

## Synthesis and Antimicrobial Evaluation of Pegylated Thiazoles

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**Abstract:** Drug-polymer conjugation is a modest and competent approach to synthesizing new, effective, and potent antimicrobial agents to counter the problem of microbial resistance. In the present study, a PEGylated thiazoles were synthesized by using the PEGylation process. A series of PEGylated amino thiazoles were evaluated for antibacterial activity against the gram negative, gram positive bacterial strains i.e., *Escherichia coli* & *Staphylococcus aureus* respectively, using cup plate method. Among all PEGylated thiazoles, many derivatives exhibited significant microbial activity against bacterial strains. The newly synthesized compounds were characterized by elemental analysis, IR and <sup>1</sup>HNMR, <sup>13</sup>CMR and Mass spectral data.

**Keywords:** PEGylation, thiazoles, antibacterial activity.

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### I. Introduction

Small drugs encountered some common problems in ADME (absorption, distribution, metabolism and excretion) protocol. Their low solubility, rapid excretion and untargeted biodistribution made the drug's pharmacokinetic profile poor. Now a days, PEGylation is highly exploited for conferring a passive targeting to the affected sites by decelerating the drug clearance from the body, or simply refining the permeability and retention effect<sup>1</sup>. Altogether, these factors could be resolved by PEGylation. PEGylation facilitated the improved pharmacokinetics, targeting approach and efficacy of the drugs like taxol, camptothecin, *cis*-platinum and doxorubicin<sup>2</sup>. The conjugation chemistry for PEGylated small molecules experiences fewer problems because of the less number of functional groups present on a small molecule, loading of the polymer, the absence of conformational constraints and the easier steps for the workup of drug-polymer conjugates. To overcome these limitations, the researchers have developed new methods of loading polymer onto small molecules by implementing active functional groups which allows to increase of the drug-polymer loading<sup>3</sup>. To exploit the drug's activity, it has to be released at targeted site. This is a vital process in drug distribution phenomenon. The drug delivery vehicles like macromolecular prodrugs are usually act as conjugates. Recently, various methods involving conjugate chemistry have been established to release the drugs from the conjugate at specific site under controlled conditions by using special linkers or bonds between the polymer and the drug. Thus, polyethylene glycol (PEG) conjugation chemistry has been developed recently as a consequence of the potential therapeutic interest of PEGylated drugs. PEG has proven to be of great value as a functionalizing agent for imparting increased solubility and bioavailability. Increased targeting potential, circulation time and flexibility of surface-attached bio medically-relevant ligands on small druglike molecules enhances efficacy.

Azaheterocycles are versatile molecules, always being a choice of researchers to develop the pharmacophores having broad range of biological significance. The thiazole ring has been extensively studied and it forms a part of vitamin B<sub>1</sub>, and penicillin. Thiazole dyes contain the color radicals of -C=N- and -S=C= which impart colors to a compound. Some thiazole derivatives can find applications for making biologically active agents such as antiviral, antibacterial, antifungal, antitubercular and antibody agents. The thiazole ring structure occurs in such important biologically active natural products as thiamine (vitamin B<sub>1</sub>), bacitracin, penicillin, and in numerous synthetic drugs, dyes, and industrial chemicals. Due to the unique biological and pharmacological activity, thiazoles have attracted considerable attention. They exhibit, antibiotic<sup>4</sup>, anti-inflammatory<sup>5, 6</sup>, antitumor<sup>7</sup> and anti cancer<sup>8-10</sup> activities. Various substituted thiazoles have been examined for their antitubercular, antifungal and antibacterial activities<sup>11-18</sup>.

