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New Novel Approaches for the Synthesis of Thiazole- Triazole Hybrids Together with Their Antimicrobial Evaluations

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ABSTRACT: A simple and efficient one-pot, two step method has been developed for the synthesis of thiazole-triazole hybrids (4a–l) using Cu-HAP as a heterogeneous catalyst for azide-alkyne [3+2] cycloaddition. The reaction, with this catalyst was carried out under mild reaction conditions with good to excellent yields (81–92%). The catalyst can be recycled very easily and reused for at least 4 runs without substantial loss in activity, which makes this methodology environmentally benign. Structures of the newly synthesized compounds were elucidated by FT-IR, ¹H NMR, ¹³C NMR and ESI-MS spectral data. The newly synthesized compounds 4a–l were evaluated for their in vitro antibacterial activity against two gram-negative bacteria cell lines such as *Pseudomonas aeruginosa*, *Streptococcus Pyogenes* strains using well plate or disc diffusion method. All the compounds are exhibiting moderate to good activity. Among all the compounds, 4c, 4h exhibited good activity against *Pseudomonas aeruginosa* with 8.5, 7.5 µg/ml MIC values respectively. 4h exhibited good activity against *Streptococcus Pyogenes* with 8.5 µg/ml MIC value. The molecular interactions with FTSZ (cell division protein) of *Streptococcus Pyogenes* were also supported by molecular docking simulations.

INTRODUCTION

Bacterial diseases are potential risk to human health and these bacterial diseases so far have not been defeat (Castillo et al., 2011). In the world populations more than one-third are infected by bacterial pathogens and nearly two million people die from bacterial infections per year (Monaghan et al., 2006). Therefore, there is an urgent require for synthesis of new antibacterial agents. Amongst the five membered heterocyclic compounds, nitrogen-containing thiazoles and triazoles are very important class of heterocyclic compounds (Marson et al., 2013; Mhaske et al., 2011), which are well known for their broad spectrum of remarkable biological and pharmaceutical activities (Messery et al., 2012; Zitouni et al., 2004; Hay et al., 2010;

Cheng et al., 2013). 1,3- Thiazoles are the heterocyclic compounds with low toxicity to mammals and a broad-spectrum of biological activities including insecticidal (Liu et al., 2004), antifungal (Jalilian et al., 2000; Vengurlekar et al., 2014), herbicidal (Wang et al., 2010; Dai et al., 2014), regulating plant growth (Qin et al., 2010; Yu et al., 2007), and antiviral activities (Mayhoub et al., 2011). Many thiazole derivatives such as thiamethoxam (Maienfisch et al., 2001), imidaclothiz, thiabendazole (Lee et al., 2011), and benthiavalicbisopropyl (Feng, 2008) had been commercialized as agrochemicals.

Thiazole containing molecules such as sulfathiazole is used as an antimicrobial drug, ritonavir as anti retroviral drug, abafungin as antifungal drug, bleomycine and thiazofurin as antineoplastic drugs (Metzger, 1979; Quiroga et al., 2002). Thiazoles containing antimicrobial agents are depicted in **Figure 1** (Desai et al., 2012; Nikhil et al., 2014; Desai et al., 2013).



Fig 1: Thiazole containing antimicrobial agents [3-5]

Likewise, compounds containing a 1,2,3-triazole nucleus show various biological activities such as anti HIV-type I protease (Da Silva et al., 2009), antimicrobial (Genin et al., 2000), antiallergic (Buckle et al., 1984), antihyperglycemic (Alexacou et al., 2008) and adrenergic receptor agonists (Brockunier et al., 2000). In addition, they are commercially used as photostabilizers and dyes (Willis et al., 1991), anticorrosive agents (Morgan, 1991) and agrochemicals (Fan, 1996). 1,2,3 triazole containing antimicrobial agents are depicted in **Figure 2** (Rahul et al., 2015; Rama et al., 2016; Narsimha et al., 2016; Ranjith kumar et al., 2015).

