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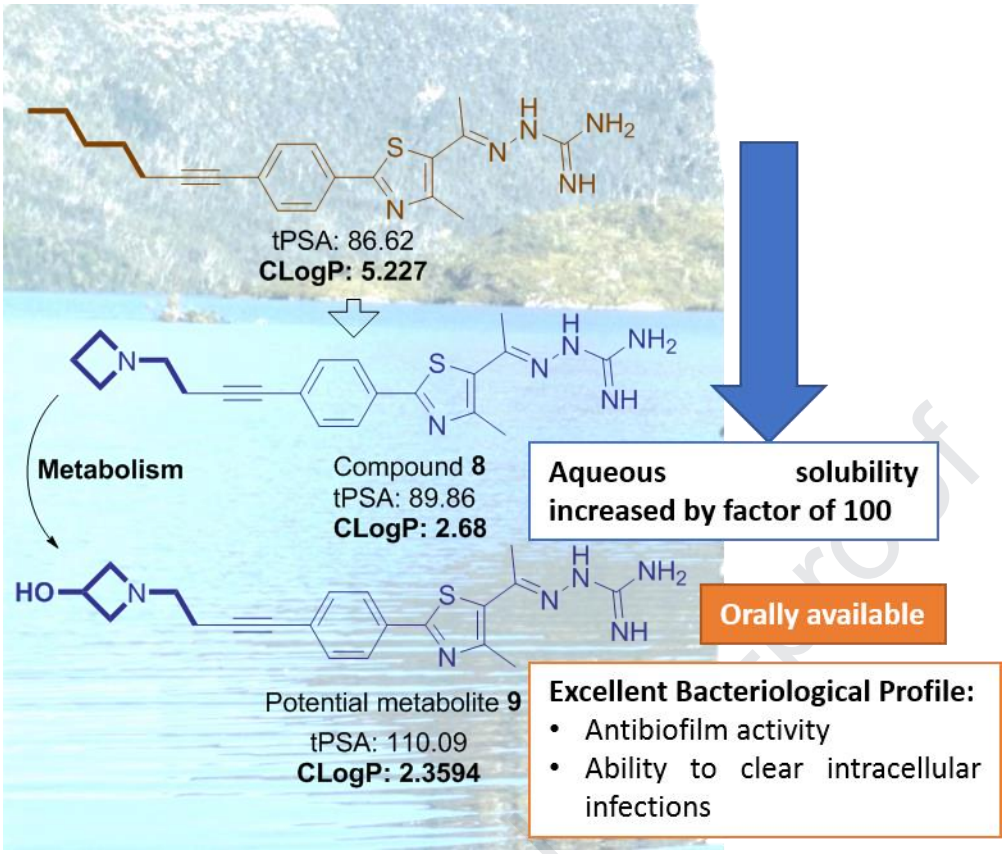

Modifying the Lipophilic Part of Phenylthiazole Antibiotics to Control Their Drug-Likeness

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Abbreviations. MIC, minimum inhibitory concentration; MBC, minimum bactericidal concentration; MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; VRSA, vancomycin-resistant *Staphylococcus aureus*; PK, pharmacokinetic; cLogP, partition coefficient value; tPSA, total polar surface area; C_{max}, maximum plasma concentration; t_{max}, time required to reach the maximum plasma concentration; CL, clearance rate; $t_{1/2}$, half-life; V_d, volume of distribution;

Abstract. Compounds with high lipophilic properties are often associated with bad physicochemical properties, triggering many off-targets, and less likely to pass clinical trials. Two metabolically stable phenylthiazole antibiotic scaffolds having notable high lipophilic characters, one with alkoxy side chain and the other one with alkynyl moiety, were derivatized by inserting a cyclic amine at the lipophilic tail with the objective of improving physicochemical properties and the overall pharmacokinetic behavior. Only alkynyl derivatives with 4- or 5-membered rings showed remarkable antibacterial activity. The azetidine-containing compound **8** was the most effective and it revealed a potent antibacterial effect against 15 multi-drug resistant (MDR)-Gram positive pathogens including *Staphylococcus aureus, Streptococcus pneumoniae, Staphylococcus epidermidis* and *enterococci.* Compound **8** was also highly effective in clearing 99.7% of the intracellular methicillin- resistant *S. aureus* (MRSA) harbored inside macrophages. In addition to the remarkable enhancement in aqueous solubility, the *in vivo* pharmacokinetic study in rats indicated that compound **8** can penetrate gut cells and reach plasma at a therapeutic concentration within 15 minutes and maintain effective plasma concentration for around 12 hours. Interestingly, the main potential metabolite (compound **9**) was also active as an antibacterial agent with potent antibiofilm activity.

Key words: MDR-bacteria; Antibiotic resistance; MRSA; Staphylococcal infections; antibiofilm; intracellular infections

1. Introduction. The high attrition rate of small molecule drug-candidates from clinical studies is still the key challenge for the pharmaceutical industry worldwide. For decades, poor pharmacokinetic behavior was the main reason for the termination of clinical studies. Hence, many rules were developed to correlate compounds' physicochemical properties with pharmacokinetic performance [1-5]. Clearly, it is hard to build a direct correlation between clinical attrition and a single descriptor, but many reports highlight the influence of excessive lipophilicity on toxicological outcomes and inappropriate pharmacokinetic profiles [6, 7]. Compounds with high lipophilic property (obese molecules), are promiscuous and commonly associated with increased off-target side effects [7-9].

For a while, the formulation technology deemed to be a novel alternative to solubilize fatty molecules allowing their oral absorption [10]. Yet, the advancement in this field led to a remarkable diminishment in the number of failures related to poor pharmacokinetic profiles [11]. Unfortunately, forcing fatty molecules to enter our systemic circulation and improving the overall oral bioavailability is only the prominent side of the story. The other dark side of the story is the excretion step in which the metabolic enzymes have to work assiduously to polarize these fatty xenobiotics in order to easily excrete them [12]. As a result, the significant decrease in failures due to pharmacokinetic problems was encountered by a sudden increase of attritions connected with toxicological aspects and the overall attrition rates from clinical trials are almost at the same level [11, 13, 14]. Therefore, there is a consensus among big pharmaceutical developers that "controlling physicochemical properties is beneficial in identifying compounds of candidate drug qualities" [11].

Phenylthiazole antibiotics, discovered by our group [15-21], originally suffered from the metabolic instability issue [15, 22]. Identifying the part of the lead compound **1a** that is exposed

to rapid metabolism, provided a route to synthesize two sets of metabolically-stable analogs; i.e., the alkoxylphenylthiazoles [22, 23] and alkynylphenylthiazoles [17] (Figure 1). The structure-activity relationships (SAR) of both groups indicated that further addition of methylene units at the lipophilic tail significantly enhanced the antibacterial activity [17, 23] (Figure 1). The improvement of the antibacterial activity was combined with a deterioration in drug-likeness. Hence, the alkynylphenylthiazole, for instance, could not be tested in an animal model in a dose of more than 40% the therapeutic one due to solubility issue [17].

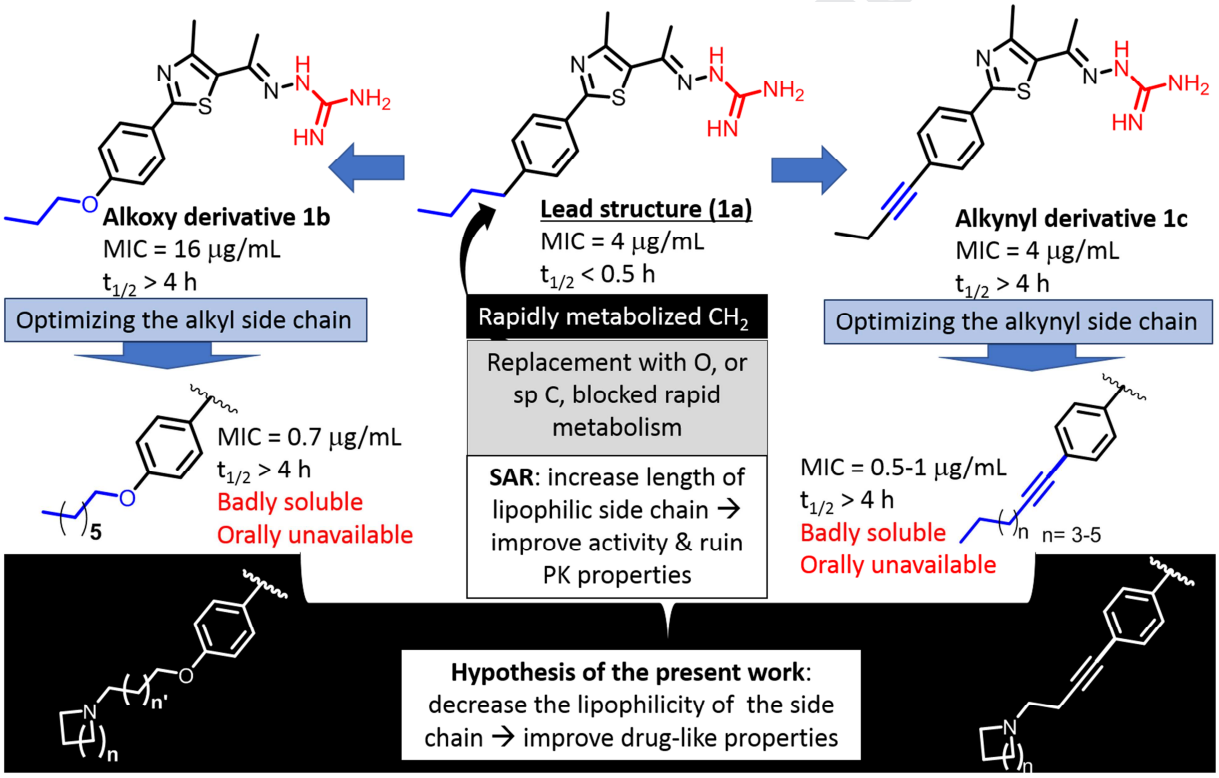


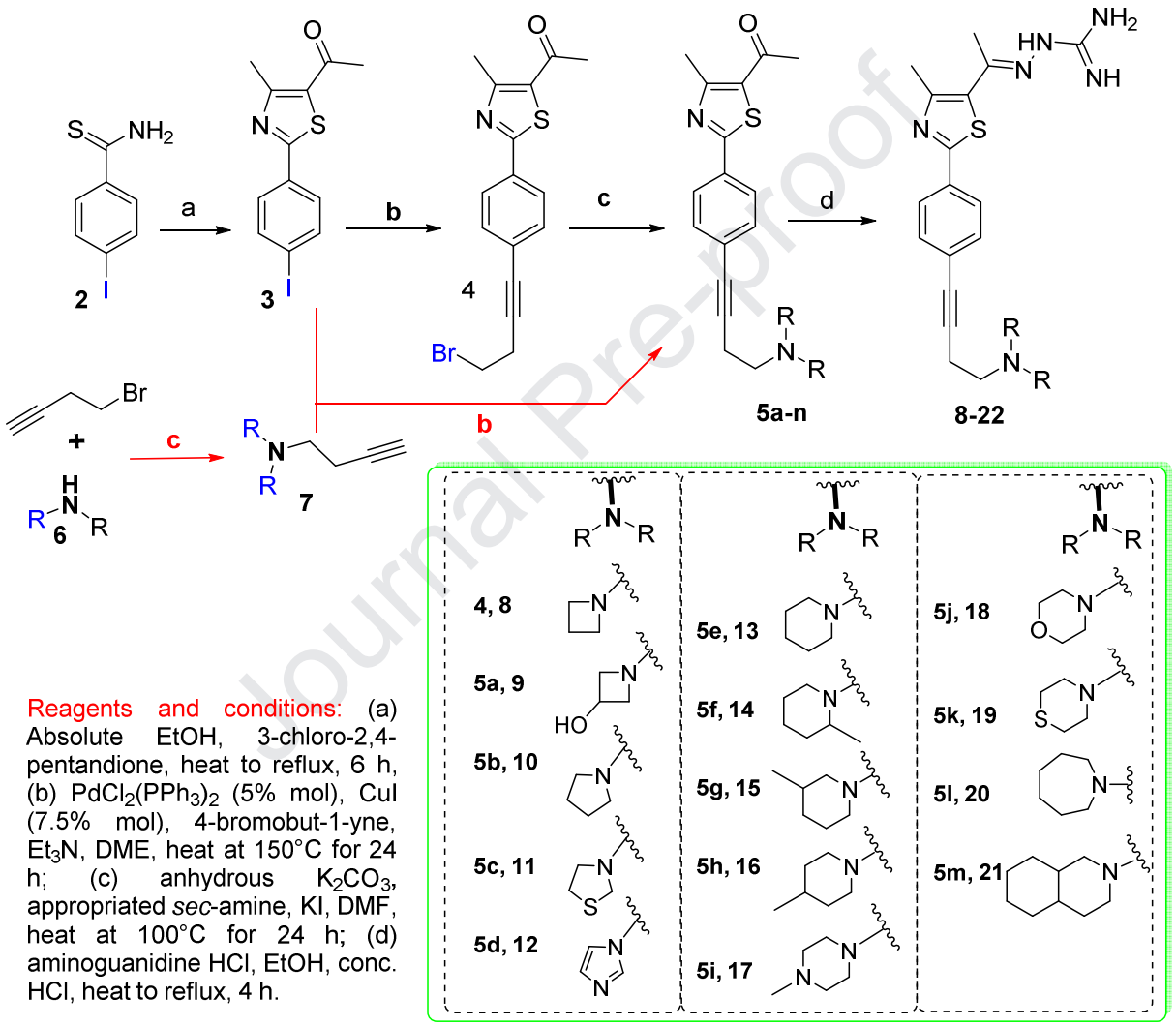
Figure 1. Progress of phenylthiazole antibiotics development and the general idea of the present work.

Taking into account the considerations of compounds' lipophilicity and their impact on drug-likeness in progressing the development of phenylthiazole antibiotics, this article aimed at controlling the molecular obesity of phenylthiazole derivatives via inserting a polar atom within the lipophilic tail connected with the phenyl ring. All designed compounds shown in Figure 1

were then subjected to comprehensive bacteriological profiling versus 15 clinical MDR-pathogens. In addition, the key physicochemical properties and *in vivo* pharmacokinetic profile of the most promising derivative were also investigated.

2. Results and Discussion

Scheme 1.

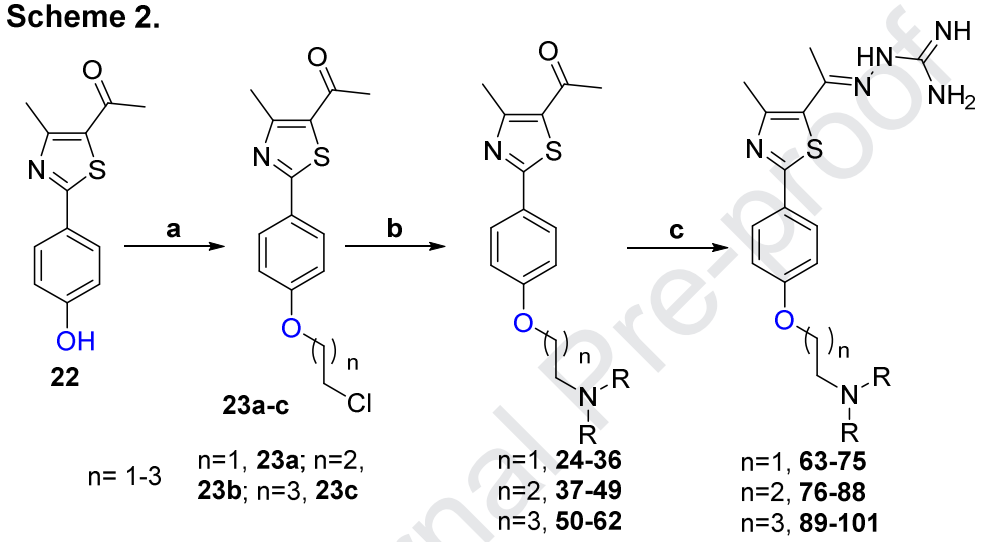


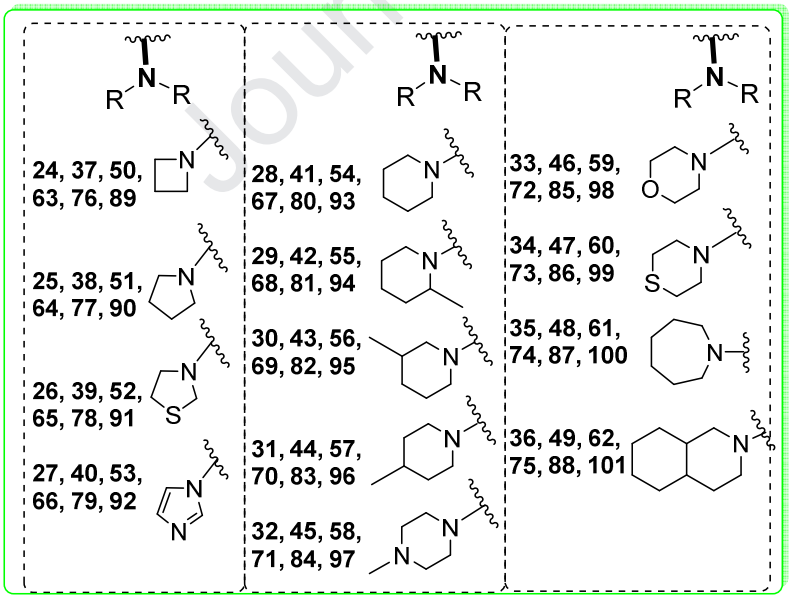
Reagents and conditions: (a) Absolute EtOH, 3-chloro-2,4-pentandione, heat to reflux, 6 h, (b) $PdCl_2(PPh_3)_2$ (5% mol), CuI (7.5% mol), 4-bromobut-1-yne, Et_3N, DME, heat at 150°C for 24 h; (c) anhydrous K_2CO_3, appropriated *sec*-amine, KI, DMF, heat at 100°C for 24 h; (d) aminoguanidine HCl, EtOH, conc. HCl, heat to reflux, 4 h.

2.1. Chemistry. The alkynyl derivatives were accessed via two synthetic routes. The first one included tethering the bromobutyl moiety to the phenylthiazole core and then replacing the bromine atom with cyclic amines. In the second approach, the *N*-alkynylamines were prepared

first and then connected with the phenylthiazole core using traditional Sonogashira C-C cross coupling reaction conditions. Both routes led us to the desired intermediates **5**; however, the second approach was with better yields, in general (Scheme 1). The final designed derivatives **8-21** were obtained by allowing compounds **5** to react with aminoguanidine in the presence of catalytical amount of hydrochloric acid.

Scheme 2.





Reagents and conditions: (a) anhydrous K_2CO_3, Br-$(CH_2)_n$-Cl, DMF, 6 h, (b) anhydrous K_2CO_3, KI, cyclic amine, heat at 100 °C for 24 h; (c) aminoguanidine HCl, EtOH, conc. HCl, heat to reflux, 4 h.