### II. Materials and methods

#### Materials and Instrumentations:

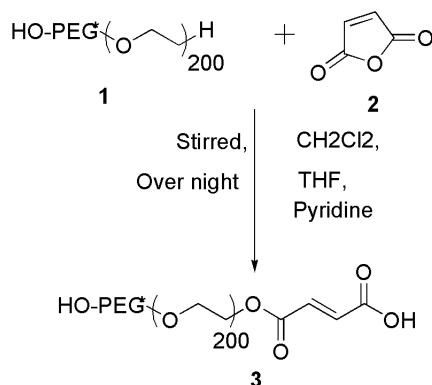
PEG200 was obtained from S D Fine chemicals Ltd., all other reagents required for the synthesis of conjugated PEGylated thiazoles were of synthesis grade and purchased from Acros Organics, Sigma-Aldrich, Qualigens and SD-Fine Chemicals. All solvents were distilled prior to use. Water purified by a Millipore system was used for making the solutions. Thin-layer chromatography was performed on silica gel G. Melting points

were determined by the open capillary method and are incorrect. The FT-IR measurements for samples were carried out using KBr pallets on Shimadzu FT-IR spectrophotometer. The  $^1\text{H}$  NMR spectra and  $^{13}\text{C}$  NMR spectra were recorded in  $\text{DMSO-}d_6/\text{CDCl}_3$  on a Bruker Avance II 400 NMR spectrometer. Chemical shifts are reported using TMS as an internal standard. Mass spectra were recorded using a Shimadzu gas chromatograph. Elemental analyses were performed on a Perkin Elmer 2400 instrument.

### General Procedure:

Synthesis of Hydroxycarboxy poly ethylene glycol ( $\text{HO-PEG}_{200}\text{COOH}$ ) :

Polyethylene glycol (28.0 mmole, 5ml 200 gm/mole) was dissolved in 20 ml of dry  $\text{CH}_2\text{Cl}_2$ . To this solution was added THF containing maleic anhydride (56.0 mmole, 0.54 mg) and pyridine (56.0 mmole, 0.46 mL). The mono acid derivative of poly (ethylene glycol) $_{200}$  was used without purification. (Scheme 1).

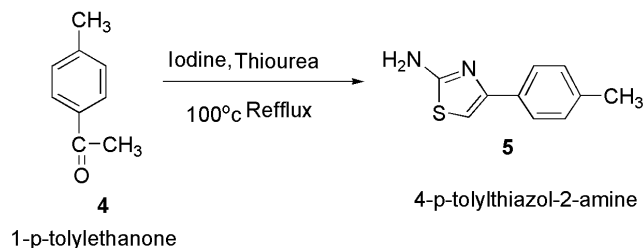


**SCHEME 1** Synthesis of Hydroxycarboxy poly ethylene glycol ( $\text{HO-PEG}_{200}\text{COOH}$ )

General procedure for the preparation of 4-p-toylthiazol-2-amine (A):

Thiazoles were prepared by reported method<sup>19</sup>. (Scheme 2).

1-1-p-tolylethanone **4** (0.03 mole) and thiourea (0.02 mol) were dissolved in rectified spirit. To the reaction mixture, (0.01mol) bromine or iodine was added. The contents were refluxed on water bath for 12 hours. The reaction mixture was diluted with water and alcohol was distilled off. The solution was filtered. On addition of ammonium hydroxide to the filtrate, thiazole **5** separated out. It was recrystallized from dilute ethanol. The yield was 89%. Melting Point:  $136^\circ\text{C}$ , IR (KBr,  $\lambda_{\text{max}}/\text{cm}^{-1}$ ): 3456 ( $\text{NH}_2$ ); 1637 ( $\text{C}=\text{N}$ ); 1491 ( $\text{C}-\text{N}$ ); 1037-730 ( $\text{C}=\text{C}-\text{Ar}$ )  $\text{cm}^{-1}$ ,  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3/\text{DMSO-}d_6$ ):  $\delta$  (ppm) 2.30 (s, 3H,  $\text{CH}_3$ ); 3.72 (s, 2H,  $\text{NH}_2$ ); 6.78 (s, 1H, thiazole-H); 7.12-7.14 (d, 1H,  $J=8.04$ , Ar-H); 7.65-7.67 (d, 1H,  $J=8.16$ , Ar-H),  $^{13}\text{C}$  NMR (200MHz  $\text{CDCl}_3$ ):  $\delta$ 20.78, 100.29, 125.41, 128.87, 131.96, 136.33, 149.54, 168.20, Mass Spectrum:  $m/z$  190M<sup>+</sup>, CHN calculated: C 63.13, H 5.30, N 14.72, S 16.85, CHN found: C 63.11, H 5.32, N 14.70, S 16.87.