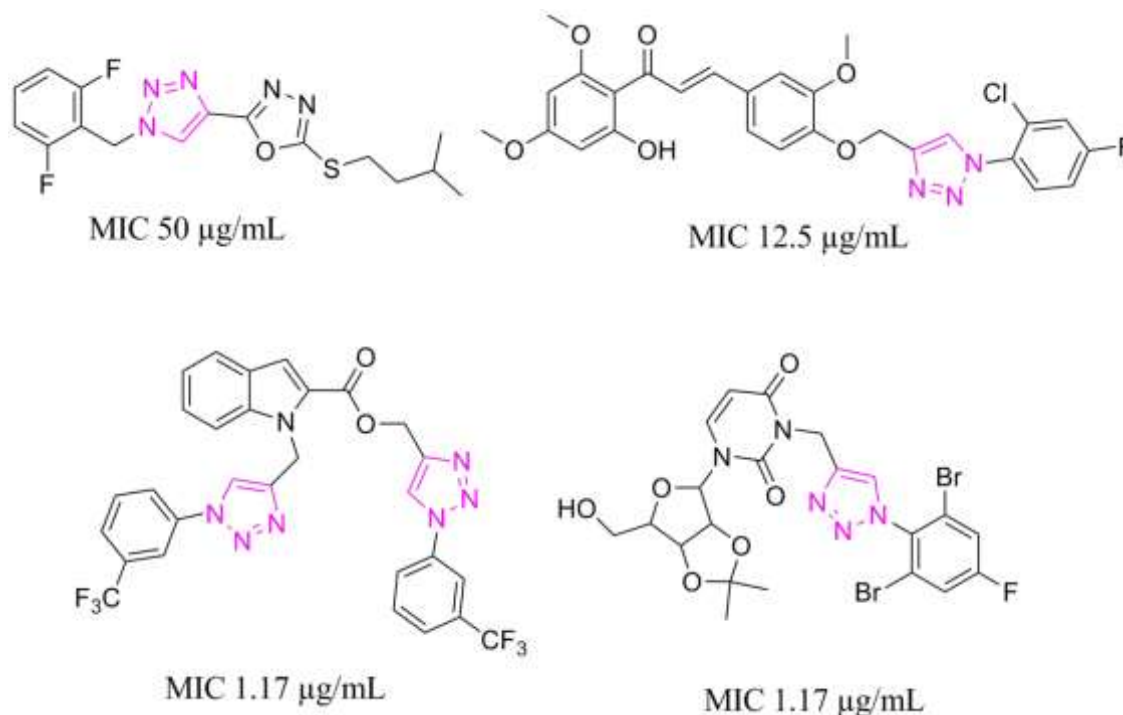


Fig 2: 1,2,3-triazole containing antimicrobial agents [6-9]

Heterogeneous catalysis in synthesis of various organic moieties has attracted the attention of organic chemists because of their synthetic utility (Hiddeh, 1995), easy isolation of product, recovery and reusability of the catalyst, non-corrosiveness and tolerance of extreme operating conditions which makes them environmentally friendly. Generally hydroxyapatites (HAP) supported transition metals, such as ruthenium, palladium, copper, and silver, have been applied as heterogeneous catalysts due to the peculiar acid–base properties of their surfaces (Gruselle et al., 2011) and for environmentally benign organic syntheses (Kaneda et al., 2004; Mori et al., 2004). An ion exchanged HAP-supported copper(II) (Cu-HAP), prepared from calcium hydroxyapatite $[\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2]$ and $\text{Cu}(\text{OAc})_2$ in water, has been applied only as a heterogeneous catalyst to the three-component coupling of amines, aldehydes and alkynes in refluxing acetonitrile (Choudary et al., 2004).

One-pot methodologies for organic synthesis have attracted chemists' and pharmacists' interest from industries and academia, because these procedures allow reaching the target compounds without isolation of synthetic intermediates (Perin et al., 2005; Bonaccorso et al., 2005). In addition, one-pot reactions also reduce the use of solvents, reagents and adsorbents commonly

employed for purifying the intermediates, being considered green protocols (Ricardo et al., 2009). Therefore, we have focused our attention in developing a clean one-pot two step protocol which allows the synthesis of triazole-triazole hybrids in good yields with less work-up and avoids side product formation.

In search of new bio-active molecule, molecular hybrid-based approaches had gained more attention by researchers to discover some more potent antimicrobial agents (Taha et al., 2015; Zawawi et al., 2016; Taha et al., 2015), which containing two or more bioactive pharmacophores. Based on these things mentioned above, and in an attempt to find new potent antimicrobial agents; we designed and synthesized a series of novel thiazole-triazole derivatives **4a-l**. The synthesized derivatives were screened for their antimicrobial activity in *in vitro* modes. In the present article, we report a novel one pot two step methodology for the regioselective synthesis of thiazole-triazole hybrids from 2-bromo-4-methylthiazole-5-carboxylic acid using ethyl chloroformate as a coupling agent for ester formation, followed by 1,3-dipolar cycloaddition using reusable Cu-HAP as efficient catalyst in DMF/H₂O (1:1) solvent system and the resulting analogues were also screened for anti microbial activity in two different strains.

MATERIAL AND METHODS

Chemistry

All the reagents and solvents were reagent grade and were used without further purification. Column chromatography was performed using Merck silica gel, 60–120 mesh. ¹H NMR spectra were recorded on a Bruker spectrometer at 400 MHz, ¹³C NMR spectra were obtained on 100 MHz with tetramethylsilane as the internal standard, and the chemical shifts (δ) are reported in ppm. The mass spectral analysis was accomplished using electro spray ionization (ESI) technique. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer.

Biology

Bacterial culture

Synthesized compounds have been assayed for their antimicrobial activity against different species of bacteria was used as test microorganisms. The entire organisms were collected from Dept. of Microbiology, Osmania University, Hyderabad. Two bacterial strains *Pseudomonas aeruginosa*, *Streptococcus Pyogenes* were used in our study. Microbial cultures were preserved at -20 °C in microcentrifuge tube having 40% sterile glycerol.

Preparation of inocula

The two test strains were freshly cultured in their respective broth media at 37 °C using 200 rpm until mid-log phase to obtain 120 reading on the spectrophotometer. A working stock of the cell suspension (1×10⁷ colony forming units/mL) was prepared by centrifugation (10,000×g for 15 min) and resuspension in 1×PBS (0.01 M), pH 7.4 (Sigma, St. Louis, MO, USA). The cells were monodispersed by repeated passaging through 26 Gauge BD syringe needle (Becton Dickinson & Co., Franklin Lakes, NJ, USA), and the cell suspensions stored at 4 °C till use. The cell viability of the working stock was verified based on standard plate count method using the respective agar media.

Anti Bacterial Activity

Synthetic compounds were tested against the strains for their inhibitory activity by well plate or disc diffusion method. Nutrient broth used for inoculum preparation and Muller-Hinton agar media have been used for screening the antimicrobial activity. The wells were created in Mueller Hinton solid agar medium with well puncture10, Trypton soy agar or Nutrient agar. The media has been pre-inoculated with test organisms. The standard inoculum size is of 1-2 x 10⁸ CFU/ml of bacteria for inoculating diffusion plates which is equal to McFarland 0.5 turbidity standard. After that all the test compounds were inoculated into the wells and plates incubated at 37°C for 24 hrs. Each test was carried out in triplicate with controls. Microbial growth was determined by measuring the diameter zone of inhibition with the help of scale.