The *p*-hydroxyphenylthiazole **22** was prepared as reported [22] and then allowed to react with bromochloroalkane under a mild nucleophilic substitution reaction conditions to yield compounds **23** (Scheme 2). The chlorine atom was them replaced with a proper cyclic amine and the final products were obtained as described previously in Scheme 1.

2.2. Biological Results and Discussion.

2.2.1. Antibacterial activity of new analogs against MRSA. Iinitial screening of the newly prepared compounds **8-21** and **63-101** against MRSA USA300, one of the most clinically important and highly-pathogenic MDR-pathogen, [24-26] resulted in only four derivatives (compounds **8**, **9**, **11** and **12**) with promising antibacterial activity (Table 1S). The active derivatives (MIC values ≤4 μg/mL) are all belonging to the alkynylphenylthiazole series. None of the alkoxyphenylthiazole derivatives **63-101** showed any promising antibacterial activity; however, the ones with shorter linker and smaller cyclic amines demonstrated moderate potency with MIC value of 8-16 μg/mL (Table 1S).

The SAR of this new set of alkynylphenylthiazole analogs seemed to be very straightforward as the antibacterial potency was directly correlated to the ring size. In this vein, the smaller ring (azetidine, compound **8**) provided the most potent compound in this series with only one-fold higher MIC value than vancomycin (MIC value of **8** is 2 μg/mL & MIC of vancomycin is 1 μg/mL; Table 1S). The promising antibacterial activity of compound **8** was further confirmed against a panel of clinically relevant MDR-staphylococcal strains including linezolid-resistant *S. aureus* (MRSA NRS119) and two vancomycin-resistant strains (VRSA 10 and VRSA 12), in addition to a couple of methicillin-sensitive strains (MSSA) (Table 1). Briefly, compound **8** was equipotent to vancomycin against MSSA NRS107 and one-fold less active than vancomycin against most other tested MRSA strains with MIC value of 4 μg/mL. Moreover, the

azetidine-containing compound **8** maintained its potency when tested against linezolid-resistant and vancomycin-resistant *S. aureus* strains (MRSA NRS119, VRSA 10 and VRSA 12) (Table 1).

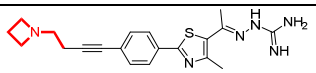
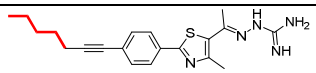
Table 1. Antibacterial activity (MICs and MBCs in µg/mL) of alkynylphenylthiazoles **8**, **9**, **11** and **12** against a panel of clinical staphylococcal strains.

	Compounds/ Control antibiotics											
Bacterial Strains	**8**		**9**		**11**		**12**		Linezolid		Vancomycin	
	MIC	**MBC**	**MIC**	**MBC**	**MIC**	**MBC**	**MIC**	**MBC**	**MIC**	**MBC**	**MIC**	**MBC**
MSSA ATCC 6538	2	8	4	4	4	32	4	16	1	16	1	2
MSSA NRS 107	2	8	4	4	8	16	4	8	1	64	2	2
MRSA NRS119	2	8	4	8	4	16	8	32	64	> 64	1	2
MRSA NRS123 (USA400)	2	4	4	8	4	32	4	8	1	32	1	1
MRSA NRS384 (USA300)	2	4	4	4	4	32	4	16	1	32	1	1
MRSA NRS 385 (USA500)	4	4	4	4	4	16	4	16	1	32	1	1
MRSA NRS 386 (USA700)	2	8	4	8	4	16	4	16	2	64	1	1
VRSA 10	2	8	4	8	4	32	4	8	1	> 64	64	> 64
VRSA 12	4	16	4	8	4	32	4	16	1	64	64	64

MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; VRSA, vancomycin-resistant *Staphylococcus aureus*

Next, increasing ring size of the terminal cyclic amine to five units provided two active derivatives **11** (with thiazolidine ring) and **12** (with imidazole ring). Both are one- to two-fold less active than the azetidine-containing compound **8**, against most of the tested strains, with MIC values ranging from 4 to 8 µg/mL (Table 1). Compounds with larger nitrogenous rings; 6 or larger units are all with very mild antibacterial activity (Table 1S).

Table 2. Key physicochemical properties of compound **8** and compound **1d**

	 Compound **8**	 Previously prepared compound **1d [17]**
cLogP[1]	2.68	5.23
tPSA[1]	89.89	86.62
Aqueous Solubility [2]	0.5 mM	< 5 μM

[1]calculated values using ChemBioDraw Ultra 14.0; [2]measured in phosphate buffer pH 6.8

Table 3. Compound **8** plasma pharmacokinetic parameters following a single oral dose (50 mg/Kg) to rats

C_{max} (μg/mL)	t_{max} (h)	AUC ((h)*(ng/mL))	CL (L/h)	t_{half} (h)	V_d (L)
15.6	1.0	161840	0.31	2.9	1.29

Taking the antibacterial data together, and before going deeper in comprehensive biological studies, compound **8** was selected to test our hypothesis, whether the new chemical modification presented in this study would improve the overall PK profile of phenylthiazole compounds or not. It is worth mentioning that both alkoxythiazole **1b** and alkynyl derivative **1c** were orally unavailable, and suffered from severe aqueous solubility issue, in which they even could not be formulated in an injectable form [17, 23]. Measurements of physicochemical properties indicate that compound **8** is with optimum values for orally administrated therapeutics, in which its partition coefficient value (cLog P) is 2.68 and its total polar surface area (tPSA) value is of 90 $Å^2$ (Table 2). Notably, the tPSA value of compound **8** is very close to that of **1d**, which has the same number of carbons; however, inserting a single nitrogen atom to the lipophilic side chain of **1d** magnificently reduced its cLogP value to the half (Table 2). As a result, the aqueous solubility of compound **8** was enhanced by a factor of more than one hundred (Table 2).

With lower lipophilic property and descent aqueous solubility, compound **8** was easily formulated, in a relatively high dose (50 mg/kg) and administrated orally to rats. The experimental *in vivo* PK data of a single oral dose showed that compound **8** is well absorbed from the gut and reached the maximum plasma concentration (C_{max}) within only one hour. Interestingly, the plasma concentration maintained over its maximum value of MIC (4 μg/mL) for more than 12-hours (Figure 1S). The other key preliminary PK data indicated that compound **8** is metabolically stable ($t_{1/2}$ = 2.9 h) with low clearance rate (less than 1 L/h) and it is very well distributed as indicated by its volume of distribution value (Table 3).

Our initial analysis of the metabolites using LC/MS/MS indicated that compound **8** is mainly metabolized by oxidation to M+18 metabolite, and the oxidation step occurs most probably at the azetidine ring (data is not shown). Therefore, compound **9**, as a potential main metabolite for **8**, was prepared, as the only hydroxylated derivative; however, it was not in the first set of synthesized alkynylphenylthiazoles. Intriguing, the main potential metabolite **9** maintained most of the antimicrobial potency of the parent compound **8**, in which it showed an MIC value of 4 μg/mL against most of the tested clinical isolates (Table 1).

Bacteriological Profiling. Next, the spectrum of antibacterial activity of the active new compounds, including the metabolite **9**, was further examined against a panel of clinically relevant Gram-positive bacterial pathogens. The four tested compounds exhibited a potent activity against *S. epidermidis*, a common colonizer of the human skin, which represents the most common source of infections on implanted medical prosthetic devices. *S. epidermidis* infections are difficult to treat due to their ability to form strong adherent biofilms that have intrinsic resistance to antibiotics and the host defense [27, 28]. Most importantly, tested compounds **8**, **9**, **11** and **12** kept their superiority over vancomycin against vancomycin-resistant

enterococci (VRE). VRE is one of the major leading cause of nosocomial infections in USA and worldwide causing about 20-30% of hospital-acquired [29]. Moreover, according to the World of Health Organization (WHO), vancomycin-resistant *E. faecium* is categorized as one of twelve bacterial pathogens that urgently need the development of new therapeutics and alternative strategies to combat their infections [30].

Table 4. Antibacterial activity (MICs and MBCs in µg/mL) of alkylphenylthiazoles **8, 9, 11** and **12** against clinically important Gram-positive bacterial pathogens including *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Enterococcus faecium*, *Listeria monocytogenes* and *Streptococcus pneumoniae*.

Bacterial Strains	**Compounds**/control antibiotics											
	8		**9**		**11**		**12**		Linezolid		Vancomycin	
	MIC	**MBC**	**MIC**	**MBC**	**MIC**	**MBC**	**MIC**	**MBC**	**MIC**	**MBC**	**MIC**	**MBC**
Methicillin-resistant *Staphylococcus epidermidis* NRS101	1	4	2	16	2	8	4	16	1	16	1	2
***Enterococcus faecalis* ATCC 51299 (VRE)[1]**	4	16	8	16	8	32	8	32	1	16	32	64
***Enterococcus faecium* ATCC 700221 (VRE)**	2	8	4	16	4	16	4	16	1	16	>64	>64
***Listeria monocytogenes* ATCC 19111**	4	8	4	32	4	32	8	32	≤0.5	16	1	1
Cephalosporin-resistant *Streptococcus pneumoniae* ATCC 51916	2	8	4	16	8	32	8	16	1	32	1	2
Methicillin-resistant *Streptococcus pneumoniae* ATCC 700677	2	8	4	16	8	32	4	16	1	16	2	2

[1]VRE: vancomycin-resistant *Enterococci*

From Tables 2 and 4, it was noted that compounds' MBC values were one- to three-folds higher than their corresponding MICs against the tested strains indicating the compounds are

bactericidal against the tested strains. This has been further confirmed by a time kill Assay (Figure 2), which indicated that the most important compounds in this study **8** and **9.** Both compounds surpassed vancomycin; the drug of choice for treatment of staphylococcal infections, in terms of the time required to exert their bactericidal activity against MRSA USA400. Briefly, vancomycin required 12-hours to exert its bactericidal activity by causing more than 3-log reduction in the high inoculum of the bacteria and completely eradicated the inoculum after 24-hours. Advantageously, our newly synthesized active compounds **8**, **9**, **11** and **12** exhibited a more rapid killing time than vancomycin, as they required 10 hours to exert their bactericidal activity and reduce the high initial MRSA USA400 count by 3-log reduction. Surprisingly, both azetidine-containing derivative **8** and its potential main metabolite **9** behave similarly in their mode of antibacterial action, in which compound **8** required 12 hours to completely eradicate the high MRSA count while its metabolite **9** required 10 hours to completely eradicate it. On the other hand, five-membered containing derivatives **11** and **12** reduced the initial count by 3-log reduction (99.9% reduction) after 10 hours but they were not able to completely eradicate it after 24 hours. This suggests that these two compounds will need to be frequently dosed when used clinically especially because the bacterial count tended to remain as it is or decreased slightly (Figure 2).

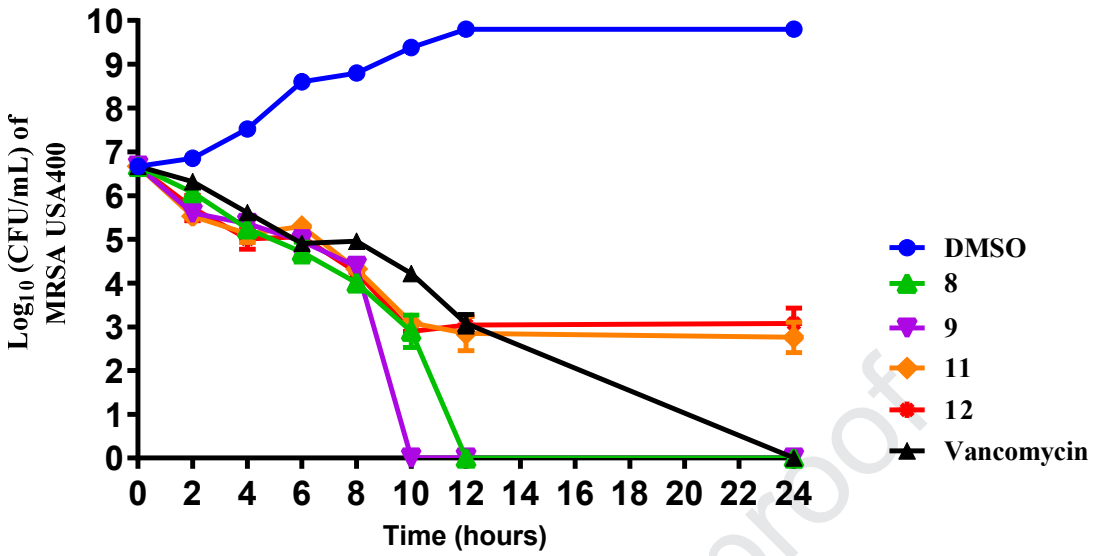


Figure 2. Killing kinetics of selected phenylthiazole compounds (tested in triplicates at 5 × MIC) against methicillin-resistant *Staphylococcus aureus* (MRSA USA400) over a 24-hour incubation period at 37 ℃. DMSO (solvent for the compounds) served as a negative control and vancomycin served as a control drug. The error bars represent standard deviation values obtained from triplicate samples used for each compound/antibiotic studied.

Assessment of cytotoxicity. Selectivity towards prokaryotic cells is an essential attribute for any antibiotic candidates. In this regard, compound **8** and its potential hydroxylated metabolite **9** were highly tolerable to caco-2 cells at a concentration higher than 128 µg/mL as represented by their 50% cytotoxic concentration (CC_{50}) (Figure 3). On the other hand, the imidazolyl derivative **12** was less tolerable as it was non-toxic to caco-2 cells at a concentration as high as 64 µg/mL where about 70% of the cells were viable at this concentration (Figure 3).

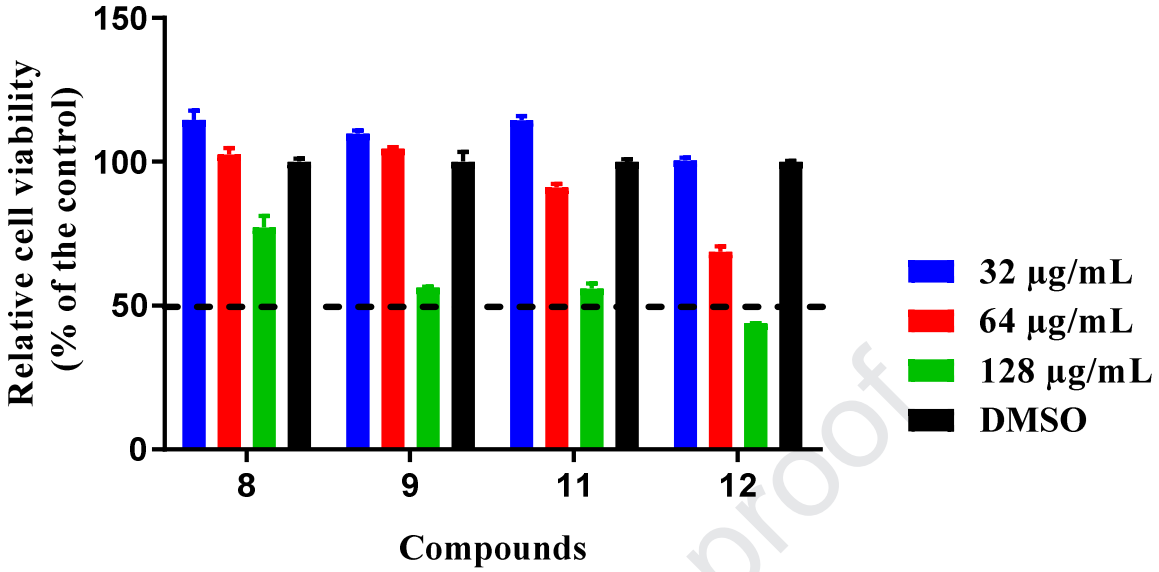


Figure 3. Analyzing the cytotoxicity of tested alkynylphenylthiazoles **8**, **9**, **11** and **12** (tested in triplicates at 32, 64 and 128 µg/mL) against human colorectal cells (Caco-2) using the MTS 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium) assay. Results are presented as percent viable cells relative to DMSO (negative control to determine a baseline measurement for the cytotoxic impact of each compound). The absorbance values represent an average of three samples analyzed for each compound. Error bars represent standard deviation values. CC_{50} (the compound's concentration that causes 50% cells viability) was determined for each compound.

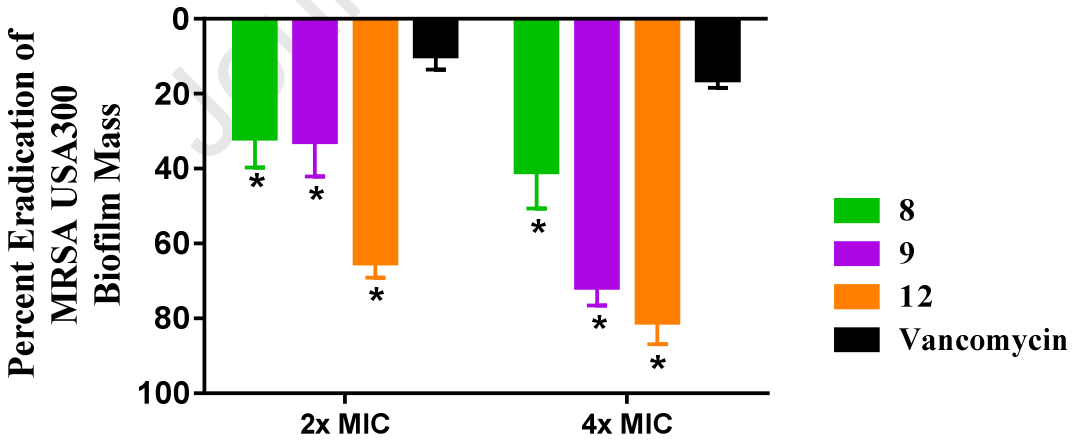


Figure 4. Disruption of mature MRSA USA300 biofilm by tested phenythiazoles and vancomycin (at 2× MIC and 4× MIC). The data are presented as percent disruption of MRSA USA300 mature biofilm in relation to DMSO (the solvent for the compounds that served as a negative control). The values represent an average of four samples analyzed for each compound/antibiotic. Error bars represent standard deviation values. An asterisk (*) denotes

statistical significance ($P < 0.05$) between results for compounds **8, 9** and **12** and vancomycin analyzed via two-way ANOVA test with post-hoc Dunnett's test for multiple comparisons.