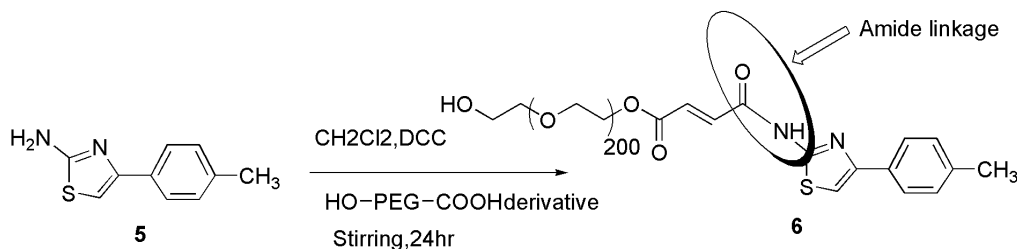


**SCHEME 2:** Synthesis of substituted thiazoles

Synthesis of Resin via N-Terminal of substituted PEGylated 4-p-toylthiazol-2-amine (a):

A mixture of mono acid derivative of hydroxycarboxy PEG ( $\text{HO-PEG}_{200}\text{COOH}$ ) (28.0mmole) activated with 1:2 molar equivalent of 4-p-tolylthiazol amine (46.0 mmole) and N, N dicyclocarbidiimide (46.0 mmole) was dissolved in dichloromethane. The solution was stirred for 24 hrs at room temperature. A syrupy resin was dried under vacuum. A syrupy resin was dissolved in 15ml of acetone. A white precipitate of dicyclohexyl urea (DCU) that appeared was discarded and filtrate was collected. The finale filtrate was evaporated to afford the product. TLC in (methanol:ethyl acetate, 7:3) was performed to check the presence of DCU. It showed a negative result that was confirmed by IR spectra. Complete amino group capping was indicated by a negative Dye test. The resin was dried in vacuum for IR,  $^1\text{HNMR}$ ,  $^{13}\text{CNMR}$  and mass characterisation. At this stage, the resin did not stick anymore to the glass wall. IR spectrum of resin showed the characteristic

absorption band PEG ether backbone ( $1120\text{ cm}^{-1}$ ) and absorption bands for (C=O),  $1720$  and  $1625\text{ cm}^{-1}$  for the ester and amide bond respectively. (Scheme 3). Syrupy liquid, Yield : 93%, density:  $1.137\text{ cm}^3$ , IR (KBr,  $\lambda_{\text{max}}/\text{cm}^{-1}$ ):  $3391$  (OH, -NH);  $2871$  (-CH<sub>3</sub>);  $1621$  (-C=O,-PEG);  $2927$  (-CH<sub>2</sub>-PEG)  $\text{cm}^{-1}$ , <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub> /DMSO-d<sub>6</sub>):  $\delta$ (ppm):  $2.35$  (s, 3H,CH<sub>3</sub>);  $3.29$ - $4.25$  (m, PEG);  $4.24$  (s,1H, -NH);  $6.58$  (s,1H, thiazole-H);  $7.14$ - $7.16$  (d, 2H, J=8.12, Ar-H)  $7.61$ - $7.63$ (d, 2H, J=8.02, Ar-H), <sup>13</sup>C NMR (200MHz CDCl<sub>3</sub>):  $\delta$   $20.85$ ,  $60.45$ - $72.51$ ,  $100.66$ ,  $125.65$ ,  $129.14$ ,  $129.27$ ,  $132.43$ ,  $136.51$ ,  $150.14$ ,  $168.37$ ,  $175.28$ , Mass Spectrum:  $m/z$   $472\text{M}^+$ , CHN calculated: C 57.43, H 5.36, N 7.44, O 21.25, S 8.52, CHN found : C 57.45, H 5.35, N 7.43, O 21.26, S 8.51, Molecular Formula: PEG-C<sub>10</sub>H<sub>9</sub>N<sub>2</sub>S.