Minimum Inhibitory Concentration (MIC)

The minimum inhibitory concentration was determined using the tube dilution techniques (Nishina et al., 1987; Niti et al., 2012). Varying concentrations each compound have been prepared using single dilution method. A 9 ml of the nutrient broth

was pipetted into the various test tubes and sterilized at 121°C for 15 minutes. Each tube was inoculated with an overnight standard inoculum size is of $1-2 \times 10^8$ CFU/ml of *Pseudomonas aeruginosa*, and *Streptococcus Pyogenes*, which is equal to McFarland 0.5 turbidity standard and then transferred into the test tube containing the compounds. The test tubes were incubated at 37°C for 24 hours. The MIC was determined by the broth micro dilution method using 96-well micro-plates (Saini et al., 2005; Bhuiyan et al., 2011). The inoculate of the microbial strains was prepared from 24 h broth cultures and suspensions were adjusted to 0.5 McFarland standard turbidity. Each sample (1.0 mg) was dissolved in DMSO (1 mL) to obtain 1000 µg/mL stock solution. A number of wells were reserved in each plate for positive and negative controls. Sterile broth (100 µL) was added to the well from row B to H. The stock solutions of samples (100 µL) were added to the wells in rows A and B. Then, the mixture of samples and sterile broth (100 µL) in row B was transferred to each well in order to obtain a tenfold serial dilution of the stock samples (concentration of 1 to 100 µg/mL). The inoculums (100 µL) were added to each well and a final volume 200 µL was obtained in each well. Ciprofloxacin, Gentamicin were used as positive controls. Plates were incubated at 37°C for 24 h. Microbial growth was indicated by the presence of turbidity and a pellet at the bottom of the well as shown in.

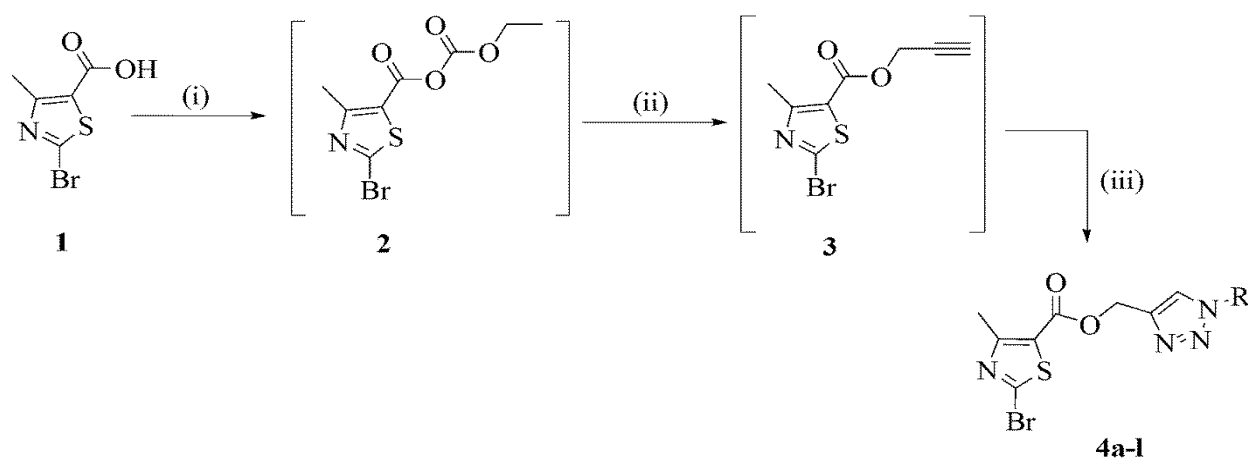
In silico Molecular docking studies

All the docking calculations were performed using Schrödinger suite 2015. 3D crystal coordinates for cell division protein (FTSZ) of *Streptococcus Pyogenes* was retrieved from protein data bank (PDB ID: 2VAW) Synthesized molecules were sketched, converted to 3D using Ligprep and protein was prepared for docking using PPrep (protein preparation wizard), which removes waters, adds missing amino acids, hydrogens and minimizes using OPLS-2005 force field. Docking was performed using Glide extra precision mode.

RESULTS AND DISCUSSION

Chemistry

The synthesis of the titled compounds (**4a-l**) was carried out as presented in **Scheme 1**. Initially, the reaction of 2-bromo-4-methylthiazole-5-carboxylic acid (**1**) was stirred in the presence of TEA in CH_2Cl_2 for 30 min, ethyl chloroformate was added to generate *in situ* the mixed unhydrate 2-bromo-4-methylthiazole-5-carboxylic (ethyl carbonic) anhydride (**2**). Then the propargyl alcohol was added to the same solution followed by stirring for an additional 2 h. The reaction between **2** and propargyl alcohol forms prop-2-yn-1-yl 2-bromo-4-methylthiazole-5-carboxylate (**3**) with the liberation of CO_2 and EtOH. Although the intermediate **3** can be isolated and characterized, we avoided their isolation in many cases. In fact, after obtaining the compound **3**, DCM was removed from reaction mixture, and then added DMF/ H_2O (1:1), azide and Cu-HAP catalyst in order to get the title compounds (1-aryl/alkyl-1H-1,2,3-triazol-4-yl)methyl 2-bromo-4-methylthiazole-5-carboxylates (**4a-l**) (**Table 1**).