A second important attribute required in antibiotic drug discovery is inhibiting the bacterial virulence factors like biofilm. Biofilm represents a shell that protects pathogens from the effect of antibiotics. Therefore, many antibiotics currently used in the clinics are unable to reach hidden bacteria within the biofilms [31]. Moreover, bacterial biofilm is the key source of infections on indwelling medical devices [32, 33]. Thus, development novel antibacterial agent with antibiofilm activity is highly advantageous. Upon testing three of our active compounds (**8**, **9** and **12**) for their ability to eradicate pre-formed, mature staphylococcal biofilm, it was found that they were superior to vancomycin in MRSA biofilm eradication, which disrupted about 9% and 16% of MRSA biofilm mass at 2× MIC and 4× MIC, respectively (Figure 4). The tested phenylthiazoles exhibited a concentration-dependent biofilm disruption activity. The most important compound in this series (compound **8**) showed the least biofilm eradication activity as it disrupted only 31% and 41% of MRSA USA300 biofilm (around 3-times better than vancomycin) at 2× MIC and 4× MIC, respectively. Interestingly, the potential metabolite of compound **8** (i.e., compound **9**) showed double efficacy in terms of anti-biofilm activity as it disrupted about 72% of the pre-formed MRSA USA300 biofilm, at 4× MIC, (Figure 4) and it was the same as **8** in terms of biofilm disruption at 2× MIC. Compound **12** exhibited the most effective biofilm disruption activity among the tested compounds where it disrupted about 65% and 81% of the pre-formed biofilm 2× MIC and 4× MIC, respectively.

A third important attribute for a future antibiotic is the ability to reach intracellular pathogens as this is one of the most deceitful mechanisms of microbial virulence. Most antibiotics are unable to target intracellular bacteria due to low levels of accumulation

intracellularly and inactivation or loss of activity due to the acidic pH within macrophages or binding to lysosomal contents [33]. For instance, vancomycin, one of our last resorts for fighting MDR-Gram positive infections, is unable to sufficiently accumulate inside macrophage cells and clear the intracellular MRSA infection even after 24-hours of treatment at a high concentration as depicted in Figure 5. On the other hand, azetidine-containing compound **8** (at 2 × MIC), generated a 1.82-$\log_{10}$ reduction (equivalent to 98% reduction) of intracellular MRSA. This increased to reach about 2.56 $\log_{10}$ reduction (equivalent to 99.7% reduction) of intracellular MRSA when its concentration was increased to 4 × MIC. The hydroxyazetidine analog **9** was less active as it generated a 0.31-$\log_{10}$ reduction (equivalent to 55% reduction) of intracellular MRSA. This increased to reach about 2.14 $\log_{10}$ reduction (equivalent to 99% reduction) of intracellular MRSA when the concentration was increased to 4 × MIC (Figure 5). Collectively, these data indicated that the most promising compound **8**, and its potential metabolite **9**, had the ability to gain entry into the infected macrophage cells at non-toxic concentrations, at non-toxic concentration as indicated in Figure 3S - (4 and 8 µg/mL), and this concentration is capable of significantly reducing the burden of MRSA inside them.

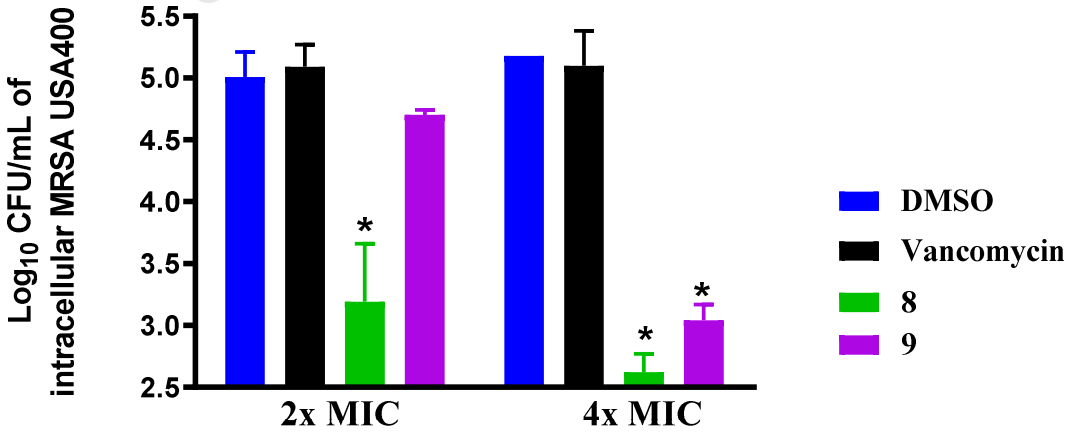


Figure 5. Examination of the activity of compounds **8** and **9** on the clearance of intracellular MRSA present in murine macrophage (J774) cells. Data are presented as $\log_{10}$ colony forming

units of MRSA USA400 per mL inside infected murine macrophages after treatment with 2×MIC and 4×MIC of either tested two compounds or vancomycin (tested in quadruplicates) for 24-hours. Data were analyzed via two-way ANOVA, with post hoc Dunnet's multiple comparisons test ($P < 0.05$), utilizing GraphPad Prism 6.0 (GraphPad Software, La Jolla, CA). Asterisks (*) represent a significant difference between the treatment of J774 cells with compound **8** and **9** in comparison to vancomycin.

3. Conclusion. Statistically, there is a strong connection between the high rate of drug-candidates attrition from clinical trials and their physicochemical properties. To advance the development of phenylthiazole antibiotics, we turned our attention to limit their lipophilic property. In this regard, two phenylthiazole cores, one carries alkoxy moiety and the other one with alkynyl side chain, were selected for the next round of structural optimization. Both selected cores have the advantage of metabolic stability over the lead compound **1a**. By using nitrogen-containing cycles as part of the lipophilic part of phenylthiazole molecules, the physicochemical properties of alkynyl-containing phenythiazoles were remarkably enhanced. Briefly, the cLogP value of azetidine-containing derivative **8** was reduced to the half value of the corresponding derivative **1d** with the same number of carbons, resulting in more than 100-times improvement in the aqueous solubility. Consequently, compound **8** was found to be well-orally absorbed and reach a plasma concentration that exceeds its maximum MIC value within only few minutes. Other advantageous PK attributes include descent metabolic stability, low rate of clearance and good body distribution. Remarkably, the hydroxyazetidine derivative **9** was identified as the main potential metabolite and it turned to be biologically potent with a notable antibiofilm activity that exceeds that of the parent molecule **8**. Therefore, this work suggests compound **8** as a good therapeutic candidate for *S. epidermidis* and *S. aureus* that are significant sources of biofilm-related infections [34]. Finally, both compounds **8** and **9** possess high ability to penetrate inside the infected macrophages at lower concentrations capable of killing the intracellular MRSA. Consequently, due to their efficient intracellular clearance activity, compounds **8** and **9**

could be nominated as perfect therapeutic options for the treatment of pneumonia-induced MRSA infection, which is difficult to treat using current antibiotics including vancomycin [35].

4. Experimental

4.1. Chemistry

4.1.1. General. ^{1}H NMR spectra were run at 400 MHz and ^{13}C spectra were determined at 100 MHz in deuterated dimethyl sulfoxide (DMSO-d_6) on a Varian Mercury VX-400 NMR spectrometer. Chemical shifts are given in parts per million (ppm) on the delta (δ) scale. Chemical shifts were calibrated relative to those of the solvents. Flash chromatography was performed on 230-400 mesh silica. The progress of reactions was monitored with Merck silica gel IB2-F plates (0.25 mm thickness). Mass spectra were recorded at 70 eV. High resolution mass spectra for all ionization techniques were obtained from a FinniganMAT XL95. Melting points were determined using capillary tubes with a Stuart SMP30 apparatus and are uncorrected. All yields reported refer to isolated yields.

4.1.2. 1-(2-(4-(4-Bromobut-1-yn-1-yl)phenyl)-4-methylthiazol-5-yl)ethan-1-one (4). To dry DME (5 mL) in a sealed tube, compound **3** (300 mg, 0.87 mmol), triethylamine (2 mL) were added. After the reaction mixture was purged with dry nitrogen gas for 15 min, dichlorobis(triphenylphosphine)palladium (II) (46 mg, 0.065 mmol), copper (I) iodide (33 mg, 0.17 mmol) and 4-bromobut-1-yn (174 mg, 0.123 mL, 1.3 mmol) were added. The sealed tube was then heated and stirred at 50 ^{o}C for 24 h. and monitored by thin-layer chromatography (TLC). After completion of the reaction, the reaction mixture was passed through a pad of silica gel with ethylacetate to remove some insoluble salts. The desired product was obtained by silica gel chromatography using eluent (EtOAc/ Hexane 9:1). Yellow solid (275 mg, 90.7%); mp = 145-147 °C; ^{1}H NMR (DMSO-d_6) δ: 8.03 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 6.22 (dd,

J = 16.0, 7.0 Hz, 2H), 5.86 (dd, *J* = 16.3, 6.8 Hz, 2H), 2.72 (s, 3H), 2.59 (s, 3H); ^{13}C NMR (DMSO-d_6) δ: 190.5, 165.1, 152.6, 133.2, 132.9, 130.3, 127.9, 122.3, 88.6, 81.7, 33.5, 30.6, 24.9, 16.1; MS (*m/*z); 346 (M^+, 29.7%), 348 (M^{+2}, 30.8%); Anal. Calc. for: $C_{16}H_{14}BrNOS$ (348): C, 55.18; H, 4.05; N, 4.02%; Found: C, 55.26; H, 4.11; N, 4.09%.

4.1.3. 1-(2-(4-(4-(*Sec*. amine derivatives-1-yl)but-1-yn-1-yl)phenyl)-4-methylthiazol-5-yl) ethan-1-one (5a-n). *General procedure*: to dry DMF (5 mL) in a round flask, compound **4** (200 mg, 0.57 mmol), anhydrous potassium carbonate (237 mg, 1.7 mmol, 3 equiv.), and appropriate *Sec*. amines (2.8 mmol, 5 equiv.), with a catalytic amount of potassium iodide was heated at 110 ^{o}C with stirring overnight. The reaction mixture was cooled, poured on crushed ice after then, the organic material was extract 3 times with ethyl acetate and dried over anhydrous sodium sulphate and concentrated over reduced pressure to get yellowish-brown oil. Yields, physical properties, and spectral data of isolated purified products are listed below:

4.1.3.1. 1-(2-(4-(4-(Azitidin-1-yl)but-1-yn-1-yl)phenyl)-4-methylthiazol-5-yl)ethan-1-one (5a). Orange oil (140 mg, 75%); ^{1}H NMR (DMSO-d_6) δ: 8.21 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 3.83 (t, *J* = 7.2 Hz, 4H), 3.71 (t, *J* = 6.8 Hz, 2H), 3.51 (t, *J* = 6.4 Hz, 2H), 2.69 (s, 3H), 2.58 (s, 3H), 2.11-1.98 (m, 2H); ^{13}C NMR (DMSO-d_6) δ: 191.5, 164.8, 150.0, 133.7, 129.4, 127.2, 122.9, 120.1, 87.8, 79.9, 57.2, 49.6, 30.1, 18.8, 17.7, 16.5; MS (*m*\z).

4.1.3.2. 1-(2-(4-(4-(3-Hydroxyazitidin-1-yl)but-1-yn-1-yl)phenyl)-4-methylthiazol-5-yl) ethan-1-one (5b). Yellowish oil (163 mg, 83.5%); ^{1}H NMR (DMSO-d_6) δ: 7.98 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 5.76 (brs, 1H), 4.71-4.68 (m, 1H), 4.41 (dd, *J* = 13.1, 3.4 Hz, 2H), 4.39 (dd, *J* = 12.3, 3.1 Hz, 2H), 4.06 (t, *J* = 5.4 Hz, 2H), 2.98 (t, *J* = 5.2 Hz, 2H), 2.61 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (DMSO-d_6) δ: 191.9, 164.7, 150.1, 134.2, 129.4, 127.4, 122.3, 121.1, 83.5, 79.2, 62.7, 57.2, 49.8, 30.6, 20.5, 18.3, 16.8; MS (*m*\z); 340 (M^+, 26.2%).

4.1.3.3. 1-(4-Methyl-2-(4-(4-(pyrrolidin-1-yl)but-1-yn-1-yl)phenyl)thiazol-5-yl)ethan-1-one (5c). Brown oil (138 mg, 71%); ^{1}H NMR (DMSO-d_6) δ: 8.21 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8.8 Hz, 2H), 3.63 (dd, J = 11.3, 5.4 Hz, 2H), 3.55-3.48 (m, 4H), 3.22 (dd, J = 10.3, 3.4 Hz, 2H), 2.71 (s, 3H), 2.56 (s, 3H), 1.93-1.89 (m, 4H); ^{13}C NMR (DMSO-d_6) δ: 191.4, 167.3, 154.8, 132.7, 131.6, 127.4, 122.6, 121.8, 94.7, 83.5, 57.6, 50.9, 24.8, 22.5, 18.1, 16.7; MS (*m*\z); 338 (M^+, 19.9%).

4.1.3.4. 1-(4-Methyl-2-(4-(4-(thiazolidin-3-yl)but-1-yn-1-yl)phenyl)thiazol-5-yl)ethan-1-one (5d). Yellow oil (167 mg, 81.8%); ^{1}H NMR (DMSO-d_6) δ: 8.12 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 8.1 Hz, 2H), 4.42 (s, 2H), 3.76 (dd, J = 11.3, 5.4 Hz, 2H), 3.59 (t, J = 6.4 Hz, 2H), 3.23 (t, J = 6.4 Hz, 2H), 2.76 (s, 3H), 2.61 (s, 3H), 2.06 (t, J = 5.4 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ: 191.6, 165.1, 150.0, 134.8, 129.6, 127.7, 122.7, 120.1, 88.4, 79.8, 66.1, 61.2, 55.3, 30.1, 25.5, 18.5, 16.7; MS (*m*\z); 356 (M^+, 39.73%).

4.1.3.5. 1-(2-(4-(4-(1*H*-Imidazol-1-yl)but-1-yn-1-yl)phenyl)-4-methylthiazol-5-yl)ethan-1-one (5e). Dark brown oil (143 mg, 74%); ^{1}H NMR (DMSO-d_6) δ: 7.81 (d, J = 8.4 Hz, 2H), 7.78 (s, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 6.8 Hz, 1H), 6.96 (d, J = 6.8 Hz, 1H), 4.55 (t, J = 9.8 Hz, 2H), 2.68 (s, 3H), 2.61 (t, J = 9.6 Hz, 2H), 2.47 (s, 3H); ^{13}C NMR (DMSO-d_6) δ: 191.1, 163.4, 154.7, 142.3, 140.4, 138.2, 129.8, 127.8, 127.3, 121.9, 119.2, 90.2, 79.7, 46.1, 32.2, 24.4, 17.7; MS (*m*\z); 335 (M^+, 43.29%).

4.1.3.6. 1-(4-Methyl-2-(4-(4-(piperidin-1-yl)but-1-yn-1-yl)phenyl)thiazol-5-yl)ethan-1-one (5f). Yellow oil (170 mg, 84%); ^{1}H NMR (DMSO-d_6) δ: 7.85 (d, J = 8.2 Hz, 2H), 7.51 (d, J = 8.2 Hz, 2H), 3.81 (t, J = 6.8 Hz, 2H), 3.56 (t, J = 6.4 Hz, 4H), 2.75 (s, 3H), 2.68 (t, J = 5.7 Hz, 2H), 2.52 (s, 3H), 1.67-1.49 (m, 6H); ^{13}C NMR (DMSO-d_6) δ: 193.8, 163.2, 153.6, 145.8, 132.4,

130.6, 127.5, 122.1, 118.6, 89.8, 82.3, 60.1, 49.2, 26.4, 25.1, 24.4, 18.3, 17.8; MS (*m\z*); 352 (M^+, 39.17%).

4.1.3.7. 1-(4-Methyl-2-(4-(4-(2-methylpiperidin-1-yl)but-1-yn-1-yl)phenyl)thiazol-5-yl)ethan -1-one (5g). Brown oil (183 mg, 87%); ^{1}H NMR (DMSO-d_6) δ: 7.88 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 3.53-3.50 (m, 2H), 2.71 (t, *J* = 5.4 Hz, 2H), 2.65 (s, 3H), 2.62-2.59 (m, 1H), 2.52 (s, 3H), 1.98-1.89 (m, 2H), 1.58-1.27 (m, 6H), 0.85 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 192.1, 168.4, 158.7, 146.8, 143.3, 131.6, 129.8, 126.8, 87.7, 82.3, 62.6, 55.3, 53.7, 33.6, 27.4, 24.6, 22.6, 18.3, 17.6, 16.1; MS (*m\z*); 366 (M^+, 49.21%).

4.1.3.8. 1-(4-Methyl-2-(4-(4-(3-methylpiperidin-1-yl)but-1-yn-1-yl)phenyl)thiazol-5-yl)ethan -1-one (5h). Yellow oil (190 mg, 90%); ^{1}H NMR (DMSO-d_6) δ: 7.97 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 4.08-3.98 (m, 2H), 3.63-3.57 (m, 2H), 3.25-3.22 (m, 2H), 2.88-2.81 (m, 2H), 2.76 (s, 3H), 2.62 (s, 3H), 1.75-1.46 (m, 5H), 1.26 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 191.4, 168.9, 158.1, 146.5, 142.2, 131.7, 129.9, 125.8, 87.4, 81.7, 61.5, 55.1, 48.3, 32.6, 26.2, 24.7, 21.6, 18.8, 18.1, 16.8; MS (*m\z*); 366 (M^+, 48.61%).

4.1.3.9. 1-(4-Methyl-2-(4-(4-(4-methylpiperidin-1-yl)but-1-yn-1-yl)phenyl)thiazol-5-yl)ethan -1-one (5i). Light-yellow oil (194 mg, 92%); ^{1}H NMR (DMSO-d_6) δ: 7.88 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 3.53-3.51 (m, 2H), 3.02-2.94 (m, 2H), 2.81-2.76 (m, 4H), 2.61 (s, 3H), 2.31 (s, 3H), 2.24 (m, 4H), 1.61-1.11 (m, 1H), 0.90 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 191.3, 161.4, 158.4, 144.3, 136.6, 132.8, 126.7, 124.5, 88.6, 84.9, 58.2, 47.6, 34.8, 30.2, 22.4, 18.1, 17.3, 16.4; MS (*m\z*); 366 (M^+, 55.61%).

4.1.3.10. 1-(4-Methyl-2-(4-(4-(4-methylpiperazin-1-yl)but-1-yn-1-yl)phenyl)thiazol-5-yl) ethan-1-one (5j). Orange oil (153 mg, 72.8%); ^{1}H NMR (DMSO-d_6) δ: 7.76 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 3.65 (s, 4H), 3.48-3.29 (m, 4H), 3.24 (s, 4H), 2.71 (s, 3H), 2.41 (s, 3H),

2.24 (s, 3H); ^{13}C NMR (DMSO-d_6) δ: 191.8, 167.3, 158.6, 148.3, 132.6, 132.3, 127.4, 122.5, 88.5, 84.3, 57.5, 54.7, 53.5, 44.1, 26.3, 21.4, 18.7; MS (*m*\z); 367 (M^+, 19.14%).

4.1.3.11. 1-(4-Methyl-2-(4-(4-(4-morpholinobut-1-yn-1-yl)phenyl)thiazol-5-yl)ethan-1-one (5k). Brown oil (148 mg, 73%); ^{1}H NMR (DMSO-d_6) δ: 7.76 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 3.83 (t, *J* = 6.4 Hz, 4H), 3.63-3.51 (m, 6H), 2.76-2.67 (m, 2H), 2.51 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (DMSO-d_6) δ: 191.6, 168.4, 158.6, 148.3, 133.2, 132.9, 127.5, 122.7, 96.6, 84.8, 57.3, 55.4, 48.4, 26.2, 21.5, 18.3; MS (*m*\z); 354 (M^+, 9.2%).