**SCHEME 3** Synthesis of Resin via N-Terminal of substituted PEGylated 4-p-toylthiazol-2-amine (a)

Synthesis of Resin via N-Terminal of substituted PEGylated 4-(4-fluorophenyl)thiazol-2-amine(b):

Yield : 91%, density:  $1.022\text{ cm}^3$ , IR (KBr,  $\lambda_{\text{max}}/\text{cm}^{-1}$ ) :  $3339$  (OH,-NH);  $2932$  (-CH<sub>2</sub>);  $1699$  (-C=O,-PEG)  $\text{cm}^{-1}$ , <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub> /DMSO-d<sub>6</sub>) :  $\delta$  (ppm)  $3.35$ - $4.79$  (m, PEG);  $4.33$  (s,1H, -NH);  $6.11$  (s,1H,thiazole-H);  $7.50$ - $7.52$  (d, 2H, J=8.4, Ar-H);  $8.21$ - $8.24$  (d, 2H, J=9.2, Ar-H), <sup>13</sup>CNMR, (200MHz CDCl<sub>3</sub>):  $\delta$   $59.00$ ,  $72.63$ ,  $105.33$ ,  $116.52$ ,  $127.84$ ,  $129.00$ ,  $130.98$ ,  $135.92$ ,  $151.00$ ,  $162.87$ ,  $164.00$ ,  $166.89$ , Mass Spectrum:  $m/z$   $476\text{M}^+$ , CHN calculated : C 53.68, H 4.50, N 7.36, O 21.03, S 8.43, F 4.99, CHN found: C 53.65, H 4.53, N 7.32, O 21.07, S 8.48, F 4.95, Molecular Formula: PEG-C<sub>9</sub>H<sub>6</sub>FN<sub>2</sub>S.

Synthesis of Resin via N-Terminal of substituted PEGylated of 4(4chlorophenyl) thiazol-2-amine(c):

Yield : 90%, density:  $1.134$ , IR (KBr,  $\lambda_{\text{max}}/\text{cm}^{-1}$ ) :  $3338$  (OH, -NH);  $2929$  (-CH<sub>2</sub>);  $1698$  (-C=O,-PEG)  $\text{cm}^{-1}$ , <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub> /DMSO-d<sub>6</sub>):  $\delta$ (ppm)  $3.33$ - $4.70$  (m, PEG);  $4.40$  (s, 1H, -NH);  $6.75$ (s,1H, thiazole-H);  $7.31$ - $7.33$  (d,2H,J=9.2,Ar-H);  $7.72$ - $7.74$  (d,2H J=8.8,Ar-H), <sup>13</sup>C NMR (200MHz CDCl<sub>3</sub>):  $\delta$   $60.24$ - $79.08$ ,  $101.92$ ,  $128.22$ ,  $131.58$ ,  $133.62$ ,  $148.60$ ,  $164.67$ ,  $168.29$ . Mass Spectrum :  $m/z$   $492\text{M}^+$ , CHN calculated : C 51.45, H 4.32, N 7.06, O 20.16, S 8.08, Cl 8.93, CHN found : C 51.36, H 4.35, N 7.08, O 20.20, S 8.10, Cl 8.91, Molecular Formula: PEG-C<sub>9</sub>H<sub>6</sub>ClN<sub>2</sub>S

Synthesis of Resin via N-Terminal of substituted PEGylated of 4-(2-aminothiazol-yl)phenol (d) :

Yield: 89%, density:  $1.180$ , IR (KBr,  $\lambda_{\text{max}}/\text{cm}^{-1}$ ) :  $3395$  (OH,-NH);  $2978$  (-CH<sub>2</sub>);  $1692$  (-C=O, -PEG)  $\text{cm}^{-1}$ , <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub> /DMSO-d<sub>6</sub>):  $\delta$ (ppm) =  $3.31$ - $4.28$  (m,PEG);  $5.38$  (s,1H,-NH);  $6.58$  (s,1H,thiazole-H);  $7.46$ - $7.44$  (d, 2H, J=9.2, Ar-H);  $7.77$ - $7.79$  (d, 2H, J=8.08, Ar-H);  $10.85$  (s, 1H, Ar-OH). <sup>13</sup>C NMR (200MHz CDCl<sub>3</sub>):  $\delta$   $60.28$ ,  $72.43$ ,  $105.71$ ,  $116.88$ ,  $125.01$ ,  $127.00$ ,  $128.02$ ,  $135.22$ ,  $150.60$ ,  $158.26$ ,  $164.59$ ,  $166.29$ . Mass Spectrum:  $m/z$   $474\text{M}^+$ ; CHN calculate: C 53.96, H 4.79, N 7.40, O 25.37, S 8.48, CHN found : C 53.99, H 4.78, N 7.42, O 25.33, S 8.48, Molecular Formula : PEG-C<sub>9</sub>H<sub>7</sub>N<sub>2</sub>OS.