Scheme 1: Synthesis of (1-aryl/alkyl-1H-1,2,3-triazol-4-yl)methyl 2-bromo-4-methylthiazole-5-carboxylates **4(a-l)**

Reaction conditions: (i) Ethyl chloroformate (1 mmol), TEA (1.5 mmol), DCM, rt, 1h; (ii) Propargyl alcohol (1.2 mmol), TEA (1 mmol), DCM, 0 °C, 3h; (iii) aryl/ alkyl azides (1.1 mmol), Cu-HAP (20 mol%), DMF, 90 °C, 1h.

Table 1 Synthesis of thiazole-triazole hybrids **4** (a-l)

Entry	R	Product	Time	Yield
1	-Ph	4a	3	88
2	-4-CH ₃ -Ph	4b	3	90
3	-4- OCH ₃ -Ph	4c	5	91
4	-4-Cl-Ph	4d	3	86
5	-4- NO ₂ -Ph	4e	3	82
6	-3-Cl-Ph	4f	4	84
7	-3-NO ₂ -Ph	4g	4	81
8	-4-OCH ₃ , 2-NO ₂ -Ph	4h	4	84
9	-n-hexyl	4i	4	85
10	-n-octyl	4j	3	82
11	-acetyl morpholine-	4k	3	78
12	-4-NO ₂ -benzyl	4l	3	83

Although, We studied the effect of the amount of Cu-HAP in [3+2] dipolar cycloaddition between prop-2-yn-1-yl 2-bromo-4-methylthiazole-5-carboxylate (**3**) and pheny azide as model reaction. As shown in Table 2, the best results were achieved with 20 mol % of Cu-HAP (**Table 2**, entry 2); on further increasing the amount of Cu-HAP (40 mol %) the yield of the reaction was almost unaffected (Table 2, entries 3). The yield decreased when the amount of catalyst was reduced to 10 mol %, and prolonging the reaction temperature did not improve the yield (**Table 2**, entries 4 & 5).

Table 2: Screening of Cu-HAP as catalyst on alkyne-azide [3+2] cycloaddition

S.No	Catalyst	mmol	Solvent	Temp(°C)	Time(h)	Yield (%)
1	Cu-HAP	0.1	DMF/H ₂ O (1:1)	90	3	66
2	Cu-HAP	0.2	DMF/H ₂ O (1:1)	90	3	92
3	Cu-HAP	0.4	DMF/H ₂ O (1:1)	90	3	83
4	Cu-HAP	0.2	DMF/H ₂ O (1:1)	110	3	82
5	Cu-HAP	0.2	DMF/H ₂ O (1:1)	60	3	72

In order to make our catalytic system greener and economical, we focused on reusability of catalyst, [3+2] cycloaddition of prop-2-yn-1-yl 2-bromo-4-methylthiazole-5-carboxylate (**3**) and azide was demonstrated under almost the same conditions as those of the typical procedure in DMF/H₂O (Table 2, entry 2), as shown in **Table 2**. Cu-HAP was recovered quantitatively by simple filtration and reused, and gave significant activity even after the fourth cycle (**Table 3**, entry 1-4). It is important to note that the catalyst was successfully reused four times in DMF medium with no further purification and activation.

Table 3: The reusability of Cu-HAP in [3+2] cycloaddition of azide and alkyne

S.No.	Cu-HAP	Yield (%)
1	1 st time	92
2	2 nd time	86
3	3 rd time	80
4	4 th time	73

ANTIBACTERIAL ACTIVITY

The synthesized compounds **4a-l** evaluated for their in vitro antibacterial activity against two gram-negative bacteria cell lines such as *Pseudomonas aeruginosa*, *Streptococcus Pyogenes* strains using standard techniques. Zone of inhibition in mm of all the synthesized compounds were measured using disc diffusion method (**Table 4**). Minimum inhibitory concentration (MIC) is defined as the concentration of the compound required to give complete inhibition of bacterial growth, and MICs of **4a-l** along with ciprofloxacin and gentamicin for comparison, are listed in **Table 5**. These data suggest that most of the target compounds **4a-l** have considerable potency against Gram-negative strains, although they are generally less active than the two reference drugs against the Gram-negative strains (**Fig 3**).