4.1.3.12. 1-(4-Methyl-2-(4-(4-(4-thiomorpholinobut-1-yn-1-yl)phenyl)thiazol-5-yl)ethan-1-one (5 l). Yellow oil (152 mg, 71%); ^{1}H NMR (DMSO-d_6) δ: 7.76 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 4.23 (t, *J* = 6.4 Hz, 4H), 3.79-3.75 (m, 2H), 2.53 (t, *J* = 6.4 Hz, 4H), 2.76-2.71 (m, 2H), 2.51 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (DMSO-d_6) δ: 191.6, 168.4, 158.9, 148.3, 133.8, 133.1, 127.6, 122.2, 96.4, 84.6, 58.5, 55.7, 34.8, 26.5, 21.1, 18.3; MS (*m*\z); 370 (M^+, 14.4%).

4.1.3.13. 1-(2-(4-(4-(Azepan-1-yl)but-1-yn-1-yl)phenyl)-4-methylthiazol-5-yl)ethan-1-one (5m). Dark-brown oil (143 mg, 68%); ^{1}H NMR (DMSO-d_6) δ: 7.88 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 3.73 (t, *J* = 5.4 Hz, 4H), 3.61-3.52 (m, 2H), 2.71 (s, 3H), 2.61-2.58 (m, 2H), 2.49 (s, 3H), 1.61-0.76 (m, 8H); ^{13}C NMR (DMSO-d_6) δ: 191.5, 167.9, 158.6, 148.8, 133.7, 133.2, 127.2, 122.8, 96.5, 84.6, 56.1, 47.1, 34.4, 25.9, 16.8, 14.7; MS (*m*\z); 366 (M^+, 8.17%).

4.1.3.14. 1-(4-Methyl-2-(4-(4-(octahydroisoquinolin-2(1*H*)-yl)but-1-yn-1-yl)phenyl)thiazol-5-yl)ethan-1-one (5n). Brown oil (175 mg, 75%); ^{1}H NMR (DMSO-d_6) δ: 7.88 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 3.51-3.48 (m, 2H), 3.23-3.18 (m, 2H), 2.77-2.64 (m, 4H), 2.56 (s, 3H), 2.26 (s, 3H), 2.20-0.89 (m, 12H); ^{13}C NMR (DMSO-d_6) δ: 191.1, 167.4, 162.6, 148.5, 146.4,131.7, 128.3, 120.2, 92.2, 80.8, 61.4, 59.8, 47.1, 36.3, 34.9, 33.7, 32.4, 26.5, 25.1, 23.7 19.1, 16.5; MS (*m*\z); 406 (M^+, 20.6%).

4.1.4. 2-(1-(2-(4-(3-(Substituted-*sec*-amine-1-yl)but-1-yn-1-yl)phenyl)-4-methylthiazol-5-yl) ethylidene)-1-carboximidamide (8-21). *General procedure:* Thiazole derivatives **5a-n** (0.57-0.64 mmol) were dissolved in absolute ethanol (20 mL), concentrated hydrochloric acid (1 mL), aminoguanidine hydrochloride (355 mg, 3.2 mmol, 5 equiv.), were added. The reaction mixture was heated at reflux for 4 h. The solvent was concentrated under reduced pressure, then poured in crushed ice and neutralized with sodium carbonate to pH 7-8, and the formed precipitated solid was collected by filtration, washed with copious amount of water. Crystallization from ethylacetate afforded the desired products as solids.

4.1.4.1. 2-(1-(2-(4-(4-(Azetidin-1-yl)but-1-yn-1-yl)phenyl)-4-methylthiazol-5-yl)ethylidene) hydrazine-1-carboximidamide (8). Orange solid (176 mg, 75%); mp = 246-247 °C. ^{1}H NMR (DMSO -d_6) δ: 8.05 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 5.77 (brs, 2H), 5.75 (brs, 2H), 3.98 (t, J = 5.2 Hz, 4H), 3.87 (t, J = 6.4 Hz, 2H), 3.51 (t, J = 6.4 Hz, 2H), 2.74 (s, 3H), 2.55 (s, 3H), 2.13-1.99 (m, 2H); ^{13}C NMR (DMSO-d_6) δ: 163.3, 158.4, 151.6, 145.2, 133.7, 133.1, 126.3, 124.7, 117.5, 93.2, 82.4, 61.1, 48.6, 24.8, 23.9, 18.3, 17.8; HRMS (EI) *m/z* 380.1785 M^+, calc. for $C_{20}H_{24}N_6S$ 380.1783; Anal. Calc. for: $C_{20}H_{24}N_6S$ (380): C, 63.13; H, 6.36; N, 22.09%; Found: C, 63.23; H, 6.44; N, 22.19%.

4.1.4.2. 2-(1-(2-(4-(4-(3-Hydroxyazetidin-1-yl)but-1-yn-1-yl)phenyl)-4-methylthiazol-5-yl) ethylidene)hydrazine-1-carboximidamide (9). Orange solid (175 mg, 75%); mp = 255-256 °C. ^{1}H NMR (DMSO -d_6) δ: 11.12 (brs, 1H), 7.86 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 5.91 (brs, 3H), 5.61 (brs, 1H), 4.65-4.58 (m, 1H), 4.15 (dd, J = 12.2, J = 5.2 Hz, 2H), 3.98 (dd, J = 11.2, J = 3.2 Hz, 2H), 2.88-2.83 (m, 2H), 2.53 (s, 3H), 2.34 (s, 3H), 1.77-1.72 (m, 2H); ^{13}C NMR (DMSO-d_6) δ: 163.6, 158.2, 151.3, 145.1, 133.7, 133.2, 127.3, 124.5, 118.1, 89.2, 81.4, 64.6, 59.7, 48.8, 23.7, 23.1, 18.3, 16.9; HRMS (EI) *m/z* 396.1745 M^+, calc. for $C_{20}H_{24}N_6OS$ 396.1732;

Anal. Calc. for: $C_{20}H_{24}N_6OS$ (396): C, 60.58; H, 6.10; N, 21.20%; Found: C, 61.04; H, 6.17; N, 21.28%.

4.1.4.3. 2-(1-(4-Methyl-2-(4-(4-(pyrrolidin-1-yl)but-1-yn-1-yl)phenyl)thiazol-5-yl)ethylidene) hydrazine-1-carboximidamide (10). Brown solid (171 mg, 73%); mp = 241-240 °C. ^{1}H NMR (DMSO -d_6) δ: 7.87 (d, *J* = 7.2 Hz, 2H), 7.51 (d, *J* = 7.2 Hz, 2H), 5.76 (brs, 2H), 5.66 (brs, 2H), 3.76 (s, 2H), 2.59 (m, 4H), 2.57 (s, 3H), 2.31 (s, 3H), 1.73 (m, 4H); ^{13}C NMR (DMSO-d_6) δ: 161.57, 160.24, 148.44, 142.99, 136.48, 133.36, 132.27, 126.22, 124.14, 88.99, 84.49, 52.43, 43.89, 23.77, 18.83, 16.55; HRMS (EI) *m/z* 394.1933 M^+, calc. for $C_{21}H_{26}N_6S$ 394.1940; Anal. Calc. for: $C_{21}H_{26}N_6S$ (394): C, 63.13; H, 6.36; N, 22.09%; Found: C, 63.16; H, 6.37; N, 22.11%.

4.1.4.4. 2-(1-(4-Methyl-2-(4-(4-(thiazolidin-3-yl)but-1-yn-1-yl)phenyl)thiazol-5-yl)ethylidene)hydrazine-1-carboximidamide (11). Brown solid (186 mg, 80%); mp = 235-237 °C. ^{1}H NMR (DMSO -d_6) δ: 7.96 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 5.67 (brs, 2H), 5.53 (brs, 2H), 3.97 (s, 2H), 3.68-3.61 (m, 2H), 3.53 (t, *J* = 6.4 Hz, 2H), 3.11-3.08 (m, 2H), 2.72 (s, 3H), 2.53 (s, 3H), 1.97 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ: 163.5, 158.6, 151.6, 145.3, 133.1, 132.8, 126.2, 124.4, 117.7, 91.4, 79.5, 66.2, 65.5, 52.3, 33.7, 21.4, 18.4, 16.5; HRMS (EI) *m/z* 412.1491 M^+, calc. for $C_{20}H_{24}N_6S_2$ 412.1504; Anal. Calc. for: $C_{20}H_{24}N_6S_2$ (412): C, 58.22; H, 5.86; N, 20.37%; Found: C, 58.29; H, 5.95; N, 20.42%.

4.1.4.5. 2-(1-(2-(4-(4-(1*H*-Imidazol-1-yl)but-1-yn-1-yl)phenyl)-4-methylthiazol-5-yl)ethylidene)hydrazine-1-carboximidamide (12). Brown solid (177 mg, 76%); mp = 201-202 °C. ^{1}H NMR (DMSO -d_6) δ: 11.23 (brs, 1H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.83 (s, 1H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 7.2 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 5.68 (brs, 3H), 3.82 (t, *J* = 6.2 Hz, 2H), 2.52 (s, 3H), 2.48 (t, *J* = 5.6 Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (DMSO-d_6) δ: 163.5, 158.6, 151.3,

145.1, 138.3, 134.7, 133.7, 132.8, 126.4, 124.5, 118.6, 116.5, 91.2, 79.7, 45.3, 21.6, 18.5, 16.8; HRMS (EI) *m/z* 391.1595 M^+, calc. for $C_{20}H_{21}N_7S$ 391.1579; Anal. Calc. for: $C_{20}H_{21}N_7S$ (391): C, 61.36; H, 5.41; N, 25.04%; Found: C, 61.42; H, 5.48; N, 25.10%.

4.1.4.6. 2-(1-(4-Methyl-2-(4-(4-(piperidin-1-yl)but-1-yn-1-yl)phenyl)thiazol-5-yl)ethylidene) hydrazine-1-carboximidamide (13). Yellow solid (196 mg, 85%); mp = 245-246 °C. ^{1}H NMR (DMSO -d_6) δ: 11.03 (brs, 1H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.80 (brs, 3H), 7.67 (d, *J* = 8.4 Hz, 2H), 3.72-3.67 (m, 4H), 3.56-3.48 (m, 2H), 2.73 (s, 3H), 2.68-2.62 (m, 2H), 2.52 (s, 3H), 1.75-1.56 (m, 6H); ^{13}C NMR (DMSO-d_6) δ: 163.4, 158.3, 151.6, 145.6, 136.7, 133.9, 133.2, 126.8, 118.1, 91.3, 79.6, 63.5, 59.6, 27.8, 27.2, 20.9, 18.5, 16.8; HRMS (EI) *m/z* 408.2099 M^+, calc. for $C_{22}H_{28}N_6S$ 408.2096; Anal. Calc. for: $C_{22}H_{28}N_6S$ (408.5): C, 64.68; H, 6.91; N, 20.57%; Found: C, 64.75; H, 6.98; N, 20.66%.

4.1.4.7. 2-(1-(4-Methyl-2-(4-(4-(2-methylpiperidin-1-yl)but-1-yn-1-yl)phenyl)thiazol-5-yl) ethylidene)hydrazine-1-carboximidamide (14). Yellow solid (196 mg, 84%); mp = 235-236 °C. ^{1}H NMR (DMSO -d_6) δ: 11.12 (brs, 1H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 5.61 (brs, 3H), 3.55-3.49 (m, 2H), 2.82-2.76 (m, 1H), 2.71-2.69 (m, 2H), 2.68 (s, 3H), 2.59-2.53 (m. 2H), 2.48 (s, 3H), 1.96-1.48 (m, 6H), 0.85 (d, *J* = 4.8 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 163.6, 158.5, 151.3, 145.4, 136.7, 134.2, 133.8, 126.7, 117.2, 91.6, 79.7, 63.4, 54.8, 53.9, 27.5, 26.8, 23.7, 20.3, 18.7, 16.4; HRMS (EI) *m/z* 422.2260 M^+, calc. for $C_{23}H_{30}N_6S$ 422.2253; Anal. Calc. for: $C_{23}H_{30}N_6S$ (422.5): C, 65.37; H, 7.16; N, 19.89%; Found: C, 65.45; H, 7.22; N, 19.95%.

4.1.4.8. 2-(1-(4-Methyl-2-(4-(4-(3-methylpiperidin-1-yl)but-1-yn-1-yl)phenyl)thiazol-5-yl) ethylidene)hydrazine-1-carboximidamide (15). Yellow solid (203 mg, 88%); mp = 257-259 °C. ^{1}H NMR (DMSO -d_6) δ: 10.87 (brs, 1H), 7.92 (d, *J* = 8.4 Hz, 2H), 7.82 (brs, 2H), 7.76 (d, *J* =

8.4 Hz, 2H), 6.84 (brs, 1H), 4.05-3.89 (m, 2H), 3.62-3.51 (m, 2H), 3.25-3.20 (m, 2H), 2.85 (d, *J* = 9.6 Hz, 2H), 2.79 (s, 3H), 2.75 (s, 3H), 1.86 (m, 1H), 1.58-1.41 (m, 4H), 1.31 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 163.5, 158.6, 152.3, 145.1, 136.4, 133.8, 133.1, 127.3, 117.7, 91.4, 79.9, 63.2, 54.2, 53.8, 30.1, 27.6, 24.1, 22.6, 18.5, 16.9; HRMS (EI) *m/z* 422.2257 M^+, calc. for $C_{23}H_{30}N_6S$ 422.2253; Anal. Calc. for: $C_{23}H_{30}N_6S$ (422.5): C, 65.37; H, 7.16; N, 19.89%; Found: C, 65.48; H, 7.25; N, 19.99%.

4.1.4.9. 2-(1-(4-Methyl-2-(4-(4-(4-methylpiperidin-1-yl)but-1-yn-1-yl)phenyl)thiazol-5-yl) ethylidene)hydrazine-1-carboximidamide (16). Yellow solid (212 mg, 92%); mp = 258-260 °C. ^{1}H NMR (DMSO -d_6) δ: 7.88 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 8.2 Hz, 2H), 5.71 (brs, 2H), 5.53 (brs, 2H), 3.62-3.51 (m, 2H), 3.03-2.92 (m, 2H), 2.63-2.51 (m, 4H), 2.59 (s, 3H), 2.31 (s, 3H), 2.22-2.16 (m, 4H), 1.61-1.18 (m, 1H), 0.91 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 163.6, 158.9, 152.2, 145.1, 133.2, 132.8, 127.4, 124.9, 117.7, 92.3, 90.8, 57.5, 43.4, 34.9, 31.6, 23.4, 21.8, 18.6, 16.4; HRMS (EI) *m/z* 422.2263 M^+, calc. for $C_{23}H_{30}N_6S$ 422.2253; Anal. Calc. for: $C_{23}H_{30}N_6S$ (422.5): C, 65.37; H, 7.16; N, 19.89%; Found: C, 65.47; H, 7.22; N, 19.99%.

4.1.4.10. 2-(1-(4-Methyl-2-(4-(4-(4-methylpiperazin-1-yl)but-1-yn-1-yl)phenyl)thiazol-5-yl) ethylidene)hydrazine-1-carboximidamide (17). Orange solid (166 mg, 72%); mp = 233-235 °C. ^{1}H NMR (DMSO -d_6) δ: 7.79 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 8.8 Hz, 2H), 5.77 (brs, 2H), 5.65 (brs, 2H), 3.81-3.75 (m, 4H), 3.48-3.38 (m, 2H), 3.21-3.18 (m, 4H), 2.72 (s, 3H), 2.52 (s, 3H), 2.41-2.38 (m, 2H), 2.25 (s, 3H); ^{13}C NMR (DMSO-d_6) δ: 163.8, 158.6, 152.5, 145.3, 133.8, 133.1, 127.2, 124.3, 117.7, 87.7, 81.1, 59.9, 58.7, 56.3, 46.7, 22.2, 19.7, 18.5, 16.6; HRMS (EI) *m/z* 423.2218 M^+, calc. for $C_{22}H_{29}N_7S$ 423.2205; Anal. Calc. for: $C_{22}H_{29}N_7S$ (423.5): C, 62.38; H, 6.90; N, 23.15%; Found: C, 62.55; H, 6.99; N, 23.25%.

4.1.4.11. 2-(1-(4-Methyl-2-(4-(4-morpholinobut-1-yn-1-yl)phenyl)thiazol-5-yl)ethylidene) hydrazine-1-carboximidamide (18). Brown solid (192 mg, 83%); mp = 250-253 °C. ^{1}H NMR (DMSO -d_6) δ: 7.77 (d, J = 7.2 Hz, 2H), 7.45 (d, J = 7.2 Hz, 2H), 5.65 (brs, 2H), 5.48 (brs, 2H), 3.85-3.76 (m, 2H), 3.65-3.60 (m, 4H), 3.58-3.52 (m, 4H), 2.79-2.7 (m, 2H), 2.53 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (DMSO-d_6) δ: 163.8, 158.9, 152.3, 145.2, 133.7, 133.5, 132.9, 126.5, 124.9, 117.6, 88.4, 80.6, 66.7, 62.3, 52.8, 22.2, 19.5, 18.5; HRMS (EI) *m/z* 410.1882 M^+, calc. for $C_{21}H_{26}N_6OS$ 410.1889; Anal. Calc. for: $C_{21}H_{26}N_6OS$ (410.5): C, 61.44; H, 6.38; N, 20.47%; Found: C, 61.61; H, 6.46; N, 20.57%.

4.1.4.12. 2-(1-(4-Methyl-2-(4-(4-thiomorpholinobut-1-yn-1-yl)phenyl)thiazol-5-yl) ethylidene)hydrazine-1-carboximidamide (19). Yellow solid (178 mg, 77%); mp = 265-266 °C. ^{1}H NMR (DMSO -d_6) δ: 7.78 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 5.71 (brs, 2H), 5.68 (brs, 2H), 4.21-4.11 (m, 4H), 3.83-3.72 (m, 2H), 3.62-3.52 (m, 4H), 2.79-2.69 (m, 2H), 2.53 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (DMSO-d_6) δ: 163.7, 158.3, 152.5, 145.2, 133.7, 133.1, 126.8, 124.5, 117.9, 88.4, 80.2, 62.3, 58.9, 33.1, 22.2, 18.9, 16.7; HRMS (EI) *m/z* 426.1658 M^+, calc. for $C_{21}H_{26}N_6S_2$ 426.1660; Anal. Calc. for: $C_{21}H_{26}N_6S_2$ (426.6): C, 59.13; H, 6.14; N, 19.70%; Found: C, 59.21; H, 6.23; N, 19.85%.