Synthesis of Resin via N-Terminal of substituted PEGylated of 4(4methoxyphenyl) thiazol-2-amine(e):

Yield : 92%, density:  $1.123$ , IR (KBr,  $\lambda_{\text{max}}/\text{cm}^{-1}$ ) :  $3398$  (OH,-NH);  $2873$  (-CH<sub>3</sub>);  $1698$  (-C=O, -PEG)  $\text{cm}^{-1}$ , <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub> /DMSO-d<sub>6</sub>):  $\delta$ (ppm)  $2.45$  (s, 3H,CH<sub>3</sub>);  $3.45$ - $4.24$  (m, PEG);  $4.24$  (s,1H,-NH);  $6.03$  (s,1H,thiazole-H);  $7.68$ - $7.66$  (d, 2H, J=8.72, Ar-H) ,  $7.86$ - $7.88$ (d, 2H, J=8.8, Ar-H). <sup>13</sup>C NMR (200MHz CDCl<sub>3</sub>) :  $\delta$   $55.22$ ,  $60.39$ - $72.45$ ,  $99.53$ ,  $113.96$ ,  $123.00$ ,  $125.50$ ,  $127.00$ ,  $135.94$ ,  $149.84$ ,  $158.70$ ,  $164.12$ ,  $168.30$ ,  $169.22$ , Mass Spectrum :  $m/z$   $488\text{M}^+$ , CHN calculated : C 55.09, H 5.14, N 7.14, O 24.46, S 8.17, CHN found : C 55.07, H 5.10, N 7.20, O 24.50, S 8.13, Molecular Formula : PEG-C<sub>10</sub>H<sub>9</sub>N<sub>2</sub>OS

Synthesis of Resin via N-Terminal of substituted PEGylated of 4(4bromophenyl) thiazol-2-amine(f):

Yield : 94%, density:  $1.152$ , IR (KBr,  $\lambda_{\text{max}}/\text{cm}^{-1}$ ):  $3337$  (OH, -NH);  $2875$  (-CH<sub>2</sub>);  $1694$  (-C=O, -PEG)  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub> /DMSO-d<sub>6</sub>) :  $\delta$ (ppm)  $3.34$ - $4.76$  (m, PEG);  $4.36$  (s, 1H, -NH);  $6.75$  (s, 1H, thiazole-H);  $7.36$ - $7.38$  (d, 2H, J=8.84, Ar-H);  $8.05$ - $8.08$  (d, 2H, J=8.8, Ar-H), <sup>13</sup>C NMR (200MHz CDCl<sub>3</sub>):  $\delta$   $60.85$ - $70.02$ ,  $105.77$ ,  $123.25$ ,  $127.00$ ,  $128.57$ ,  $132.76$ ,  $135.81$ ,  $151.00$ ,  $164.04$ ,  $167.57$ , Mass Spectrum:  $m/z$   $537\text{M}^+$ , CHN calculated:  $46.27$ , H  $3.88$ , N  $6.35$ , O  $18.13$ , S  $7.26$ , Br  $18.11$ , CHN found : C  $46.30$ , H  $3.91$ , N  $6.30$ , O  $18.12$ , S  $7.25$ , Br  $18.12$ , Molecular Formula : PEG-C<sub>9</sub>H<sub>6</sub>BrN<sub>2</sub>S.