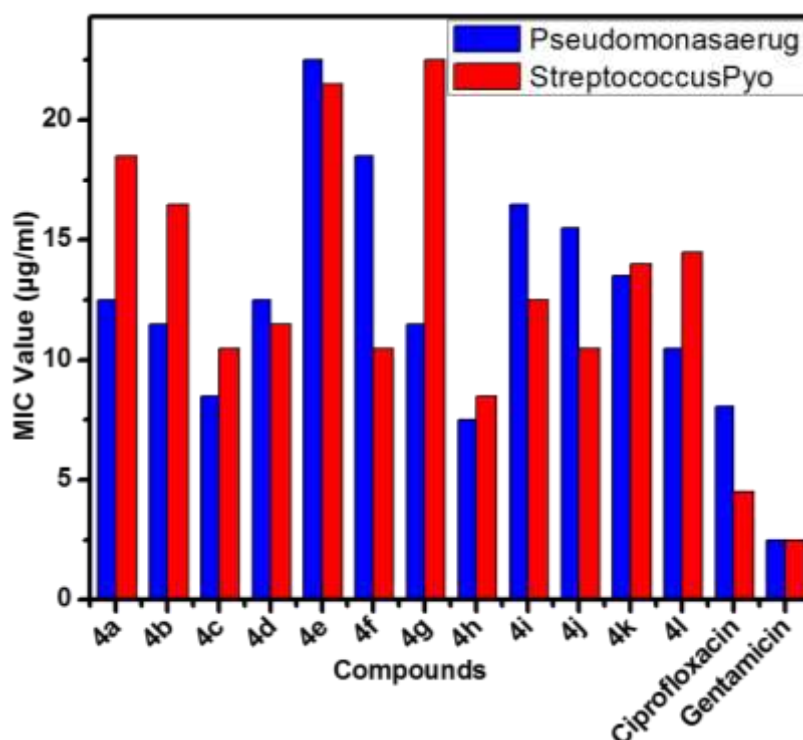


Fig 3: Antimicrobial activity of **4a-l**

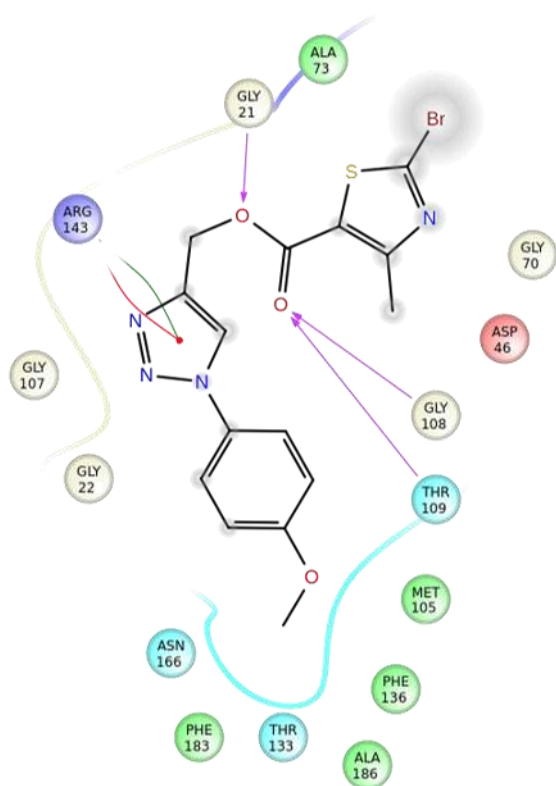
All the compounds are exhibiting moderate to good activity. Among all the compounds, Compound **4h** exhibited potent activity against *Pseudomonas aeruginosa* with 7.5 µg/ml MIC value and compound **4c** showed good activity against *Pseudomonas aeruginosa* with 8.5 µg/ml MIC value. **4h** showed comparable activity against *Streptococcus Pyogenes* with 8.5 µg/ml. Phenyl containing substrate **4a** showed moderate activity against two cell lines. Compare with **4a**, electron donating groups like methyl, methoxy, chloro containing analogues **4b**, **4c**, **4d** exhibiting better activity against tested cell lines. *p*-Cl containing derivative (**4d**, 12.5µg/ml) is better active than *m*-Cl derivative (**4f**, 18.5µg/ml) against *Pseudomonas aeruginosa*. *p*-NO₂ benzyl derivative (**4l**) showed good activity than *p*-NO₂ phenyl derivative (**4e**) against two bacterial strains. Interestingly observe that the effect of length of alkyl chain on antibacterial activity. *n*-octyl derivative (**4j**) showed good activity than *n*-hexyl derivative (**4i**) against two bacterial strains. Morpholine derivative (**4k**) exhibiting moderate activity against tested two cell lines. Electron donating (methoxy) and withdrawing (nitro) containing derivative (**4h**) is potent than ciprofloxacin against *Pseudomonas aeruginosa* and exhibited good activity than all other synthesized analogues against *Streptococcus Pyogenes*. Synthesized hybrid analogues **4c**, **4h** are exhibiting better activity than single compounds like **1** and **3** against *Pseudomonas aeruginosa*, *Streptococcus Pyogenes*. Structure activity relationship (SAR) studies from the results of the antibacterial activity revealed that the effect of length of alkyl chain, electron donating and withdrawing groups presence. These results suggest that introducing of electron donating and withdrawing groups compact in one derivative could increase antibacterial activity. This result indicated that aliphatic, aromatic and location of the substituent also had an influence on the antibacterial activity.

Table 5: In vitro antibacterial activity of compounds **4 (a-l)**

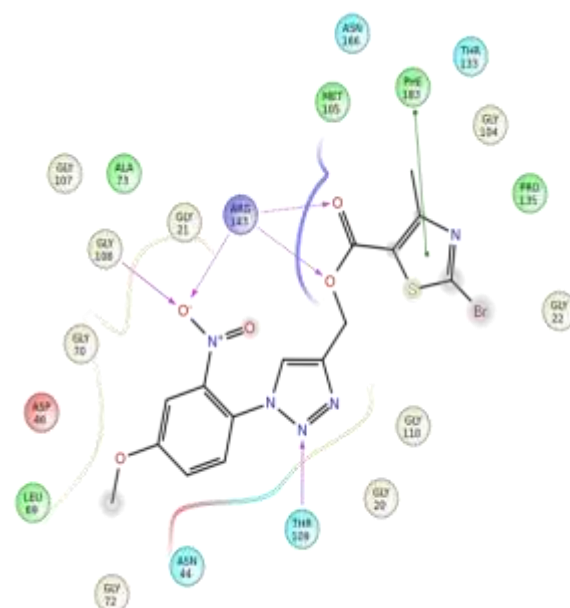
S.No	Entry	MIC Value ($\mu\text{g/ml}$)		Docking Score
		<i>Pseudomonas aeruginosa</i>	<i>Streptococcus Pyogenes</i>	
1	4a	12.5	18.5	-3.354
2	4b	11.5	16.5	-2.497
3	4c	8.5	10.5	-4.771
4	4d	12.5	11.5	-2.499
5	4e	22.5	21.5	-2.684
6	4f	18.5	10.5	-3.747
7	4g	11.5	22.5	-3.346
8	4h	7.5	8.5	-3.484
9	4i	16.5	12.5	-0.29
10	4j	15.5	10.5	-4.68
11	4k	13.5	14	-3.753
12	4l	10.5	14.5	-5.028
13	1	10.25	11.45	
14	3	13.15	9.75	
	Ciprofloxacin	8.08	4.5	
	Gentamicin	2.5	2.5	
	GDP			-9.313