4.1.4.13. 2-(1-(2-(4-(4-(Azepan-1-yl)but-1-yn-1-yl)phenyl)-4-methylthiazol-5-yl)ethylidene) hydrazine-1-carboximidamide (20). Brown solid (166 mg, 72%); mp = 265-267 °C. ^{1}H NMR (DMSO -d_6) δ: 11.12 (brs, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.74 (brs, 2H), 7.32 (d, J = 8.4 Hz, 2H), 6.80 (brs, 1H), 3.92 (t, J = 6.8 Hz, 4H), 3.61-3.51 (m, 2H), 2.56 (s, 3H), 2.49-2.33 (m, 2H), 2.29 (s, 3H), 1.76-1.25 (m, 8H); ^{13}C NMR (DMSO-d_6) δ: 164.2, 158.9, 151.8, 145.1, 133.7, 132.9, 127.4, 124.3, 117.5, 91.6, 90.0, 58.6, 47.6, 32.1, 30.1, 23.2, 18.4, 16.7; HRMS (EI) *m/z* 422.2238

M^+, calc. for $C_{23}H_{30}N_6S$ 422.2253; Anal. Calc. for: $C_{23}H_{30}N_6S$ (422.5): C, 65.37; H, 7.16; N, 19.89%; Found: C, 65.50; H, 7.24; N, 19.99%.

4.1.4.14. 2-(1-(4-Methyl-2-(4-(4-(octahydroisoquinolin-2(1*H*)-yl)but-1-yn-1-yl)phenyl) thiazol-5-yl)ethylidene)hydrazine-1-carboximidamide (21). Yellow solid (163 mg, 71%); mp = 244-246 °C. ^{1}H NMR (DMSO -d_6) δ: 7.88 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 6.05 (brs, 4H), 3.51-3.48 (m, 2H), 3.15-3.09 (m, 2H), 2.81-2.75 (m, 2H), 2.19-2.12 (m, 2H), 2.49 (s, 3H), 2.26 (s, 3H), 2.18-0.65 (m, 12H); HRMS (EI) *m/z* 462.2570 M^+, calc. for $C_{26}H_{34}N_6S$ 462.2566; Anal. Calc. for: $C_{26}H_{34}N_6S$ (462.6): C, 67.50; H, 7.41; N, 18.16%; Found: C, 67.61; H, 7.55; N, 18.26%.

4.1.5. 1-(2-(4-(*n*-Chloroalkoxy)phenyl)-4-methylthiazol-5-yl)ethan-1-one (23a-c). *General procedure*: To dry DME in a round flask, *p*-hydroxyphenylthiazole **22** (0.86 mmol), anhydrous potassium carbonate (2.56 mmol, 3 equiv.) and appropriate bromochloroalkanes (2.56 mmol, 3 equiv.) were all mixed and refluxed overnight. The solvent was then evaporated under reduced pressure, and the product was washed with water, filtered and dried.

4.1.5.1. 1-(2-(4-(3-Chloropropoxy)phenyl)-4-methylthiazol-5-yl)ethan-1-one (23a). Yellow solid (254 mg, 96%); mp= 92-93 °C; ^{1}H NMR (DMSO-d_6) δ: 7.94 (d, *J* = 8.1 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 4.17 (t, *J* = 6.2 Hz, 2H), 3.80 (t, *J* = 6.2 Hz, 2H), 2.70 (s, 3H), 2.56 (s, 3H), 2.19 (t, *J* = 6.4 Hz, 2H); MS (*m*\z); 309 (M^+, 100%); Anal. Calc. for: $C_{15}H_{16}ClNO_2S$ (309): C, 58.15; H, 5.21; N, 4.52%; Found: C, 58.43; H, 5.52; N, 5.11%.

4.1.5.2. 1-(2-(4-(4-Chlorobutoxy)phenyl)-4-methylthiazol-5-yl)ethan-1-one (23b). White solid (258 mg, 93%); mp = 67-69 °C; ^{1}H NMR (DMSO-d_6) δ: 7.93 (d, *J* = 8.1 Hz, 2H), 7.07 (d, *J* = 8 Hz, 2H), 4.08 (t, *J* = 6 Hz, 2H), 3.73 (t, *J* = 6 Hz, 2H), 2.68 (s, 3H), 2.54 (s, 3H), 1.90-1.87

(m, 4H); MS (*m*\z); 323 (M^+, 100%); Anal. Calc. for: $C_{16}H_{18}ClNO_2S$ (323): C, 59.34; H, 5.60; N, 4.33%; Found: C, 59.51; H, 5.87; N, 5.05%.

4.1.5.3. 1-(2-(4-((5-Chloropenty1)oxy)phenyl)-4-methylthiazol-5-yl)ethan-1-one (23c). Yellow solid (272 mg, 94%); mp = 80-81 °C; ^{1}H NMR (DMSO-d_6) δ: 7.93 (d, *J* = 9.2 Hz, 2H), 7.06 (d, *J* = 9.2 Hz, 2H), 4.04 (t, *J* = 7.6 Hz, 2H), 3.66 (t, *J* = 6.8 Hz, 2H), 3.56 (t, *J* = 8.2 Hz, 2H), 2.67 (s, 3H), 2.54 (s, 3H), 1.89-1.85 (m, 2H), 1.77-1.54 (m, 2H); MS (*m*\z); 337 (M^+, 100%); Anal. Calc. for: $C_{17}H_{20}ClNO_2S$ (337): C, 60.43; H, 5.97; N, 4.15%; Found: C, 60.93; H, 6.41; N, 5.46%.

4.1.6. 1-(4-Methyl-2-(4-(*n*-*Sec*.amino)alkoxy)phenyl)thiazol-5-yl)ethan-1-one (24-62).

General procedure: to dry DMF (5 mL) in a round flask, compounds **23a-c** (300 mg), anhydrous potassium carbonate (3 equiv.), and appropriate *Sec*. amines (5 equiv.), with a catalytic amount of potassium iodide were heated at 110 ^{o}C with stirring overnight. The reaction mixture was cooled, and then poured on crushed ice, the organic material was extract 3 times with ethylacetate and dried over anhydrous sodium sulphate and concentrated over reduced pressure to get yellowish-brown oil. The desired product was obtained by silica gel chromatography using eluent (DCM/ Methanol 9:1). Yields, physical properties, and spectral data of isolated purified products are listed below:

4.1.6.1. 1-(2-(4-(3-Azetidin-1-yl)propoxy)phenyl)-4-methylthiazol-5-yl)ethan-1-one (24). Orange solid (280mg, 83%); mp = 66-68 °C; ^{1}H NMR (DMSO-d_6) δ: 7.99 (d, *J* = 8.6 Hz, 2H), 7.01 (d, *J* = 8.6 Hz, 2H), 4.15 (t, *J* = 7.2 Hz, 2H), 3.81 (t, *J* = 5.7 Hz, 4H), 2.69 (s,3H), 2.65-2.59 (m, 2H), 2.56 (s, 3H), 1.86-1.25 (m, 4H); MS (*m*\z); 330 (M^+, 22.45%); Anal. Calc. for: $C_{18}H_{22}N_2O_2S$ (330): C, 65.43; H, 6.71; N, 8.48%; Found: C, 65.73; H, 7.04; N, 8.62%.

4.1.6.2. 1-(4-Methyl-2-(4-(3-pyrrolidin-1-yl)propoxy)phenyl)thiazol-5-yl)ethan-1-one (25). Orange solid (271 mg, 81%); mp = 46-48 °C; ^{1}H NMR (DMSO-d_6) δ: 7.95 (d, J = 9.6 Hz, 2H), 7.07 (d, J = 9.6 Hz, 2H), 4.15 (t, J = 6.2 Hz, 2H), 2.69 (s,3H), 2.56 (s, 3H), 2.51-2.49 (m, 4H), 2.14-1.95 (m, 8H); MS (*m*\z); 344 (M^+, 26.27%); Anal. Calc. for: $C_{19}H_{24}N_2O_2S$ (344): C, 66.25; H, 7.02; N, 8.13%; Found: C, 66.43; H, 7.12; N, 8.91%.

4.1.6.3. 1-(4-Methyl-2-(4-(3-thiazolidine-3-yl)propoxy)phenyl)thiazol-5-yl)ethan-1-one (26). Orange solid (291 mg, %); mp = 78-80 °C; ^{1}H NMR (DMSO-d_6) δ: 7.94 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 8.1 Hz, 2H), 4.19 (t, J = 6.2 Hz, 2H), 3.11 (t, J = 4.8 Hz, 2H), 2.66 (s, 2H), 2.55 (s, 3H), 2.39 (s, 3H), 2.05- 1.95 (m, 6H); MS (*m*\z); 362 (M^+, 6.69%); Anal. Calc. for: $C_{18}H_{22}N_2O_2S_2$ (362): C, 59.64; H, 6.12; N, 7.73%; Found: C, 59.91; H, 6.28; N, 7.94%.

4.1.6.4. 1-(2-(4-(3-(1*H*-Imidazol-1-yl)propoxy)phenyl)-4-methylthiazol-5-yl)ethan-1-one (27). Orange solid (261 mg, 79%); mp = 75-77 °C; ^{1}H NMR (DMSO-d_6) δ: 7.92 (d, J = 9.2 Hz, 2H), 7.71 (s, 1H), 7.22 (s, 1H), 7.05 (d, J = 9.2 Hz, 2H), 6.94 (s, 1H), 4.13 (t, J = 6.9 Hz, 2H), 3.97 (t, J = 6.3 Hz, 2H), 2.66 (s, 3H), 2.54 (s, 3H), 2.23-2.17 (m, 2H); MS (*m*\z); 341 (M^+, 100%); Anal. Calc. for: $C_{18}H_{19}N_3O_2S$ (341): C, 63.32; H, 5.61; N, 12.31%; Found: C, 63.09; H, 5.88; N, 12.54%.

4.1.6.5. 1-(4-Methyl-2-(4-(3-(piperidin-1-yl)propoxy)phenyl)thiazol-5-yl)ethan-1-one (28). White solid (303 mg, 87%); mp = 99-101 °C; ^{1}H NMR (DMSO-d_6) δ: 7.97 (d, J = 6.4 Hz, 2H), 7.07 (d, J = 6.4 Hz, 2H), 4.07 (t, J = 10.2 Hz, 2H), 2.68 (s, 3H), 2.54 (s, 3H), 2.49- 2.40 (m, 6H), 1.92- 1.90 (m, 2H), 1.60- 1.40 (m, 6H); MS (*m*\z); 358 (M^+, 25.65%); Anal. Calc. for: $C_{20}H_{26}N_2O_2S$ (358): C, 67.01; H, 7.31; N, 7.81%; Found: C, 66.87; H, 7.49; N, 7.93%.

4.1.6.6. 1-(4-Methyl-2-(4-(3-(2-methylpiperidin-1-yl)propoxy)phenyl)thiazol-5-yl)ethan-1-one (29). Yellow solid (296 mg, 82%); mp = 85-86 °C; ^{1}H NMR (DMSO-d_6) δ: 7.95 (d, J = 8.8

Hz, 2H), 7.07 (d, *J* = 8.8 Hz, 2H), 4.08 (t, *J* = 7.6 Hz, 2H), 2.89-2.74 (m, 2H), 2.69 (s, 3H), 2.55 (s, 3H), 2.39-2.32 (m, 1H), 2.25- 2.12 (m, 2H), 1.89-1.82 (m, 2H), 1.69-1.18 (m, 6H), 1.00 (d, *J* = 6 Hz, 3H); MS (*m*\z); 372 (M^+, 30.77%); Anal. Calc. for: $C_{21}H_{28}N_2O_2S$ (372): C, 67.71; H, 7.58; N, 7.52%; Found: C, 67.83; H, 7.80; N, 7.69%.

4.1.6.7. 1-(4-Methyl-2-(4-(3-(3-methylpiperidin-1-yl)propoxy)phenyl)thiazol-5-yl)ethan-1-one (30). Yellow solid (310 mg, 86%); mp = 98-100 °C; ^{1}H NMR (DMSO-d_6) δ: 7.95 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 4.10 (t, *J* = 5.2 Hz, 2H), 3.11-3.00 (m, 2H), 2.69 (s, 3H), 2.55 (s, 3H), 2.30-2.10 (m, 2H), 2.00-1.95 (m, 2H), 1.67- 1.63 (m, 4H), 1.46-1.35 (m, 1H), 1.25-1.15 (m, 2H), 0.91 (d, *J* = 8.1 Hz, 3H); MS (*m*\z); 372 (M^+, 21.04%); Anal. Calc. for: $C_{21}H_{28}N_2O_2S$ (372): C, 67.71; H, 7.58; N, 7.52%; Found: C, 67.54; H, 7.79; N, 7.75%.

4.1.6.8. 1-(4-Methyl-2-(4-(3-(4-methylpiperidin-1-yl)propoxy)phenyl)thiazol-5-yl)ethan-1-one (31). Yellow solid (318 mg, 88%); mp = 91-93 °C; ^{1}H NMR (DMSO-d_6) δ: 7.96 (d, *J* = 8.8 Hz, 2H), 7.08 (d, *J* = 8.8 Hz, 2H), 4.10 (t, *J* = 6.4 Hz, 2H), 3.29-3.10 (m, 2H), 2.69 (s, 3H), 2.51 (s, 3H), 2.45-2.35 (m, 2H), 2.04-1.66 (m, 4H), 1.43-1.35 (m, 1H), 1.24-1.22 (m, 4H), 0.89 (d, *J* = 6.4 Hz, 3H); MS (*m*\z); 372 (M^+, 45.45%); Anal. Calc. for: $C_{21}H_{28}N_2O_2S$ (372): C, 67.71; H, 7.58; N, 7.52%; Found: C, 67.80; H, 7.81; N, 7.69%.

4.1.6.9. 1-(4-Methyl-2-(4-(3-(4-methylpiperazin-1-yl)propoxy)phenyl)thiazol-5-yl)ethan-1-one (32). Yellow solid (290 mg, 80%); mp = 53-54 °C; ^{1}H NMR (DMSO-d_6) δ: 7.98 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 4.16 (t, *J* = 6.4 Hz, 2H), 2.67 (s, 3H), 2.53 (s, 3H), 2.46-2.36 (m, 2H), 2.25 (s, 8H), 2.22 (s, 3H), 1.91-1.85 (m, 2H); MS (*m*\z); 373 (M^+, 100%); Anal. Calc. for: $C_{20}H_{27}N_3O_2S$ (373): C, 64.31; H, 7.29; N, 11.25%; Found: C, 64.57; H, 7.47; N, 11.49%.

4.1.6.10. 1-(4-Methyl-2-(4-(3-morpholinopropoxy)phenyl)thiazol-5-yl)ethan-1-one (33). White solid (298 mg, 85%); mp = 119-120 °C; ^{1}H NMR (DMSO-d_6) δ: 7.94 (d, *J* = 8.2 Hz, 2H),

7.07 (d, *J* = 8.2 Hz, 2H), 4.08 (t, *J* = 4.8 Hz, 2H), 3.55 (t, *J* = 7.2 Hz, 4H), 2.68 (s, 3H), 2.55 (s, 3H), 2.45-2.37 (m, 6H), 1.93-1.86 (m, 2H); MS (*m*\z); 360 (M^+, 100%); Anal. Calc. for: $C_{19}H_{24}N_2O_3S$ (360): C, 63.31; H, 6.71; N, 7.77%; Found: C, 63.56; H, 6.98; N, 7.89%.

4.1.6.11. 1-(4-Methyl-2-(4-(3-thiomorpholinopropoxy)phenyl)thiazol-5-yl)ethan-1-one (34). Orange solid (285 mg, 78%); mp = 113-114 °C; ^{1}H NMR (DMSO-d_6) δ: 7.98 (d, *J* = 9.2 Hz, 2H), 7.09 (d, *J* = 9.2 Hz, 2H), 4.07 (t, *J* = 6.3 Hz, 2H), 2.68 (s, 3H), 2.63-2.54 (m, 8H), 2.51 (s, 3H), 2.49-2.46 (m, 2H), 1.89-1.83 (m, 2H); MS (*m*\z); 376 (M^+, 56.70%), 377 (M^{+1}, 45.89%); Anal. Calc. for: $C_{19}H_{24}N_2O_2S_2$ (376): C, 60.61; H, 6.42; N, 7.44%; Found: C, 60.84; H, 6.70; N, 7.68%.

4.1.6.12. 1-(2-(4-(3-(Azepan-1-yl)propoxy)phenyl)-4-methylthiazol-5-yl)ethan-1-one (35). Yellow solid (300 mg, 83%); mp = 68-70 °C; ^{1}H NMR (DMSO-d_6) δ: 7.96 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 4.07 (t, *J* = 5.1 Hz, 2H), 2.68 (s, 3H), 2.62-2.57 (m, 4H), 2.51 (s, 3H), 2.39 (t, *J* = 8 Hz, 2H), 1.91-1.84 (m, 2H), 1.58-1.54 (m, 8H); MS (*m*\z); 372 (M^+, 21.96%); Anal. Calc. for: $C_{21}H_{28}N_2O_2S$ (372): C, 67.71; H, 7.58; N, 7.52%; Found: C, 67.89; H, 7.71; N, 7.69%.

4.1.6.13. 1-(4-Methyl-2-(4-(3-(octahydroisoquinolin-2(1*H*)-yl)propoxy)phenyl)thiazol-5-yl)ethan-1-one (36). Orange solid (336 mg, 84%); mp = 54-55°C; ^{1}H NMR (DMSO-d_6) δ: 7.94 (d, *J* = 7.5 Hz, 2H), 7.08 (d, *J* = 7.5 Hz, 2H), 4.10 (t, *J* = 5.1 Hz, 2H), 3.11-3.02 (m, 2H), 2.93-2.88 (m, 4H), 2.69 (s, 3H), 2.55 (s, 3H), 2.27-1.38 (m, 10H), 1.31-0.95 (m, 4H); MS (*m*\z); 412 (M^+, 65.40%); Anal. Calc. for: $C_{24}H_{32}N_2O_2S$ (412): C, 69.87; H, 7.82; N, 6.79%; Found: C, 69.59; H, 7.64; N, 7.05%.

4.1.6.14. 1-(2-(4-(4-(Azetidin-1-yl)butoxy)phenyl)-4-methylthiazol-5-yl)ethan-1-one (37). Orange solid (256 mg, 80%); mp = 93-95 °C; ^{1}H NMR (DMSO-d_6) δ: 8.02 (d, *J* = 8.7 Hz, 2H), 7.01 (d, *J* = 8.7 Hz, 2H), 4.18 (t, *J* = 7.2 Hz, 2H), 3.87 (t, *J* = 7.2 Hz, 2H), 3.09-2.97 (m, 2H),

2.67 (s, 3H), 2.54 (s, 3H), 1.98-1.61 (m, 8H); MS (*m*\z); 344 (M^+, 18.41%); Anal. Calc. for: $C_{19}H_{24}N_2O_2S$ (344): C, 66.25; H, 7.02; N, 8.13%; Found: C, 67.19; H, 7.45; N, 8.29%.

