifts are reported as (ppm). Mass spectra (MS) were recorded on a GC/MS Incos XL Finnegan MAT instrument.

General method for Synthesis of bistriazoles (4a-i)

The title compound was prepared by to a stirred solution of 1,3-dibromopropane (1.5 mmol) in DMF:H_2O 15 ml (4:1) was added NaN_3(3.2mmol) , Na_2CO_3 (2.2 mmol) , $CuSO_4.5H_2O$ (0.6 mmol) , ascorbic acid (2.2 mmol) , substituted alkynes (3a-i) (3.1 mmol) was added and the reaction mixture was stirred at room temperature for 15-20 h. To check the TLC, TLC is complies. Then added aqueous NH_4OH 100 ml and $CHCl_3$ 50 ml and the layers separated. The organic phase was washed with H_2O 100 ml and brine 100 ml, dried $MgSO_4$ and the solvent was evapourated to obtained crude product, which was crystallized by ethanol to obtained pure products.

Spectral data of representative compound:

Synthesis of 1, 3-bis (4-phenyl-1H-1, 2, 3-triazol-1-yl) propane (4a): white solid ,Yield = 85%. , M.P.= 130-132℃ ; IR (cm^{-1}) : 2981 , 2888 , 1594 , 1335 , 1107, 707 [1]; H NMR (300 MHz, $CDCl_3$, δ ppm) : 7.31-7.35 (t,1H) , 7.43-7.46 (d,2H) , 7.83-7.84 (d,2H) , 8.61 (s,1H,triazole) , 3.52-3.56 (t,2H) , 2.41-2.55 (quintet ,2H) . MS: m/e 330 (M+1) .

Synthesis of 1,3-bis(4-p-tolyl-1H-1,2,3-triazol-1yl)propane (4b): yellow solid ,Yield = 52 % ; M.P. = 135-137℃ ; IR (cm^{-1}) : 2950 , 1628 , 1588 , 1430 , 1265 , 1233 , 797 ; [1]H NMR (300 MHz, CDCl, δ ppm) : 7.43-7.46 (d,2H),7.83-7.84 (d,2H) , 8.61 (s,1H,triazole) , 3.52-3.56 (t,2H) , 2.41-2.55 (quintet ,2H),2.56 (s,3H).

Synthesis of (1, 1'- (propane-1, 3-diyl) bis (1H-1, 2, 3-triazol-4,1diyl) dimethanol (4c): white solid ,Yield = 75 % ; M.P. = 140-142℃ ; IR (cm^{-1}) : 3648 , 2922 , 1617, 1588 , 1430 ,1265 , 1233 , 797 [1]; H NMR (300 MHz, $CDCl_3$, δ ppm) : 3.35 (s,1H) , 5.34 (s,2H) , 8.14 (s,1H ,triazole) , 4.36-4.43 (t,2H) , 2.41-2.53 (quintet ,2H)

Synthesis of 1, 3 –bis (4-bromomethyl)-1H-1, 2, 3-triazol-1yl) propane (4d): brown solid ,Yield = 69 % ; M.P. = 142-144℃ ; IR (cm^{-1}) : 2988 , 1655 , 1578 , 1430 ,1235 , 1273 , 707 ; 1H NMR (300 MHz, $CDCl_3$, δ ppm) : 5.68 (s,2H) , 8.18 (s,1H, triazole) , 4.45-4.49 (t,2H) , 3.33-3.43 (quintet, 2H) .

Synthesis of 1,3-bis (4-(4-bromobenzyl)methyl) 1H-1,2,3-triazol-1-yl) propane (4e): yellow solid , Yield = 76% ; m.p.= 150-152 ℃ ; IR (cm^{-1}) : 2938 , 1622 , 1588 , 1430 , 1265 , 1233 , 797 1H NMR (300 MHz, $CDCl_3$, δ ppm) : 8.21-8.23 (d,2H) , 7.25-7.28 (d,1H) , 5.32 (s,2H) , 8.31 (s,1H, triazole) , 4.41-4.45 (t,2H) , 2.37-2.43 (quintet ,2H) , 4.62 (s,2H).

Synthesis of 1,3-bis(4-(phenylmethyl) 1H-1,2,3-triazol-1-yl)propane (4f): white solid , Yield = 78 % , M.P. = 150-152 ℃ ; IR (cm^{-1}) : 2988 , 1632 , 1578 , 1450 ,1265 , 1233 , 867 1H NMR (300 MHz, CDCl,δ ppm) : 7.31-7.33 (d,1H) ,7.43-7.46 (t,2H) ,7.83-7.85 (d,2H) , 5.16(s.2H) , 8.16 (s,1H,triazole) , 4.37-4.40 (t,2H) , 2.40-2.45 (quintet ,2H).