Molecular docking simulations

Molecular docking simulation study to understand the interaction of **4c** and **4h** with the cell division protein FTSZ of *Streptococcus Pyogenes* indicated hydrogen bond interactions with back bone of Gly108, Thr109 and Arg 143 played key role with the docking score of -4.771 and -3.484 respectively whereas standard GDP showed similar interactions with docking score of -9.313. Compound **4h** showed pi-pi stacking with Phe183. Both the compounds showed strong hydrophobic interactions with Met105, Phe136, Ala73 and Phe183 which are in comparison to standard GDP. Docking pose and interacting amino acids within 5 Å⁰ distances are shown in **Fig 4**.



4c



4h

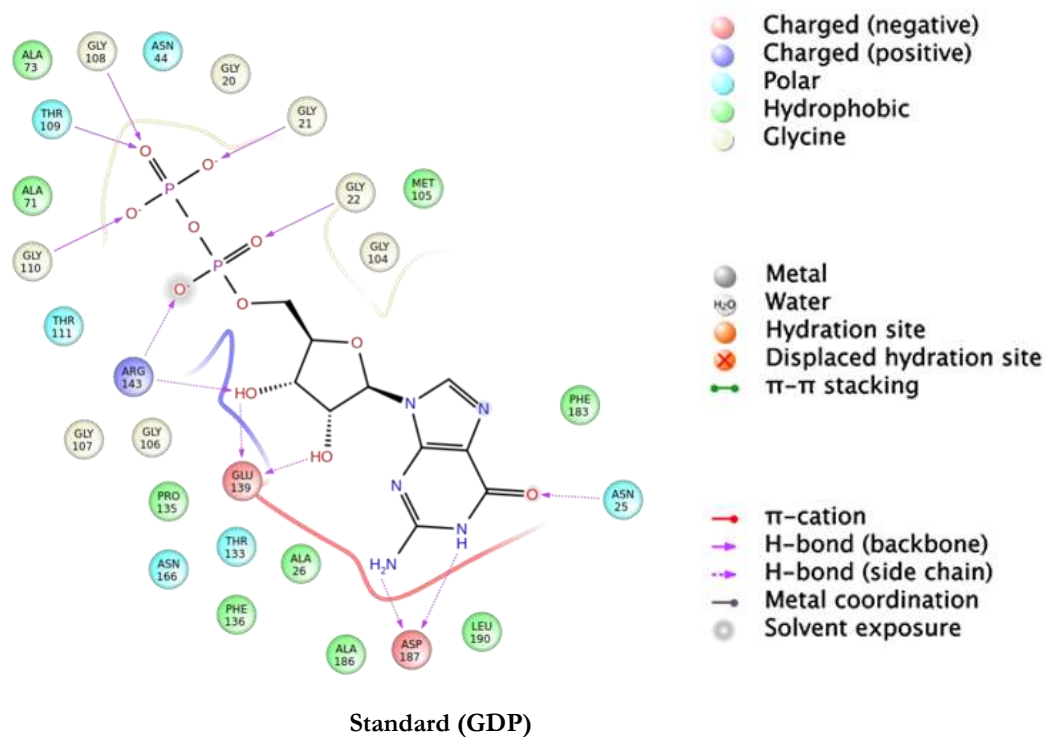


Fig 4: Docking pose and amino acids interaction

CONCLUSION

In summary, we have developed an alternate new method to synthesize thiazole-triazole hybrids from 2-bromo-4-methylthiazole-5-carboxylic acid, propargyl alcohol and aryl/alkyl azides using ethyl chloroformate as a coupling agent and Cu-HAP as heterogeneous and reusable catalyst for [3+2] cycloaddition. The desired thiazole-triazole hybrids **4a-l** has been obtained in excellent yields after simple work-up. Synthesized analogues were evaluated antibacterial activity against gram negative bacterial strains such as *Pseudomonas aeruginosa*, *Streptococcus Pyogenes*. **4c**, **4h** exhibited good activity against *Pseudomonas aeruginosa* with MIC 8.5, 7.5 µg/ml respectively. **4h** exhibited good activity against *Streptococcus Pyogenes* with MIC 8.5 µg/ml. These results verify that the thiazole-triazole hybrid aromatic analogues are promising bactericide candidates for treating gram negative bacteria.