4.1.6.15. 1-(4-Methyl-2-(4-(4-(pyrrolidin-1-yl)butoxy)phenyl)thiazol-5-yl)ethan-1-one (38). Orange solid (236 mg, 71%); mp = 75-77 °C; ^{1}H NMR (DMSO-d_6) δ: 7.94 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 4.08-4.04 (m, 2H), 3.67-2.97 (m, 6H), 2.67 (s, 3H), 2.54 (s, 3H), 1.98-1.81 (m, 6H), 1.23-1.11 (m, 2H); MS (*m*\z); 358 (M^+, 18.41%); Anal. Calc. for: $C_{20}H_{26}N_2O_2S$ (358): C, 67.01; H, 7.31; N, 7.81%; Found: C, 66.89; H, 7.45; N, 8.09%.

4.1.6.16. 1-(4-Methyl-2-(4-(4-(thiazolidin-3-yl)butoxy)phenyl)thiazol-5-yl)ethan-1-one (39). Yellow oil (277 mg, 79%); ^{1}H NMR (DMSO-d_6) δ: 7.98 (d, *J* = 7.2 Hz, 2H), 7.08 (d, *J* = 7.2 Hz, 2H), 4.09 (t, *J* = 7.2 Hz, 2H), 3.51 (s, 2H), 3.02-2.98 (m, 2H), 2.79 (s, 3H), 2.73-2.61 (m, 4H), 2.55 (s, 3H), 1.85-1.68 (m, 4H); MS (*m*\z); 376 (M^+, 6.95%), 377 (M^{+1}, 86.9%); Anal. Calc. for: $C_{19}H_{24}N_2O_2S_2$ (376): C, 60.61; H, 6.42; N, 7.44%; Found: C, 60.87; H, 6.59; N, 7.63%.

4.1.6.17. 1-(2-(4-(4-(1*H*-Imidazol-1-yl)buyoxy)phenyl)-4-methylthiazol-5-yl)ethan-1-one (40). Orange oil (254 mg, 77%); 7.92 (d, *J* = 8.2 Hz, 2H), 7.71 (s, 1H), 7.09 (d, *J* = 8.2 Hz, 2H), 6.94 (s, 1H), 6.54 (s, 1H), 4.13 (t, *J* = 6.9 Hz, 2H), 3.97 (t, *J* = 6.3 Hz, 2H), 2.66 (s, 3H), 2.54 (s, 3H), 2.23-2.17 (m, 4H); MS (*m*\z); 355 (M^+, 23.98%); Anal. Calc. for: $C_{19}H_{21}N_3O_2S$ (355): C, 64.20; H, 5.95; N, 11.82%; Found: C, 64.47; H, 6.12; N, 12.11%.

4.1.6.18. 1-(4-Methyl-2-(4-(4-(piperidin-1-yl)butoxy)phenyl)thiazol-5-yl)ethan-1-one (41). Orange oil (288 mg, 82%); ^{1}H NMR (DMSO-d_6) δ: 7.93 (d, *J* = 8.2 Hz, 2H), 7.06 (d, *J* = 8.2 Hz, 2H), 4.06 (t, *J* = 5.6 Hz, 2H), 2.68 (s, 3H), 2.55 (s, 3H), 2.39-2.34 (m, 6H), 1.76-1.72 (m, 2H), 1.62-1.58 (m, 2H), 1.56-1.47 (m, 6H); MS (*m*\z); 372 (M^+, 81%), 373 (M^{+1}, 100%); Anal. Calc. for: $C_{21}H_{28}N_2O_2S$ (372): C, 67.71; H, 7.58; N, 7.52%; Found: C, 67.54; H, 7.80; N, 7.78%.

4.1.6.19. 1-(4-Methyl-2-(4-(4-(2-methylpiperidin-1-yl)butoxy)phenyl)thiazol-5-yl)ethan-1-one (42). Orange oil (291 mg, 81%); ^{1}H NMR (DMSO-d_6) δ: 7.90 (d, J = 6.9 Hz, 2H), 7.03 (d, J = 6.9 Hz, 2H), 4.05 (t, J = 5.7 Hz, 2H), 2.90-2.68 (m, 2H), 2.65 (s, 3H), 2.51 (s, 3H), 2.49-2.40 (m, 2H), 2.33-2.21 (m, 1H), 1.72-1.68 (m, 2H), 1.60-1.18 (m, 8H), 1.02 (d, J = 6.2 Hz, 3H); MS (*m*\z); 386 (M^+, 17.17%); Anal. Calc. for: $C_{22}H_{30}N_2O_2S$ (386): C, 68.36; H, 7.82; N, 7.25%; Found: C, 68.17; H, 7.90; N, 7.51%.

4.1.6.20. 1-(4-Methyl-2-(4-(4-(3-methylpiperidin-1-yl)butoxy)phenyl)thiazol-5-yl)ethan-1-one (43). Yellow solid (305 mg, 85%); mp = 187-188 °C; ^{1}H NMR (DMSO-d_6) δ: 7.95 (d, J = 7.6 Hz, 2H), 7.09 (d, J= 7.6 Hz, 2H), 4.08 (t, J = 5.7 Hz, 2H), 3.05-3.03 (m, 2H), 2.76-2.73 (m, 2H), 2.68 (s, 3H), 2.55 (s, 3H), 2.47-2.43 (m, 2H), 2.00-1.78 (m, 9H), 0.90 (d, J = 6.2 Hz, 3H); MS (*m*\z); 386 (M^+, 100%); Anal. Calc. for: $C_{22}H_{30}N_2O_2S$ (386): C, 68.36; H, 7.82; N, 7.25%; Found: C, 68.59; H, 8.04; N, 7.47%.

4.1.6.21. 1-(4-Methyl-2-(4-(4-(4-methylpiperidin-1-yl)butoxy)phenyl)thiazol-5-yl)ethan-1-one (44). White solid (298 mg, 83%); mp = 176-178 °C; ^{1}H NMR (DMSO-d_6) δ: 7.97 (d, J = 10.0 Hz, 2H), 7.09 (d, J = 10.0 Hz, 2H), 4.09 (t, J = 7.2 Hz, 2H), 3.43-3.40 (m, 2H), 3.05-3.02 (m, 2H), 2.84-2.80 (m, 1H), 2.69 (s, 3H), 2.55 (s, 3H), 1.89-1.85 (m, 2H), 1.80-1.75 (m, 4H), 1.50-1.17 (m, 4H), 0.93 (d, J = 8.2 Hz, 3H); MS (*m*\z); 386 (M^+, 37.32%); Anal. Calc. for: $C_{22}H_{30}N_2O_2S$ (386): C, 68.36; H, 7.82; N, 7.25%; Found: C, 68.19; H, 7.89; N, 7.43%.

4.1.6.22. 1-(4-Methyl-2-(4-(4-(4-methylpiperazin-1-yl)butoxy)phenyl)thiazol-5-yl)ethan-1-one (45). Yellow solid (277 mg, 77%); mp = 131-132 °C; ^{1}H NMR (DMSO-d_6) δ: 7.94 (d, J = 8.8 Hz, 2H), 7.07 (d, J = 8.8 Hz, 2H), 4.08-3.98 (m, 2H), 2.69 (s, 3H), 2.65-2.44 (m, 13H), 2.43 (s, 3H), 1.75-171 (m, 2H), 1.62-1.58 (m, 2H); MS (*m*\z); 387 (M^+, 9.42%); Anal. Calc. for: $C_{21}H_{29}N_3O_2S$ (387): C, 65.08; H, 7.54; N, 10.84%; Found: C, 65.31; H, 7.80; N, 10.71%.

4.1.6.23. 1-(4-Methyl-2-(4-(4-morpholinobutoxy)phenyl)thiazol-5-yl)ethan-1-one (46). Orange solid (240 mg, 69%); mp = 84-87 °C; ^{1}H NMR (DMSO-d_6) δ: 7.94 (d, J = 9.1 Hz, 2H), 7.07 (d, J = 9.1 Hz, 2H), 4.07 (t, J = 6.2 Hz, 2H), 3.55 (t, J = 4.8 Hz, 4H), 2.68 (s, 3H), 2.54 (s, 3H), 2.48-2.33 (m, 6H), 1.79-1.72 (m, 2H), 1.65-1.55 (m, 2H); MS (*m*\z); 374 (M^+, 5.47%), 375 (M^{+1}, 10.87%); Anal. Calc. for: $C_{20}H_{26}N_2O_3S$ (374): C, 64.14; H, 7.00; N, 7.48%; Found: C, 64.43; H, 6.89; N, 7.71%.

4.1.6.24. 1-(4-Methyl-2-(4-(4-thiomorpholinobutoxy)phenyl)thiazol-5-yl)ethan-1-one (47). Orange oil (312 mg, 86%); ^{1}H NMR (DMSO-d_6) δ: 7.90 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 8.8 Hz, 2H), 4.04 (t, J = 8.1 Hz, 2H), 2.66 (s, 3H), 2.61-2.58 (m, 8H), 2.52 (s, 3H), 2.34 (t, J = 8.1 Hz, 2H), 1.79-1.52 (m, 4H); MS (*m*\z); 390 (M^+, 17.03%); Anal. Calc. for: $C_{20}H_{26}N_2O_2S_2$ (390): C, 61.51; H, 6.71; N, 7.17%; Found: C, 61.34; H, 6.97; N, 7.43%.

4.1.6.25. 1-(2-(4-(4-(Azepan-1-yl)butoxy)phenyl)-4-methylthiazol-5-yl)ethan-1-one (48). Orange solid (273 mg, 76%); mp = 161-163 °C; ^{1}H NMR (DMSO-d_6) δ: 7.96 (d, J = 10.2 Hz, 2H), 7.09 (d, J = 10.2 Hz, 2H), 4.10 (t, J = 5.6 Hz, 2H), 3.18-3.06 (m, 6H), 2.68 (s, 3H), 2.55 (s, 3H), 1.80-1.61 (m, 12H); MS (*m*\z); 386 (M^+, 100%); Anal. Calc. for: $C_{22}H_{30}N_2O_2S$ (386): C, 68.36; H, 7.82; N, 7.25%; Found: C, 68.53; H, 9.11; N, 7.49%.

4.1.6.26. 1-(4-Methyl-2-(4-(4-octhydroisoquinolin-2(1*H*)-yl)butoxy)phenyl)thiazol-5-yl) ethan-1-one (49). Orange oil (317 mg, 76%); ^{1}H NMR (DMSO-d_6) δ: 7.94 (d, J = 9.2 Hz, 2H), 7.09 (d, J = 9.2 Hz, 2H), 4.07 (t, J = 5.6 Hz, 2H), 3.03-2.86 (m, 2H), 2.69 (s, 3H), 2.54 (s, 3H), 2.10-2.02 (m, 2H), 1.78-1.47 (m, 9H), 1.25-0.90 (m, 9H); MS (*m*\z); 426 (M^+, 100%); Anal. Calc. for: $C_{25}H_{34}N_2O_2S$ (426): C, 70.38; H, 8.03; N, 6.57%; Found: C, 70.14; H, 8.27; N, 6.80%.

4.1.6.27. 1-(2-(4-((5-(Azetidin-1-yl)pentyl)oxy)phenyl)-4-methylthiazol-5-yl)ethan-1-one (50). Orange oil (268 mg, 84%); ^{1}H NMR (DMSO-d_6) δ: 7.98 (d, J = 9.3 Hz, 2H), 7.03 (d, J =

9.3 Hz, 2H), 4.05 (t, *J* = 6.3 Hz, 2H), 3.19-3.11 (m, 2H), 2.68 (s, 3H), 2.49 (s, 3H), 1.77-1.12 (m, 8H), 0.92-0.83 (m, 4H); MS (*m*\z); 358 (M^+, 33.27%); Anal. Calc. for: $C_{20}H_{26}N_2O_2S$ (358): C, 67.01; H, 7.31; N, 7.81%; Found: C, 67.94; H, 7.87; N, 8.98%.

4.1.6.28. 1-(4-Methyl-2-(4-((5-(pyrrolidin-1-yl)pentyl)oxy)phenyl)thiazol-5-yl)ethan-1-one (51). Yellow oil (268 mg, 81%); ^{1}H NMR (DMSO-d_6) δ: 7.93 (d, *J* = 9.3 Hz, 2H), 7.06 (d, *J* = 9.3 Hz, 2H), 4.05 (t, *J* = 6.3 Hz, 2H), 2.68 (s, 3H), 2.53-2.46 (m, 6H), 2.43 (s, 3H), 1.77-1.68 (m, 6H), 1.58-1.43 (m, 4H); MS (*m*\z); 372 (M^+, 33.27%), 373 (M^{+1}, 100%); Anal. Calc. for: $C_{21}H_{28}N_2O_2S$ (372): C, 67.71; H, 7.58; N, 7.52%; Found: C, 67.54; H, 7.80; N, 7.78%.

4.1.6.29. 1-(4-Methyl-2-(4-((5-(thiazolidin-3-yl)pentyl)oxy)phenyl)thiazol-5-yl)ethan-1-one (52). Orange oil (271 mg, 78%); ^{1}H NMR (DMSO-d_6) δ: 7.98 (d, *J* = 8.2 Hz, 2H), 7.11 (d, *J* = 8.2 Hz, 2H), 4.09 (t, *J* = 6.8 Hz, 2H), 3.61 (s, 2H), 3.02-2.98 (m, 2H), 2.79 (s, 3H), 2.73-2.61 (m, 4H), 2.55 (s, 3H), 1.85-1.68 (m, 6H); MS (*m*\z); 390 (M^+, 16.16%); Anal. Calc. for: $C_{20}H_{26}N_2O_2S_2$ (390): C, 61.50; H, 6.71; N, 7.17%; Found: C, 61.74; H, 6.98; N, 7.42%.

4.1.6.30. 1-(2-(4-((5-(1*H*-Imidazol-1-yl)pentyl)oxy)phenyl)-4-methylthiazol-5-yl)ethan-1-one (53). Orange oil (239 mg, 73%); ^{1}H NMR (DMSO-d_6) δ: 7.96 (d, *J* = 8.4 Hz, 2H), 7.76 (s, 1H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.82 (s, 1H), 6.35 (s, 1H), 4.21 (t, *J* = 7.5 Hz, 2H), 4.05 (t, *J* = 6.3 Hz, 2H), 2.68 (s, 3H), 2.55 (s, 3H), 1.91-1.86 (m, 2H), 1.80-1.75 (m, 2H), 1.41-1.39 (m, 2H); MS (*m*\z); 369 (M^+, 19.93%); Anal. Calc. for: $C_{20}H_{23}N_3O_2S$ (369): C, 65.02; H, 6.27; N, 11.37%; Found: C, 65.19; H, 6.43; N, 11.60%.

4.1.6.31. 1-(4-Methyl-2-(4-((5-(piperidin-1-yl)pentyl)oxy)phenyl)thiazol-5-yl)ethan-1-one (54). Orange solid (306 mg, 89%); mp = 60-63 °C; ^{1}H NMR (DMSO-d_6) δ: 7.94 (d, *J* = 9.2 Hz, 2H), 7.07 (d, *J* = 9.2 Hz, 2H), 4.06 (t, *J* = 8.2 Hz, 2H), 2.68 (s, 3H), 2.55 (s, 3H), 2.46-2.40 (m, 6H), 1.79-1.72 (m, 2H), 1.57-1.54 (m, 4H), 1.45-1.42 (m, 4H), 1.29-1.22 (m, 2H); MS (*m*\z); 386

(M^+, 70.0%); Anal. Calc. for: $C_{22}H_{30}N_2O_2S$ (386): C, 68.36; H, 7.82; N, 7.25%; Found: C, 68.60; H, 8.09; N, 7.54%.

4.1.6.32. 1-(4-Methyl-2-(4-((5-(2-methylpiperidin-1-yl)pentyl)oxy)phenyl)thiazol-5-yl)ethan-1-one (55). Orange oil (300 mg, 87%); ^{1}H NMR (DMSO-d_6) δ: 7.81 (d, *J* = 7.6 Hz, 2H), 7.03 (d, *J* = 7.6 Hz, 2H), 4.05 (t, *J* = 7.2 Hz, 2H), 3.32 (t, *J* = 5.4 Hz, 2H), 2.68 (s, 3H), 2.55 (s, 3H), 2.39-2.35 (m, 2H), 1.77- 1.73 (m, 4H), 1.59- 1.21 (m, 10H), 1.05 (d, *J* = 4.2 Hz, 3H); MS (*m*\z); 400 (M^+, 24.42%); Anal. Calc. for: $C_{23}H_{32}N_2O_2S$ (400): C, 68.96; H, 8.05; N, 6.99%; Found: C, 68.74; H, 8.32; N, 7.21%.

4.1.6.33. 1-(4-Methyl-2-(4-((5-(3-methylpiperidin-1-yl)pentyl)oxy)phenyl)thiazol-5-yl)ethan-1-one (56). Orange oil (313 mg, 88%); ^{1}H NMR (DMSO-d_6) δ: 7.92 (d, *J* = 7.2 Hz, 2H), 7.05 (d, *J* = 7.2 Hz, 2H), 4.01 (t, *J* = 6.2 Hz, 2H), 2.81- 2.76 (m, 2H), 2.66 (s, 3H), 2.55 (s, 3H), 2.30-2.26 (m, 4H), 1.86- 1.83 (m, 2H), 1.80- 1.69 (m, 2H), 1.58- 1.39 (m, 7H), 0.82 (d, *J* = 6 Hz, 3H); MS (*m*\z); 400 (M^+, 87.07%); Anal. Calc. for: $C_{23}H_{32}N_2O_2S$ (400): C, 68.96; H, 8.05; N, 6.99%; Found: C, 68.78; H, 8.23; N, 7.24%.

4.1.6.34. 1-(4-Methyl-2-(4-((5-(4-methylpiperidin-1-yl)pentyl)oxy)phenyl)thiazol-5-yl)ethan-1-one (57). Orange solid (317 mg, 89%); mp = 51-54 °C; ^{1}H NMR (DMSO-d_6) δ: 7.94 (d, *J* = 9.6 Hz, 2H), 7.06 (d, *J* = 9.6 Hz, 2H), 4.05 (t, *J* = 7.6 Hz, 2H), 2.93-2.88 (m, 2H), 2.69 (s, 3H), 2.55 (s, 3H), 2.42-2.04 (m, 4H), 1.78-1.72 (m, 2H), 1.61-1.51 (m, 4H), 1.44-1.37 (m, 2H), 1.24-1.15 (m, 3H), 0.90 (d, *J* = 7.6 Hz, 3H); MS (*m*\z); 400 (M^+, 32.45%); Anal. Calc. for: $C_{23}H_{32}N_2O_2S$ (400): C, 68.96; H, 8.05; N, 6.99%; Found: C, 68.68; H, 8.27; N, 7.16%.

4.1.6.35. 1-(4-Methyl-2-(4-((5-(4-methylpiperazin-1-yl)pentyl)oxy)phenyl)thiazol-5-yl)ethan-1-one (58). Yellow oil (296 mg, 83%); ^{1}H NMR (DMSO-d_6) δ: 7.94 (d, *J* = 9.1 Hz, 2H), 7.07 (d, *J* = 9.1 Hz, 2H), 4.05 (t, *J* = 6.6 Hz, 2H), 2.68 (s, 3H), 2.55 (s, 3H), 2.34- 2.28 (m,

10H), 2.16 (s, 3H), 1.80-1.72 (m, 2H), 1.52- 1.43 (m, 4H); MS (*m*\z); 401 (M^+, 20.76%), 402 (M^{+1}, 62.24%); Anal. Calc. for: $C_{22}H_{31}N_3O_2S$ (401): C, 65.80; H, 7.78; N, 10.46%; Found: C, 65.63; H, 8.96; N, 10.71%.