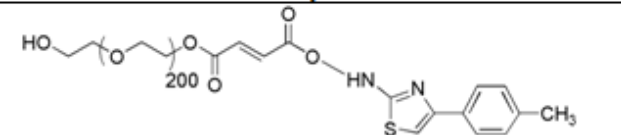
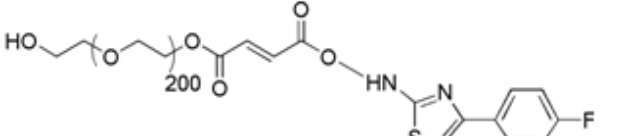
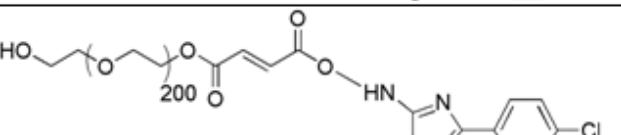
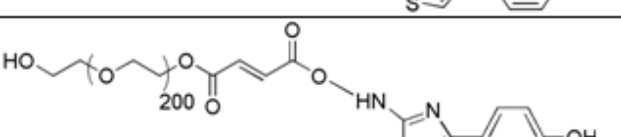
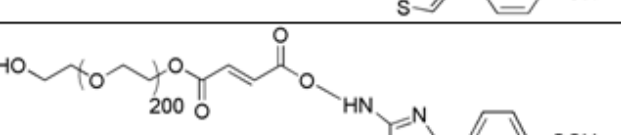
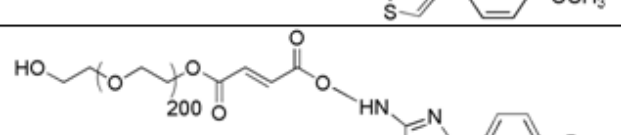
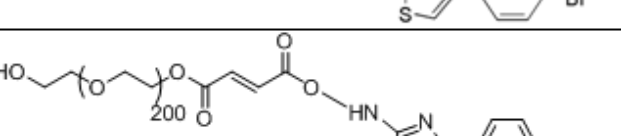
Synthesis of Resin via N-Terminal of substituted PEGylated of 4(4nitrophenyl) thiazol-2-amine(g)

Yield : 92%, IR (KBr,  $\lambda_{\text{max}}/\text{cm}^{-1}$ ) :  $3391$  (OH, -NH);  $2876$  (-CH<sub>2</sub>);  $169$  (-C=O, -PEG)  $\text{cm}^{-1}$ , <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub> /DMSO-d<sub>6</sub>) :  $\delta$ (ppm)  $3.30$ - $4.21$  (m,PEG);  $4.76$  (s, 1H, -NH);  $6.38$  (s,1H, thiazole-H);  $8.13$ - $8.15$ (d, 2H, J=8.00, Ar-H);  $8.33$  - $8.35$  (d, 2H, J=9.2, Ar-H), <sup>13</sup>CNMR(200 MHz CDCl<sub>3</sub>):  $\delta$   $60.45$ - $72.55$ ,  $100.26$ ,

123.90, 126.30, 127.80, 135.12, 139.45, 147.00, 150.94, 164.10, 166.60, Mass Spectrum : m/z 503M<sup>+</sup>, CHN calculated: C 50.12, H 4.21, N 10.31, O 27.49, S 7.87 CHN found: C 50.10, H 4.26, N 10.28, O 27.53, S 7.83, Molecular Formula : PEG-C<sub>9</sub>H<sub>6</sub>N<sub>3</sub>O<sub>2</sub>S.

Anti-bacterial activity:

All pegylated thiazoles and nanoparticles linked PEGylated thiazoles, **6a-g** were screened against clinically isolated strains of gram-negative bacteria *Escherichia coli* & gram-positive bacteria *Staphylococcus aureus*. The cytotoxicity of all scaffolds was compared with Ampicillin and Doxycyclin, at (25, 50, 100 ug/mL) in solvent DMSO. for antibacterial study. The antibacterial screening was carried out by cup-plate method at different levels of concentration (25, 50, 100 ug/mL) in solvent DMSO and nutrient agar were used as culture method. After 24hr of incubation at 37<sup>o</sup>C, the zones of inhibition were measured in mm.