EXPERIMENTAL SECTION

Chemistry

One pot two step procedure for the synthesis of (1-aryl/alkyl-1H-1,2,3-triazol-4-yl)methyl 2-bromo-4-methylthiazole-5-carboxylates (**4a-l**)

2-bromo-4-methylthiazole-5-carboxylic acid (**1**) (1.6 mmol) was dissolved in dry CH₂Cl₂ (8.0 mL) and placed in a round bottom flask followed by the addition of TEA (0.33g, 2.4 mmol) under stirring and kept as such for 30 min at room temperature. Later, ethyl chloroformate (0.2 mL, 2.4 mmol) was added to the same flask and stirred for an additional 30 min. Finally, the addition of propargyl alcohol (1.6 mmol) with continuous agitation for 2 h completed the reaction. Filtration and solvent evaporation under reduced pressure furnished the crude product (**3**). Then the solution of crude product **3** in DMF/H₂O (1:1) was added aryl or alkyl azides (1 mmol), 20 mol% of Cu-HAP. The reaction mixture was stirred at 90 °C until the starting material was consumed as judged by TLC analysis. Then the mixture was cooled to room temperature, the catalyst was filtered and the filtrate was diluted with ice cold water. The precipitate was filtered, washed with icecold water and dried, to gave (1-aryl/alkyl-1H-1,2,3-triazol-4-yl)methyl 2-bromo-4-methylthiazole-5-carboxylates (**4a-l**) as light brown solids with 80-92% of yields.

(1-phenyl-1H-1,2,3-triazol-4-yl)methyl-2-bromo-4-methylthiazole-5-carboxylate (**4a**): Yield 88%, mp 194-198 °C. IR (KBr): 1703 (C=O). ¹H NMR (CDCl₃, 400 MHz): δ 8.13 (s, 1H), 7.74 (d, *J* = 7.7 Hz, 2H), 7.54 - 7.46 (m, 3H), 5.51 (s, 2H), 2.70 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 160.8, 159.9, 155.1, 140.2, 136.8, 129.8, 129.0, 123.3, 122.4, 120.6, 58.3, 17.4. ESI-MS: *m/z* 379 [M+H]⁺. Found, %: C 44.31, H 2.96, N 14.72. C₁₄H₁₁BrN₄O₂S. Calculated, %: C 44.34, H 2.92, N 14.77.

(1-(*p*-tolyl)-1H-1,2,3-triazol-4-yl)methyl-2-bromo-4-methylthiazole-5-carboxylate (**4b**): Yield 90%, mp 186-189 °C. IR (KBr): 1699 (C=O). ¹H NMR (CDCl₃, 400 MHz): δ 8.04 (s, 1H), 7.81 - 7.76 (m, 2H), 7.50 - 7.34 (m, 2H), 5.40 (s, 2H), 2.59 (s, 3H), 2.36 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 160.6, 159.1, 155.0, 140.6, 138.4, 135.2, 133.3, 131.8, 128.6, 120.8, 58.1, 29.3, 16.8. ESI-MS: *m/z* 393 [M+H]⁺. Found, %: C 45.78, H 3.30, N 14.29. C₁₅H₁₃BrN₄O₂S. Calculated, %: C 45.81, H 3.33, N 14.25.

(1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl-2-bromo-4-methylthiazole-5-carboxylate (**4c**): Yield 91%, mp 149-151 °C. IR (KBr): 1719 (C=O). ¹H NMR (CDCl₃, 400 MHz): δ 8.08 (s, 1H), 7.82 (d, *J* = 7.7 Hz, 2H), 7.38 - 7.46 (m, 2H), 5.44 (s, 2H), 4.32 (s, 3H), 2.58 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 161.1, 159.2, 158.9, 155.4, 138.2, 136.8, 129.3, 122.1, 120.9, 118.3, 58.0, 54.9, 16.8. ESI-MS: *m/z* 409 [M+H]⁺. Found, %: C 44.01, H 3.15, N 13.72. C₁₅H₁₃BrN₄O₃S. Calculated, %: C 44.02, H 3.20, N 13.69.

(1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl-2-bromo-4-methylthiazole-5-carboxylate (**4d**): Yield 86%, mp 166-168 °C. IR (KBr): 1714 (C=O). ¹H NMR (CDCl₃, 400 MHz): δ 8.03 (s, 1H), 7.74 - 7.55 (m, 2H), 7.51 - 7.38 (m, 2H), 5.42 (s, 2H), 2.62 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 160.0, 159.8, 158.9, 154.2, 139.3, 134.2, 133.8, 129.0, 121.3, 120.7, 57.2, 16.4, 16.3. ESI-MS: *m/z* 413 [M+H]⁺. Found, %: C 40.62, H 2.49, N 13.55. C₁₄H₁₀BrClN₄O₂S. Calculated, %: C 40.65, H 2.44, N 13.54.

(1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl-2-bromo-4-methylthiazole-5-carboxylate (**4e**): Yield 82%, mp 188-190 °C. IR (KBr): 1713 (C=O). ¹H NMR (CDCl₃, 400 MHz): δ 8.13 (s, 1H), 7.74 (d, *J* = 7.7 Hz, 2H), 7.54 (d, *J* = 7.6 Hz, 2H), 5.58 (s, 2H), 2.69 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 164.2, 161.8, 154.8, 140.9, 137.9, 132.8, 129.2, 123.4, 121.8, 120.1, 57.9, 17.3. ESI-MS: *m/z* 424 [M+H]⁺. Found, %: C 39.60, H 2.42, N 16.49. C₁₄H₁₀BrN₅O₄S. Calculated, %: C 39.64, H 2.38, N 16.51.

(1-(3-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl-2-bromo-4-methylthiazole-5-carboxylate (**4f**): Yield 84%, mp 163-165 °C. IR (KBr): 1723 (C=O). ¹H NMR (CDCl₃, 400 MHz): δ 8.06 (s, 1H), 7.78 - 7.62 (m, 3H), 7.75 - 7.49 (m, 1H), 5.49 (s, 2H), 2.56 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 161.9, 159.9, 154.3, 138.2, 136.4, 133.9, 132.8, 128.9, 128.3, 127.4, 123.9, 120.8, 59.4, 18.1. ESI-MS: *m/z* 413 [M+H]⁺. Found, %: C 40.59, H 2.41, N 13.58. C₁₄H₁₀BrClN₄O₂S. Calculated, %: C 40.65, H 2.44, N 13.54.