4.1.6.36. 1-(4-Methyl-2-(4-((5-morpholinopentyl)oxy)phenyl)thiazol-5-yl)ethan-1-one (59). Yellow solid (290 mg, 84%); mp = 72-74 °C; ^{1}H NMR (DMSO-d_6) δ: 7.91 (d, *J* = 8.7 Hz, 2H), 7.04 (d, *J* = 8.7 Hz, 2H), 4.35-4.26 (m, 2H), 4.02 (t, *J* = 6.6 Hz, 4H), 3.41-3.35 (m, 6H), 2.66 (s, 3H), 2.52 (s, 3H), 1.75-1.70 (m, 2H), 1.46-1.39 (m, 4H); MS (*m*\z); 388 (M^+, 19.50%); Anal. Calc. for: $C_{21}H_{28}N_2O_3S$ (388): C, 64.92; H, 7.26; N, 7.21%; Found: C, 64.76; H, 7.49; N, 7.45%.

4.1.6.37. 1-(4-Methyl-2-(4-((5-thiomorpholinopentyl)oxy)phenyl)thiazol-5-yl)ethan-1-one (60). Yellow solid (284 mg, 79%); mp = 84-85 °C; ^{1}H NMR (DMSO-d_6) δ: 7.94 (d, *J* = 9.2 Hz, 2H), 7.07 (d, *J* = 9.2 Hz, 2H), 4.04 (t, *J* = 6.6 Hz, 2H), 2.68 (s, 3H), 2.66- 2.58 (m, 8H), 2.55 (s, 3H), 2.30 (t, *J* = 6.3 Hz, 2H), 1.76-1.72 (m, 2H), 1.45-1.41 (m, 4H); MS (*m*\z); 404 (M^+, 100%); Anal. Calc. for: $C_{21}H_{28}N_2O_2S_2$ (404): C, 62.34; H, 6.98; N, 6.92%; Found: C, 62.50; H, 6.79; N, 7.16%.

4.1.6.38. 1-(2-(4-((5-(azepan-1-yl)pentyl)oxy)phenyl)-4-methylthiazol-5-yl)ethan-1-one (61). Orange oil (263 mg, 74%); ^{1}H NMR (DMSO-d_6) δ: 7.93 (d, *J* = 7.5 Hz, 2H), 7.06 (d, *J* = 7.5 Hz, 2H), 4.04 (t, *J* = 6.9 Hz, 2H), 2.68 (s, 3H), 2.55 (s, 3H), 2.49-2.45 (m, 2H), 1.76-1.72 (m, 6H), 1.53- 1.23 (m, 12H); MS (*m*\z); 400 (M^+, 23.16%); Anal. Calc. for: $C_{23}H_{32}N_2O_2S$ (400): C, 68.96; H, 8.05; N, 6.99%; Found: C, 69.17; H, 8.29; N, 7.15%.

4.1.6.39. 1-(4-Methyl-2-(4-((5-(octahydroisoquinolin-2(1*H*)-yl)pentyl)oxy)phenyl)thiazol-5-yl)ethan-1-one (62). Orange solid (282 mg, 72%); mp = 54-56 °C; ^{1}H NMR (DMSO-d_6) δ: 7.94 (d, *J* = 9.0 Hz, 2H), 7.07 (d, *J* = 9.0 Hz, 2H), 4.05 (t, *J* = 6.6 Hz, 2H), 3.00-2.80 (m, 2H), 2.68 (s, 3H), 2.54 (s, 3H), 2.45-2.39 (m, 2H), 2.10-2.03 (m, 2H), 1.77- 0.89 (m, 18H); MS (*m*\z); 440

(M^+, 72.93%); Anal. Calc. for: $C_{26}H_{36}N_2O_2S$ (440): C, 70.87; H, 8.23; N, 6.36%; Found: C, 70.61; H, 8.40; N, 6.53%.

4.1.7. 2-(1-(4-Methyl-2-(4-(*n*-amino)alkoxy)phenyl)thiazol-5-yl)ethylidene)hydrazine-1-carboximidamide (63-101). *General procedure*: to absolute ethanol (15 mL) in a round flask, compounds **24-62** (150 mg) were heated at reflux with aminoguanidine hydrochloride (5 equiv.) and 200 µL *conc*. hydrochloric acid for 4 h. After reaction completion, the solvent was concentrated under reduced pressure, then poured in crushed ice and neutralized with sodium carbonate to pH 7-8, and the formed precipitated solid was collected by filtration, washed with copious amount of water then dried. Yields, physical properties and spectral data of final products are listed below:

4.1.7.1. 2-(1-(2-(4-(3-(Azetidin-1-yl)propoxy)phenyl)-4-methylthiazol-5-yl)ethylidene) hydrazine-1-carboximidamide (63). Orange solid (157 mg, 93%); mp = 132-134 °C; ^{1}H NMR (DMSO-d_6) δ: 7.99 (d, *J* =8.6 Hz, 2H), 7.00 (d, *J* = 8.6 Hz, 2H), 5.85 (brs, 4H), 4.16 (t, *J* = 6.6 Hz, 2H), 3.81 (t, *J* = 5.9 Hz, 4H), 2.69 (s, 3H), 2.65-2.59 (m, 2H), 2.56 (s, 3H), 1.86-1.25 (m, 4H); ^{13}C NMR (DMSO-d_6) δ: 162.8, 160.4, 148.1, 143.3, 134.5, 127.7, 126.4, 115.3, 66.5, 54.0, 52.6, 28.5, 23.5, 18.6, 16.6; Anal. Calc. for: $C_{19}H_{26}N_6OS$ (386): C, 59.04; H, 6.78; N, 21.74%; Found: C, 60.21; H, 7.24; N, 22.72%.

4.1.7.2. 2-(1-(4-Methyl-2-(4-(3-(pyrrolidin-1-yl)propoxy)phenyl)thiazol-5-yl)ethylidene) hydrazine-1-carboximidamide (64). Orange solid (156 mg, 90%); mp = 120-123 °C; ^{1}H NMR (DMSO-d_6) δ: 7.79 (d, *J* =7.8 Hz, 2H), 7.00 (d, *J* = 7.8 Hz, 2H), 5.91-5.58 (brs, 4H), 4.05 (t, *J* = 6.8 Hz, 2H), 2.53 (s, 3H), 2.44 (s, 3H), 2.30-2.15 (m, 6H), 1.92-1.68 (m, 6H); ^{13}C NMR (DMSO-d_6) δ: 162.8, 160.4, 148.1, 143.3, 134.5, 127.7, 126.4, 115.3, 66.5, 54.0, 52.6, 45.6, 28.5, 23.5,

18.6, 16.6; Anal. Calc. for: $C_{20}H_{28}N_6OS$ (400): C, 59.97; H, 7.05; N, 20.98%; Found: C, 60.21; H, 7.24; N, 20.72%.

4.1.7.3. 2-(1-(4-Methyl-2-(4-(3-(thiazolidin-3-yl)propoxy)phenyl)thiazol-5-yl)ethylidene) hydrazine-1-carboximidamide (65). Orange solid (159 mg, 92%); mp = 70-74 °C; ^{1}H NMR (DMSO-d_6) δ: 7.82 (d, *J* = 9.1 Hz, 2H), 7.01 (d, *J* = 9.1 Hz, 2H), 5.95 (brs, 4H), 4.05 (t, *J* = 6.6 Hz, 2H), 3.62 (s, 2H), 2.55 (s, 3H), 2.40-2.36 (m, 2H), 2.29 (s,3H), 2.15-1.79 (m, 6H); ^{13}C NMR (DMSO-d_6) δ: 175.2, 163.6, 160.6, 159.0, 149.6, 144.7, 133.0, 127.8, 126.1, 115.3, 66.4, 55.8, 45.3, 27.0, 23.4, 18.6, 17.3; MS (*m*\z); 418 (M^+, 19.44%); Anal. Calc. for: $C_{19}H_{26}N_6OS_2$ (418): C, 54.52; H, 6.26; N, 20.08%; Found: C, 54.80; H, 6.40; N, 19.89%.

4.1.7.4. 2-(1-(2-(4-(3-(1*H*-Imidazol-1-yl)propoxy)phenyl)-4-methylthiazol-5-yl)ethylidene) hydrazine-1-carboximidamide (66). Orange solid (157 mg, 90%); mp = 208-212 °C; ^{1}H NMR (DMSO-d_6) δ: 7.82 (d, *J* = 9.1 Hz, 2H), 7.62 (s, 1H), 7.19 (s, 1H), 7.02 (d, *J* = 9.1 Hz, 2H), 6.89 (s, 1H), 5.79 (brs, 4H), 4.14 (t, *J* = 6.6 Hz, 2H), 3.97 (t, *J* = 6.3 Hz, 2H), 2.55 (s, 3H), 2.29 (s, 3H), 2.22-2.14 (m, 2H); ^{13}C NMR (DMSO-d_6) δ: 162.7, 160.2, 159.9, 148.1, 143.4, 137.8, 134.6, 128.9, 127.7, 126.6, 119.8, 115.4, 65.1, 43.3, 30.6, 18.6, 16.6; MS (*m*\z); 397 (M^+, 20.0%); Anal. Calc. for: $C_{19}H_{23}N_7OS$ (397): C, 57.41; H, 5.83; N, 24.67%; Found: C, 57.70; H, 5.97; N, 24.51%.

4.1.7.5. 2-(1-(4-Methyl-2-(4-(3-(piperidin-1-yl)propoxy)phenyl)thiazol-5-yl)ethylidene) hydrazine-1-carboximidamide (67). Yellow solid (163 mg, 94%); mp = 138-140 °C; ^{1}H NMR (DMSO-d_6) δ: 7.82 (d, *J* = 10.4 Hz, 2H), 7.02 (d, *J* = 10.4 Hz, 2H), 5.59 (brs, 2H), 5.71 (brs, 2H), 4.05 (t, *J* = 10.4 Hz, 2H), 2.56 (s, 3H), 2.45-2.25 (m, 6H), 2.23 (s, 3H), 1.89-1.84 (m, 2H), 1.55-1.35 (m, 6H); ^{13}C NMR (DMSO-d_6) δ: 162.7, 160.4, 160.0, 147.9, 143.2, 134.6, 127.7, 126.4, 115.3, 66.6, 55.5, 54.5, 26.6, 26.0, 24.6, 18.6, 16.5; MS (*m*\z); 414 (M^+, 100%); Anal.

Calc. for: $C_{21}H_{30}N_6OS$ (414): C, 60.84; H, 7.29; N, 20.27%; Found: C, 61.05; H, 7.42; N, 20.14%.

4.1.7.6. 2-(1-(4-Methyl-2-(4-(3-(2-methylpiperidin-1-yl)propoxy)phenyl)thiazol-5-yl) ethylidene)hydrazine-1-carboximidamide (68). Orange solid (154 mg, 89%); mp = 84-85 °C; ^{1}H NMR (DMSO-d_6) δ: 7.82 (d, *J* = 7.6 Hz, 2H), 7.21 (d, *J* = 7.6 Hz, 2H), 5.85-5.63 (brs, 4H), 4.06 (t, *J* = 9.6 Hz, 2H), 2.81-2.78 (m, 2H), 2.60 (s, 3H), 2.39-2.21 (m, 5H), 2.13-2.03 (m, 1H), 1.85-1.82 (m, 2H), 1.62-1.45 (m, 2H), 1.41-1.30 (m, 2H), 1.29-1.11 (m, 2H), 0.97 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 165.2, 162.8, 160.5, 159.9, 148.1, 143.4, 134.4, 126.3, 115.3, 66.5, 55.7, 51.9, 50.1, 34.6, 26.2, 25.7, 25.1, 18.6, 18.1, 16.6; MS (*m*\z); 428 (M^+, 23.61%); Anal. Calc. for: $C_{22}H_{32}N_6OS$ (428): C, 61.65; H, 7.53; N, 19.61%; Found: C, 61.94; H, 7.67; N, 19.85%.

4.1.7.7. 2-(1-(4-Methyl-2-(4-(3-(3-methylpiperidin-1-yl)propoxy)phenyl)thiazol-5-yl) ethylidene)hydrazine-1-carboximidamide (69). Orange solid (157 mg, 91%); mp = 98-102 °C; ^{1}H NMR (DMSO-d_6) δ: 7.94 (d, *J* = 8.1 Hz, 2H), 7.06 (d, *J* = 8.2 Hz, 2H), 5.65 (brs, 4H), 4.08 (t, *J* = 8.0 Hz, 2H), 2.80-2.76 (m, 2H), 2.68 (s, 3H), 2.55 (s, 3H), 2.42-2.38 (m, 4H), 1.92-1.41 (m, 7H), 0.85 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 162.8, 160.4, 159.9, 148.1, 143.4, 134.5, 127.7, 126.4, 115.3, 66.6, 62.0, 55.2, 54.0, 33.1, 31.1, 26.7, 25.5, 20.0, 18.6, 16.6; MS (*m*\z); 428 (M^+, 100%); Anal. Calc. for: $C_{22}H_{32}N_6OS$ (428): C, 61.65; H, 7.53; N, 19.61%; Found: C, 61.81; H, 7.78; N, 7.76%.

4.1.7.8. 2-(1-(4-Methyl-2-(4-(3-(4-methylpiperidin-1-yl)propoxy)phenyl)thiazol-5-yl) ethylidene) hydrazine-1-carboximidamide (70). Yellow solid (159 mg, 92%); mp = 132-133 °C; ^{1}H NMR (DMSO-d_6) δ: 7.82 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 5.73-5.63 (brs, 4H), 4.06 (t, *J* = 7.8 Hz, 2H), 2.79-2.74 (m, 2H), 2.56 (s, 3H), 2.36 (t, *J* = 8.2 Hz, 2H), 2.30 (s,

3H), 1.91-1.81 (m, 4H), 1.65-1.45 (m, 5H), 0.82 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 162.7, 160.4, 159.9, 148.0, 143.3, 134.6, 127.7, 126.4, 115.3, 66.6, 55.1, 53.9, 34.4, 30.9, 26.8, 22.3, 18.6, 16.5; MS (*m*\z); 428 (M^+, 26.21%); Anal. Calc. for: $C_{22}H_{32}N_6OS$ (428): C, 61.65; H, 7.53; N, 19.61%; Found: C, 61.87; H, 7.75; N, 19.43%.

4.1.7.9. 2-(1-(4-Methyl-2-(4-(3-(4-methylpiperazin-1-yl)propoxy)phenyl)thiazol-5-yl) ethylidene)hydrazine-1-carboximidamide (71). Yellow solid (152 mg, 88%); mp = 108-111 °C; ^{1}H NMR (DMSO-d_6) δ: 7.82 (d, *J* = 9.2 Hz, 2H), 7.02 (d, *J* = 9.2 Hz, 2H), 5.71-5.59 (brs, 4H), 4.06 (t, *J* = 7.2 Hz, 2H), 2.67 (s, 3H), 2.56 (s, 3H), 2.42-2.29 (m, 10H), 2.15 (s, 3H), 1.89-1.85 (m, 2H); ^{13}C NMR (DMSO-d_6) δ: 162.8, 160.4, 159.8, 148.1, 143.4, 134.5, 127.7, 126.4, 115.3, 66.5, 55.2, 54.7, 53.1, 46.2, 26.6, 18.6, 16.5; MS (*m*\z); 429 (M^+, 100%); Anal. Calc. for: $C_{21}H_{31}N_7OS$ (429): C, 58.71; H, 7.27; N, 22.82%; Found: C, 58.89; H, 7.40; N, 22.71%.

4.1.7.10. 2-(1-(4-Methyl-2-(4-(3-morpholinopropoxy)phenyl)thiazol-5-yl)ethylidene) hydrazine-1-carboximidamide (72). Yellow solid (163 mg, 94%); mp = 205-207 °C; ^{1}H NMR (DMSO-d_6) δ: 11.43 (brs, 1H), 7.86 (d, *J* = 9.1 Hz, 2H), 7.66 (brs, 3H), 7.07 (d, *J* = 9.1 Hz, 2H), 4.11 (t, *J* = 6.3 Hz, 2H), 3.67-3.55 (m, 4H), 2.64-2.59 (m, 6H), 2.58 (s, 3H), 2.42 (s, 3H), 2.1-1.89 (m, 2H); ^{13}C NMR (DMSO-d_6) δ: 165.3, 160.8, 156.3, 152.7, 147.7, 130.0, 128.1, 125.9, 115.5, 66.1, 65.2, 54.5, 52.7, 30.1, 24.8, 18.6; MS (*m*\z); 416 (M^+, 100%); Anal. Calc. for: $C_{20}H_{28}N_6O_2S$ (416): C, 57.67; H, 6.78; N, 20.18%; Found: C, 57.91; H, 6.89; N, 20.43%.

4.1.7.11. 2-(1-(4-Methyl-2-(4-(3-thiomorpholinopropoxy)phenyl)thiazol-5-yl)ethylidene) hydrazine-1-carboximidamide (73). Orange solid (146 mg, 85%); mp = 178-179 °C; ^{1}H NMR (DMSO-d_6) δ: 7.82 (d, *J* = 8.7 Hz, 2H), 7.01 (d, *J* = 8.7 Hz, 2H), 5.66 (brs, 2H), 5.47 (brs, 2H), 4.05 (t, *J* = 6.6 Hz, 2H), 2.65 (s, 3H), 2.64-2.55 (m, 6H), 2.49-2.37 (m, 4H), 2.29 (s, 3H), 1.89-1.85 (m, 2H); ^{13}C NMR (DMSO-d_6) δ: 162.7, 160.4, 160.0, 147.9, 143.2, 134.7, 127.7, 126.4,

115.3, 66.5, 55.4, 55.1, 27.6, 26.2, 18.6, 16.5; MS (*m*\z); 432 (M^+, 100%); Anal. Calc. for: $C_{20}H_{28}N_6OS_2$ (432): C, 55.53; H, 6.52; N, 19.43%; Found: C, 55.81; H, 6.79; N, 19.70%.

4.1.7.12. 2-(1-(2-(4-(3-(Azepan-1-yl)propoxy)phenyl)-4-methylthiazol-5-yl)ethylidene) hydrazine-1-carboximidamide (74). Orange solid (144 mg, 83%); mp = 113-114 °C; ^{1}H NMR (DMSO-d_6) δ: 7.82 (d, *J* = 11.6 Hz, 2H), 7.01 (d, *J* = 11.6 Hz, 2H), 5.91-5.61 (brs, 4H), 4.06 (t, *J* = 11.2 Hz, 2H), 2.59 (s, 3H), 2.55 (s, 3H), 2.38-2.32 (m, 6H), 1.87-1.83 (m, 2H), 1.64-1.58 (m, 8H); ^{13}C NMR (DMSO-d_6) δ: 162.7, 160.5, 160.1, 147.9, 143.1, 134.6, 127.7, 126.3, 115.3, 66.5, 56.0, 45.6, 28.4, 27.5, 27.0, 18.6, 16.5; MS (*m*\z); 428 (M^+, 100%); Anal. Calc. for: $C_{22}H_{32}N_6OS$ (428): C, 61.65; H, 7.53; N, 19.61%; Found: C, 61.92; H, 7.81; N, 19.47%.