Entry	Structures of PEGylated Thiazoles	Density ( $\rho$ ) in Cm <sup>3</sup>
6a		1.137
6b		1.022
6c		1.134
6d		1.180
6e		1.123
6f		1.152
6g		1.089

**Table 1:** Structures of PEGylated thiazoles

### III. Results and discussion

The focal point of our research was to determine effective synthetic routes for the preparation of pegylated thiazole hybrids. The thiazoles were prepared by reported methods (Scheme 2 and Table 1). We have prepared novel PEG N-terminal thiazole substituted derivatives and showed that, when compared to a heterogeneous commercially available counterpart, they possess favorable reaction kinetic in both the Staudinger and Mitsunobu etherification reactions. To explore the synergistic effects of such pharmacophores, the present study expands on those preliminary investigations.

The PEGylation chemistry has been successfully demonstrated at the amino group situated at C-2 of thiazole hybrids (Scheme 3). To couple a PEG to a thiazole molecule, it is first necessary to 'activate' the

polymer by converting the hydroxyl terminus to some functional group capable of reacting with the functional group situated on thiazole molecule. We opted to activate the PEG by converting it to its acid derivative (Scheme 1) and coupling it with amino group of thiazole molecule. This PEGylation methodology involves conjugation of thiazole onto hetero bifunctional PEG derivatives having –OH on one terminus and –COOH on the other for covalent attachment of amino group. The free carboxyl group was used for conjugation via amine coupling. We have determined that this conjugation proceeds through formation of amide linkage between the PEG chain and thiazole under mild reaction conditions. The resin was dried in vacuum for IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and Mass characterization. At this stage the resin did not stick any more to the glass wall. IR spectrum of resin showed the characteristic absorption band of PEG ether backbone (1120 cm<sup>-1</sup>) and absorption bands 1760 and 1685 cm<sup>-1</sup> for the ester and amide bond respectively (C=O).

The IR spectra of compounds **6a-g** showed strong, sharp absorption bands observed at 1610-1640cm<sup>-1</sup> attributable to the carbonyl groups of amides and PEG (–C=O) and (–C=O,-PEG), bands at 3391 suggested the presence of (OH, -NH). However, the peaks observed at 2871 and 2927 cm<sup>-1</sup> correlated to (–CH<sub>3</sub>) and (–CH<sub>2</sub>-PEG) respectively.

The <sup>1</sup>H NMR spectra of compounds **6a-g** displayed signals at δ 3.29-4.25 due to the multiple-H-PEG group. For compounds **6a**, **6d** and **6e**, the singlets at δ 2.35 integrated for the –CH<sub>3</sub> protons. Peak at δ 2.45 was observed due to the –OCH<sub>3</sub> group for compound **6e**. All the compounds **6a-g** showed singlet peak in the range δ 4.72-5.29 corresponding for –NH group, disappearance of singlet for two protons of –NH<sub>2</sub> group of amino thiazoles **6a-g** and appearance of singlet in the range δ 4.72-5.29 corresponding for –NH group supports the formation of –CONH bond and hence pegylation. In addition, -OH group of the compounds **6d** resonated as singlet at δ 10.18 integrating for one proton. The spectra of compounds **6a-g** revealed the multiplets at δ 6.58-8.35 indicating the presence of aromatic -H.

<sup>13</sup>CNMR and MASS spectral analysis also support the formation of products **6a-g**. The compounds **6a-g** gave satisfactory elemental analysis. The physicochemical data and general structures of compounds **6a-g** are depicted in **Table 1**.

The newly synthesized compounds **6a-g** were tested for their *in vitro* antimicrobial activity against clinical isolates of Gram-positive bacteria *Staphylococcus aureus*, Gram-negative bacteria *Escherichia coli*. All the compounds along with standard for bacteria Doxycyclin, Ampicillin were used at a concentration of 25ug/mL, 50ug/mL and 100ug/mL in DMSO as a solvent control and nutrient agar were used as culture method. After 24h of incubation at 37°C, the zones of inhibition were measured in mm.