(1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl-2-bromo-4-methylthiazole-5-carboxylate (**4g**): Yield 81%, mp 177-179 °C. IR (KBr): 1716 (C=O). ¹H NMR (CDCl₃, 400 MHz): δ 8.14 (s, 1H), 7.87 - 7.75 (m, 3H), 7.64 - 7.58 (m, 1H), 5.52 (s, 2H), 2.58 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 163.8, 161.7, 154.3, 141.2, 138.6, 133.9, 132.6, 129.1, 128.8, 123.8, 121.6, 113.2, 61.2, 18.0. ESI-MS: m/z 424 [M+H]⁺. Found, %: C 39.61, H 2.44, N 16.48. C₁₄H₁₀BrN₅O₄S. Calculated, %: C 39.64, H 2.38, N 16.51.

(1-(4-methoxy-2-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl-2-bromo-4-methyl thiazole-5-carboxylate (**4h**): Yield 84%, mp 206-208 °C. IR (KBr): 1708 (C=O). ¹H NMR (CDCl₃, 400 MHz): δ 8.01 (s, 1H), 7.68 (s, 1H), 7.54-7.48 (m, 2H), 5.61 (s, 2H), 4.28 (s, 3H), 2.58 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 166.7, 162.8, 159.9, 154.3, 141.6, 138.7, 133.8, 130.2, 122.3, 121.8, 120.2, 112.6, 58.8, 54.3, 17.3. ESI-MS: m/z 454 [M+H]⁺. Found, %: C 39.60, H 2.62, N 15.39. C₁₅H₁₂BrN₅O₅S. Calculated, %: C 39.66, H 2.66, N 15.42.

(1-hexyl-1H-1,2,3-triazol-4-yl)methyl-2-bromo-4-methylthiazole-5-carboxylate (**4i**): Yield 85%, mp 96-98 °C. IR (KBr): 1711 (C=O). ¹H NMR (CDCl₃, 400 MHz): δ 7.66 (s, 1H), 5.36 (s, 2H), 4.37 (t, J = 5.8 Hz, 2H), 2.57 (s, 3H), 1.95 - 1.84 (m, 4H), 1.48 - 1.28 (m, 4H), 0.96 (t, J = 7.4 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 175.7, 162.2, 157.6, 142.7, 123.7, 113.1, 68.1, 57.9, 50.1, 32.2, 19.7, 17.6, 14.3, 13.4. ESI-MS: m/z 387 [M+H]⁺. Found, %: C 43.40, H 4.91 N 14.42. C₁₄H₁₉BrN₄O₂S. Calculated, %: C 43.42, H 4.94 N 14.47.

(1-octyl-1H-1,2,3-triazol-4-yl)methyl-2-bromo-4-methylthiazole-5-carboxylate (**4j**): Yield 82%, mp 115-118 °C. IR (KBr): 1722 (C=O). ¹H NMR (CDCl₃, 400 MHz): δ 7.72 (s, 1H), 5.41 (s, 2H), 4.35 (t, J = 5.5 Hz, 2H), 2.59 (s, 3H), 1.81- 1.75 (m, 2H), 1.15 - 1.33 (m, 10H), 0.85 (t, J = 7.0 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 174.8, 161.8, 157.1, 142.0, 123.9, 112.9, 67.7, 58.2, 49.8, 32.6, 19.8, 19.3, 18.3, 17.8, 14.6, 13.6. ESI-MS: m/z 415 [M+H]⁺. Found, %: C 46.22, H 5.66, N 13.44. C₁₆H₂₃BrN₄O₂S. Calculated, %: C 46.27, H 5.58, N 13.49.

(1-(2-morpholino-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl-2-bromo-4-methyl thiazole-5-carboxylate (**4k**): Yield 78%, mp 209-211 °C. IR (KBr): 1636 (C=O), 1704 (C=O). ¹H NMR (CDCl₃, 400 MHz): δ 7.85 (s, 1H), 5.38 (s, 2H), 5.24 (d, J = 7.2 Hz, 2H), 3.67 - 3.63 (m, 2H), 3.62 - 3.56 (m, 2H), 3.55 - 3.50 (m, 2H), 3.49 - 3.43 (m, 2H) 2.58 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 171.8, 163.4, 161.1, 143.5, 136.8, 133.4, 125.4, 66.6, 66.3, 65.9, 57.4, 47.9, 45.8, 17.7. ESI-MS: m/z 430 [M+H]⁺. Found, %: C 39.01, H 3.72, N 16.23. C₁₄H₁₆BrN₅O₄S. Calculated, %: C 39.08, H 3.75, N 16.28.

(1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl)methyl-2-bromo-4-methylthiazole-5-carboxylate (**4l**): Yield 83%, mp 154-157 °C. IR (KBr): 1728 (C=O). ¹H NMR (CDCl₃, 400 MHz): δ 8.25 (d, J = 8.78 Hz, 2H), 7.68 (s, 1H), 7.43 (d, J = 8.78 Hz, 2H), 5.66 (s, 2H), 5.41 (s, 2H), 2.67 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 163.9, 160.8, 155.6, 154.1, 139.2, 136.1, 129.1, 123.8, 122.6, 120.6, 58.8, 54.2, 18.1. ESI-MS: m/z 438 [M+H]⁺. Found, %: C 45.78, H 3.28, N 14.28. C₁₅H₁₃BrN₄O₂S. Calculated, %: C 45.81, H 3.33, N 14.25.

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