In vitro antibacterial Activity

The compounds were dissolved in dimethyl sulfoxide (DMSO) with required concentrations for bioassay. Antibacterial activity was evaluated by screening of the compounds by standard method i.e. agar cup plate[22] method against a panel of human pathogenic microorganisms, Staph.aureus , Stap.epidermidis , Certia , Pseudomonas and Bacillius were used for the antibacterial assay, The commercial antibiotics such as penicillin in DMSO served as reference standards to compare inhibition of growth. The plate containing bacterial organism were incubated at 370C for 48h. The zone of inhibition was calculated by measuring the diameter of zone of inhibition for bacterial and fungal growth around the well or cup.

Carcinogenicity study

The E.coli AB 1157, a wild-type strain, proficient to repair damage in the DNA is considered for this study [23]. Initially, the stock culture of bacteria was revived by inoculating in broth medium and grown at 37ºC for 18 hrs. The LB agar plates were prepared and wells were made in the solidified LB agar plate. Each plate was inoculated with 18 hrs , old cultures (100 µl, 10-4 cfu) and spread evenly on the plate. After 20 min, the wells were filled with compound at different concentrations. Standard compound plate was also prepared in the same manner. All the plates were incubated at 37?C for 24 hrs and the diameter of inhibition zone were noted. Media Used: Tryptone-10 g, NaCl-10g and yeast extract 5g, agar 20g in 1000 ml of distilled water .

RESULTS AND DISCUSSION

Chemistry

1,3 dibromopropane 1 reacted with sodium azide 2 and substituted alkynes 3a-i in DMF : H_2O at RT to give bistriazoles 4a-I ,as shown (Scheme 1) .Which was confermed by 1H NMR ,IR and Mass spectroscopy.

Antibacterial activity and carcinogenicity study

All the synthesized compounds (4a-i) were evaluated for antimicrobial activity and carcinogenicity study , against various bacterial strains such as S.aureus, stap.epidermidis , certia , pseudomonas and bacillus . Antibacterial activity was determined by measuring the diameter of inhibition zone. Antibacterial activity of each compound was compared with Penicillin as standard drug and the results are summarized in (Table 1).Against certia 30(10) and 29(10) staph.Aureus 18 (25) , stap.ephidermidis 29(10) and Bacillus 29(10) the maximum zone of inhibition of compounds 4a,4c,4d and 4f comparison with standard Penicillin antibacterial drug.

In carcinogenicity study of 1, 2, 3-bistriazoles , except 4e (only at 1mg and 2mg concentrations) none of the compounds showed MIC in the concentrations tested suggests that these compounds do not exhibit any deleterious

effect or toxicity to the bacterial cell in this study. Stannous chloride, a toxic chemical which induces free radicals, showed an MIC of 0.25 mg, result shown in Table 2.

Table No.1 Antibacterial activity of 1,2,3-bistriazoles (4a-I)

Sr.No.	Comp. Code	*Staph.aureus*	*Stap.epidermidis*	*Certia*	*Pseudomonas*	*Bacillius*
1	4a	14(10)	10(10)	**30(10)**	-	12(10)
2	4b	10(10)	-	18(10)	13(10)	10(10)
3	4c	12(10)	13(10)	**29(10)**	-	**29(10)**
4	4d	-	**29(10)**	12(15)	-	-
5	4e	-	-	12 (15)	12(15)	-
6	4f	**18(25)**	-	22(25)	-	12(25)
Penicillin		17(10)	25(10)	25(10)	15(10)	20(10)

a. Bold values indicate better results.
b. (-) not found results

Table No.2 Carcinogenicity for 1, 2, 3-bistriazoles (4a-I)

	E. coli AB 1157					
	Zone of Inhibition (mm)					**MIC**
compounds code No.	**0.125mg**	**0.25mg**	**0.5mg**	**1.0mg**	**2.0mg**	**mg**
4a	0	0	0	0	0	1.0
4b	0	0	0	0	0	>2.0
4c	0	0	0	0	0	>2.0
4d	0	0	0	0	0	>2.0
4e	0	0	0	**2**	**5**	>2.0
4f	0	0	0	0	0	>2.0
Stannous chloride	0	2	6	9	11	0.25

CONCLUSION

We have conclusion, 1, 2, 3-bistriazoles also tested against the maximum zone of inhibition of compounds 4a certia 30(10) good antibacterial activity , Among the listed compounds 4c , 4d and 4f moderate antibacterial activity comparison with standard penicillin antibacterial drugs results shown in Table 1. Carcinogenicity study, Among the results 4a , 4b , 4c , 4d and 4f derivatives except 4e as shown in Table 2 were found non toxic. The importance of such work lies in the possibility that the new compounds might be more efficacious drugs against bacteria activity and Carcinogenicity study which could be helpful in designing more potent antibacterial and antitoxic agents for therapeutic use.

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