All synthesized compounds exhibited good to moderate activity against all microbes. All compounds displayed significant activity against strains of *Escherichia coli* and *Staphylococcus aureus*.

The toxicity increased with the increase in concentration of the test solution containing new compounds, suggesting a maximum tolerance dose. Some compounds did not meet the conventional bacteriostatic standards at lower concentration levels. The variance in the effectiveness of different compounds against different organisms depends either on the impermeability of the cells of the microbes or diffusion in ribosomes of microbial cells.

Results obtained after screening the synthesized compounds against various micro-organisms are shown in (Table 2):

**Table 2:** In vitro antibacterial activity of compounds **6a-g** against *Escherichia coli* and *Staphylococcus aureus*, zone of inhibitions expressed in diameter in mm

Sr. No.	Compound No.	Diameter of zone of inhibition in mm					
		<i>Escherichia coli</i>			<i>Staphylococcus aureus</i>		
		100ug/ML	50 ug/ML	25 ug/ML	100 ug/ML	50 ug/ML	25 ug/ML
1	a	20	18	12	32	16	9
2	b	21	14	13	18	13	10
3	c	30	22	10	22	15	10
4	d	18	12	9	16	11	8
5	e	22	13	9	18	13	10
6	f	21	17	10	14	12	8
7	g	32	16	8	14	13	9
Std.	Ampicillin	31	28	18	30	17	14
Std.	Doxycycline	30	26	15	29	18	15
	Solvent	DMSO	Absent	Absent	Absent	Absent	Absent

Structure activity relationship: Depending upon the structural features, the newly synthesized molecules **6a-g** could be divided into two discrete segments viz. diversely substituted central core thiazole ring A and a PEGylation centre (**Figure 1**).

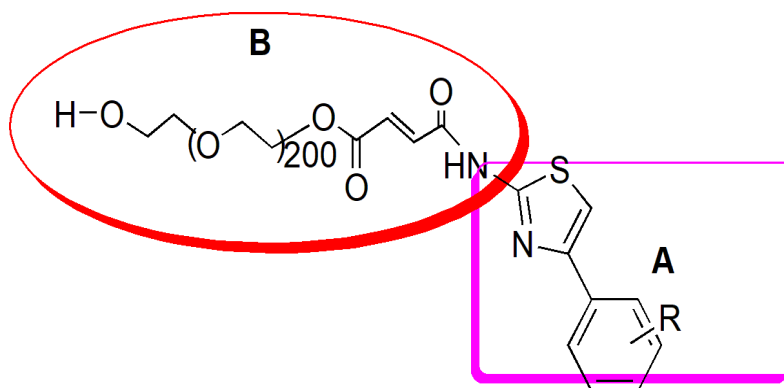


Figure 1

The exceptionally high microbial activity of PEGylated thiazole derivatives is suggestive of the fact that the enhanced efficacy of molecules may be because of the high mobility of the end terminal of the tethered PEG molecules and due to the presence of inter-repulsive forces exerted between the hydrated PEG chains, there is a strong possibility of single PEG molecule conjugation with the approaching protein.

The data evident from table 1 leads to another noteworthy deduction that the molecules more electron withdrawing centres of aryl rings C-4 position exhibited good to moderate antimicrobial activity against microorganisms. However, electron donating groups situated at thiazole moiety of PEGylated thiazoles did not display significant activity. These annotations proposed that electron donating groups and electron withdrawing centers played a vital role in **6a-g** structure activity relationship.

#### IV. Conclusion

A facile and efficient syntheses of 7 appropriately substituted PEGylated thiazoles have been reported. Diversity of substitution at various points on the skeleton of PEGylated thiazole derivatives leads to significantly modulated selectivity in the active site. Target analogs **6a-g** were tested for their *in vitro* antimicrobial activity against clinical isolates of gram-positive bacteria *Staphylococcus aureus*, gram-negative bacteria *Escherichia coli* at various concentrations. Some compounds did not meet pre-defined bacteriostatic standards at lower concentration levels. The variation in the effectiveness of different compounds against different organisms depends either on the impermeability of the cells of the microbes or diffusion in ribosomes of microbial cells.

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