4.1.7.13. 2-(1-(4-Methyl-2-(4-(3-(octahydroisoquinolin-2(1*H*)-yl)propoxy)phenyl)thiazol-5-yl)ethylidene)hydrazine-1-carboximidamide (75). Orange solid (136 mg, 80%); mp = 58-59 °C; ^{1}H NMR (DMSO-d_6) δ: 7.82 (d, *J* = 9.6 Hz, 2H), 7.02 (d, *J* = 9.6 Hz, 2H), 5.73-5.61 (brs, 4H), 4.05 (t, *J* = 8.4 Hz, 2H), 2.55 (s, 3H), 2.35 (t, *J* = 8.4 Hz, 2H), 2.29 (s, 3H), 1.90-1.20 (m, 18H); ^{13}C NMR (DMSO-d_6) δ: 162.8, 160.4, 159.9, 148.1, 143.3, 134.5, 128.8, 127.7, 115.3, 66.4, 65.3, 56.0, 45.6, 27.2, 25.0, 20.7, 19.7, 19.2, 18.6, 16.6; MS (*m*\z); 468 (M^+, 24%); Anal. Calc. for: $C_{25}H_{36}N_6OS$ (468): C, 64.07; H, 7.74; N, 17.93%; Found: C, 64.31; H, 7.98; N, 18.14%.

4.1.7.14. 2-(1-(2-(4-(4-(Azetidine-1-yl)butoxy)phenyl)-4-methylthiazol-5-yl)ethylidene) hydrazine-1-carboximidamide (76). Orange solid (256 mg, 83%); mp = 105-107 °C; ^{1}H NMR (DMSO-d_6) δ: 8.02 (d, *J* = 8.7 Hz, 2H), 7.01 (d, *J* = 8.7 Hz, 2H), 5.83 (brs, 4H), 4.18 (t, *J* = 7.2 Hz, 2H), 3.87 (t, *J* = 7.2 Hz, 2H), 3.09-2.97 (m, 2H), 2.67 (s, 3H), 2.54 (s, 3H), 1.98-1.61 (m, 8H); ^{13}C NMR (DMSO-d_6) δ: 162.7, 160.4, 160.0, 147.9, 143.3, 134.6, 127.7, 126.3, 115.3, 68.0,

55.7, 54.0, 27.1, 25.2, 23.5, 18.6, 16.55; MS (*m*\z); 400 (M^+, 29.84%); Anal. Calc. for: $C_{20}H_{28}N_6OS$ (400): C, 59.97; H, 7.05; N, 20.98%; Found: C, 60.68; H, 7.53; N, 21.49%.

4.1.7.15. 2-(1-(4-Methyl-2-(4-(4-(pyrrolidin-1-yl)butoxy)phenyl)thiazol-5-yl)ethylidene) hydrazine-1-carboximidamide (77). Orange solid (154 mg, 89%); mp = 96-97 °C; ^{1}H NMR (DMSO-d_6) δ: 7.79 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 8.0 Hz, 2H), 5.69 (brs, 2H), 5.57 (brs, 2H), 4.01 (t, *J* = 6.8 Hz, 2H), 2.53 (s, 3H), 2.41-2.38 (m, 6H), 2.27 (s, 3H), 1.75-1.72 (m, 2H), 1.65-1.63 (m, 4H), 1.57-1.54 (m, 2H); ^{13}C NMR (DMSO-d_6) δ: 162.7, 160.4, 160.0, 147.9, 143.3, 134.6, 127.7, 126.3, 115.3, 68.0, 55.7, 54.0, 27.1, 25.2, 23.5, 18.6, 16.55; MS (*m*\z); 414 (M^+, 27.84%); Anal. Calc. for: $C_{21}H_{30}N_6OS$ (414): C, 60.84; H, 7.29; N, 20.27%; Found: C, 61.08; H, 7.43; N, 20.41%.

4.1.7.16. 2-(1-(4-Methyl-2-(4-(4-(thiazolidin-3-yl)butoxy)phenyl)thiazol-5-yl)ethylidene) hydrazine-1-carboximidamide (78). Orange solid (150 mg, 87%); mp = 93-95 °C; ^{1}H NMR (DMSO-d_6) δ: 7.80 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 5.70-5.62 (brs, 4H), 4.03 (t, *J* = 7.2 Hz, 2H), 3.28 (s, 2H), 2.98 (t, *J* = 6.4 Hz, 2H), 2.75 (t, *J* = 6.2 Hz, 2H), 2.53 (s, 3H), 2.36-2.30 (m, 2H), 2.27 (s, 3H), 1.78-1.73 (m, 2H), 1.58-1.55 (m, 2H); ^{13}C NMR (DMSO-d_6) δ: 162.9, 160.5, 159.8, 148.2, 143.5, 134.3, 127.7, 126.3, 115.3, 67.9, 60.7, 57.9, 51.8, 29.3, 26.8, 25.3, 18.6, 16.6; MS (*m*\z); 432 (M^+, 49.86%); Anal. Calc. for: $C_{20}H_{28}N_6OS_2$ (432): C, 55.53; H, 6.52; N, 19.43%; Found: C, 55.76; H, 6.81; N, 19.28%.

4.1.7.17. 2-(1-(2-(4-(4-(1*H*-Imidazol-1-yl)butoxy)phenyl)-4methylthiazol-5-yl)ethylidene) hydrazine-1-carboximidamide (79). Orange solid (139 mg, 80%); mp = 171-173 °C; ^{1}H NMR (DMSO-d_6) δ: 7.81 (d, *J* = 8.4 Hz, 2H), 7.63 (s, 1H), 7.18 (s, 1H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.88 (s, 1H), 5.75 (brs, 4H), 4.03 (t, *J* = 6.6 Hz, 2H), 2.55 (s, 3H), 2.29 (s, 3H), 1.89-1.61 (m, 6H); ^{13}C NMR (DMSO-d_6) δ: 162.8, 160.3, 159.8, 148.2, 143.4, 137.7, 134.4, 128.8, 127.7, 126.4, 119.7,

115.4, 67.5, 46.0, 45.5, 27.7, 26.1, 18.6, 16.63; Anal. Calc. for: $C_{20}H_{25}N_7OS$ (411): C, 58.37; H, 6.12; N, 23.83%; Found: C, 58.60; H, 6.38; N, 23.69%.

4.1.7.18. 2-(1-(4-Methyl-2-(4-(4-(piperidin-1-yl)butoxy)phenyl)thiazol-5-yl)ethylidene) hydrazine-1-carboximidamide (80). Orange solid (163 mg, 94%); mp = 109-112 °C; ^{1}H NMR (DMSO-d_6) δ: 7.81 (d, *J* = 5.8 Hz, 2H), 7.01 (d, *J* = 5.8 Hz, 2H), 5.70 (brs, 2H), 5.57 (brs, 2H), 4.03 (t, *J* = 6.6 Hz, 2H), 2.59 (s, 3H), 2.58-2.55 (m, 2H), 2.34 (s, 3H), 2.29-2.24 (m, 4H), 1.72-1.69 (m, 2H), 1.57-1.55 (m, 2H), 1.49-1.45 (m, 4H), 1.38-1.36 (m, 2H); ^{13}C NMR (DMSO-d_6) δ: 162.7, 160.4, 160.0, 148.0, 143.3, 134.6, 127.7, 126.3, 115.3, 68.0, 58.5, 54.4, 27.0, 26.0, 24.6, 23.2, 18.6, 16.5; MS (*m*\z); 428 (M^+, 47.88%); Anal. Calc. for: $C_{22}H_{32}N_6OS$ (428): C, 61.65; H, 7.53; N, 19.61%; Found: C, 61.89; H, 7.66; N, 19.54%.

4.1.7.19. 2-(1-(4-Methyl-2-(4-(4-(2-methylpiperidin-1-yl)butoxy)phenyl)thiazol-5-yl) ethylidene)hydrazine-1-carboximidamide (81). Orange solid (159 mg, 92%); mp = 76-77 °C; ^{1}H NMR (DMSO-d_6) δ: 7.81 (d, *J* = 9.2 Hz, 2H), 7.01 (d, *J* = 9.1 Hz, 2H), 5.80-5.55 (brs, 4H), 4.04 (t, *J* = 6.6 Hz, 2H), 2.80-2.62 (m, 2H), 2.55 (s, 3H), 2.29 (s, 3H), 2.26-2.23 (m, 2H), 2.18-2.02 (m, 1H), 1.74-1.68 (m, 2H), 1.57-1.50 (m, 4H), 1.30-1.19 (m, 4H), 0.99 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 162.7, 160.4, 160.0, 148.0, 143.3, 134.5, 127.7, 126.3, 115.3, 68.0, 62.0, 58.3, 53.9, 33.2, 31.1, 27.0, 25.5, 23.2, 20.0, 18.6, 16.5; MS (*m*\z); 442 (M^+, 11.07%); Anal. Calc. for: $C_{23}H_{34}N_6OS$ (442): C, 62.41; H, 7.74; N, 18.99%; Found: C, 62.63; H, 7.85; N, 18.76%.

4.1.7.20. 2-(1-(4-Methyl-2-(4-(4-(3-methylpiperidin-1-yl)butoxy)phenyl)thiazol-5-yl) ethylidene)hydrazine-1-carboximidamide (82). Orange solid (163 mg, 95%); mp = 115-116 °C; ^{1}H NMR (DMSO-d_6) δ: 7.81 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 5.77-5.66 (brs, 4H), 4.01 (t, *J* = 5.7 Hz, 2H), 2.74-2.59 (m, 4H), 2.56 (s, 3H), 2.39 (s, 3H), 2.30-2.23 (m, 2H),

1.77-1.62 (m, 4H), 1.56-1.36 (m, 5H), 0.81 (d, *J* = 8.0 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 162.7, 160.4, 160.0, 148.0, 143.3, 134.5, 127.7, 126.3, 115.3, 68.0, 62.0, 58.3, 53.9, 33.2, 31.1, 27.0, 25.5, 23.2, 20.0, 18.6, 16.5; MS (*m*\z); 442 (M^+, 72.90%); Anal. Calc. for: $C_{23}H_{34}N_6OS$ (442): C, 62.41; H, 7.74; N, 18.99%; Found: C, 62.68; H, 7.90; N, 18.78%.

4.1.7.21. 2-(1-(4-Methyl-2-(4-(4-(4-methylpiperidin-1-yl)butoxy)phenyl)thiazol-5-yl) ethylidene)hydrazine-1-carboximidamide (83). Orange solid (163 mg, 95%); mp = 98-100 °C; ^{1}H NMR (DMSO-d_6) δ: 7.95 (d, *J* = 9.2 Hz, 2H), 7.01 (d, *J* = 9.2 Hz, 2H), 5.89-5.60 (brs, 4H), 4.02 (t, *J* = 7.2 Hz, 2H), 2.80-2.79 (m, 2H), 2.56 (s, 3H), 2.30 (s, 3H), 2.27-2.25 (m, 4H), 1.83-1.78 (m, 2H), 1.75-1.67 (m, 2H), 1.58-1.52 (m, 4H), 1.22-1.08 (m, 1H), 0.88 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 162.7, 160.4, 159.9, 151.3, 148.0, 134.5, 127.7, 126.3, 115.3, 68.0, 58.2, 53.8, 34.5, 30.9, 29.5, 27.0, 23.3, 22.3, 18.6, 16.5; MS (*m*\z); 442 (M^+, 7.99%); Anal. Calc. for: $C_{23}H_{34}N_6OS$ (442): C, 62.41; H, 7.74; N, 18.99%; Found: C, 68.50; H, 7.98; N, 18.85%.

4.1.7.22. 2-(1-(4-Methyl-2-(4-(4-(4-methylpiperazin-1-yl)butoxy)phenyl)thiazol-5-yl) ethylidene)hydrazine-1-carboximidamide (84). Yellow solid (162 mg, 94%); mp = 100-102 °C; ^{1}H NMR (DMSO-d_6) δ: 7.81 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 5.78-5.65 (brs, 4H), 4.01-3.94 (m, 2H), 2.56 (s, 3H), 2.51 (s, 3H), 2.48-2.15 (m, 10H), 2.13 (s, 3H), 1.72-1.55 (m, 4H); ^{13}C NMR (DMSO-d_6) δ: 162.7, 160.4, 160.0, 147.9, 143.2, 134.6, 127.7, 126.3, 115.3, 68.0, 57.8, 55.2, 53.1, 46.2, 27.0, 23.1, 18.6, 16.5; MS (*m*\z); 443 (M^+, 100%); Anal. Calc. for: $C_{22}H_{33}N_7OS$ (443): C, 59.56; H, 7.50; N, 22.10%; Found: C, 59.78; H, 7.63; N, 21.89%.

4.1.7.23. 2-(1-(4-Methyl-2-(4-(4-morpholinobutoxy)phenyl)thiazol-5-yl)ethylidene) hydrazine-1-carboximidamide (85). Orange solid (165 mg, 96%); mp = 125-128 °C; ^{1}H NMR (DMSO-d_6) δ: 7.81 (d, *J* = 8.7 Hz, 2H), 7.01 (d, *J* = 8.7 Hz, 2H), 5.68 (brs, 4H), 4.04 (t, *J* = 6.6 Hz, 2H), 3.55 (t, *J* = 7.8 Hz, 4H), 2.55 (s, 3H), 2.33-2.31 (m, 6H), 2.29 (s, 3H), 1.77-1.72 (m,

2H), 1.59-1.57 (m, 2H); ^{13}C NMR (DMSO-d_6) δ: 162.8, 160.4, 148.0, 143.4, 134.5, 130.0, 127.7, 126.3, 115.3, 67.9, 66.6, 58.2, 53.7, 29.5, 26.9, 22.7, 18.6, 16.6; MS (*m*\z); 430 (M^+, 100%); Anal. Calc. for: $C_{21}H_{30}N_6O_2S$ (430): C, 58.58; H, 7.02; N, 19.52%; Found: C, 58.79; H, 7.25; N, 19.34%.

4.1.7.24. 2-(1-(4-Methyl-2-(4-(4-thiomorpholinobutoxy)phenyl)thiazol-5-yl)ethylidene) hydrazine-1-carboximidamide (86). Yellow solid (148 mg, 86%); mp = 104-105 °C; ^{1}H NMR (DMSO-d_6) δ: 7.79 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 5.70-5.62 (brs, 4H), 4.01 (t, *J* = 6.2 Hz, 2H), 2.60-2.55 (m, 8H), 2.53 (s, 3H), 2.33 (t, *J* = 6.8 Hz, 2H), 2.27 (s, 3H), 1.73-1.66 (m, 2H), 1.58-1.52 (m, 2H); ^{13}C NMR (DMSO-d_6) δ: 162.7, 160.4, 159.9, 148.0, 143.3, 134.5, 127.7, 126.3, 115.3, 68.0, 58.4, 55.0, 27.7, 26.9, 22.8, 18.6, 16.5; MS (*m*\z); 446 (M^+, 9.17%); Anal. Calc. for: $C_{21}H_{30}N_6OS_2$ (446): C, 56.47; H, 6.77; N, 18.82%; Found: C, 56.70; H, 6.94; N, 18.69%.

4.1.7.25. 2-(1-(2-(4-(4-(Azepan-1-yl)butoxy)phenyl)-4-methylthiazol-5-yl)ethylidene) hydrazine-1-carboximidamide (87). Orange solid (151 mg, 88%); mp = 110-112 °C; ^{1}H NMR (DMSO-d_6) δ: 7.82 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 5.77 (brs, 4H), 4.04 (t, *J* = 8 Hz, 2H), 2.56 (s, 3H), 2.31 (s, 3H), 1.89-1.85 (m, 4H), 1.77-1.70 (m, 6H), 1.56-1.23 (m, 8H); ^{13}C NMR (DMSO-d_6) δ: 162.9, 160.5, 159.8, 148.2, 143.5, 134.3, 127.7, 126.3, 115.3, 68.0, 57.5, 55.2, 28.2, 26.9, 25.1, 18.6, 16.6; MS (*m*\z); 442 (M^+, 100%); Anal. Calc. for: $C_{23}H_{34}N_6OS$ (442): C, 62.41; H, 7.74; N, 18.99%; Found: C, 62.70; H, 7.82; N, 18.78%.

4.1.7.26. 2-(1-(4-Methyl-2-(4-(4-(octahydroisoquinolin-2(1*H*)-yl)butoxy)phenyl)thiazol-5-yl) ethylidene)hydrazine-1-carboximidamide (88). Orange solid (143 mg, 84%); mp = 111-114 °C; ^{1}H NMR (DMSO-d_6) δ: 7.82 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 5.73-5.67 (brs, 4H), 4.03 (t, *J* = 8.0 Hz, 2H), 2.83-2.70 (m, 2H), 2.56 (s, 3H), 2.38 (s, 3H), 2.30-2.26 (m, 4H),

1.88-1.45 (m, 7H), 1.23- 0.83 (m, 9H); ^{13}C NMR (DMSO-d_6) δ: 162.8, 160.4, 159.8, 148.1, 143.4, 134.4, 127.7, 126.3, 115.3, 68.0, 60.4, 58.1, 54.3, 33.0, 30.6, 27.0, 26.4, 26.1, 23.2, 18.6, 16.6; MS (*m\z*); 482 (M^+, 13.39%); Anal. Calc. for: $C_{26}H_{38}N_6OS$ (482): C, 64.70; H, 7.94; N, 17.41%; Found: C, 64.97; H, 8.15; N, 17.63%.

4.1.7.27. 2-(1-(2-(4-((5-(Azetidin-1-yl)pentyl)oxy)phenyl)-4-methylthiazol-5-yl)ethylidene) hydrazine-1-carboximidamide (89). Orange oil (268 mg, 87%); ^{1}H NMR (DMSO-d_6) δ: 7.98 (d, *J* = 9.3 Hz, 2H), 7.03 (d, *J* = 9.3 Hz, 2H), 5.87 (brs, 4H), 4.05 (t, *J* = 6.3 Hz, 2H), 3.19-3.11 (m, 2H), 2.68 (s, 3H), 2.49 (s, 3H), 1.77-1.12 (m, 8H), 0.92-0.83 (m, 4H); MS (*m\z*); 414 (M^+, 100%); Anal. Calc. for: $C_{21}H_{30}N_6OS$ (414): C, 60.84; H, 7.29; N, 20.27%; Found: C, 61.87; H, 7.85; N, 21.44%.

4.1.7.28. 2-(1-(4-Methyl-2-(4-((5-(pyrrolidine-1-yl)pentyl)oxy)phenyl)thiazol-5-yl) ethylidene)hydrazine-1-carboximidamide (90). Yellow solid (154 mg, 89%); mp = 161-163 °C; ^{1}H NMR (DMSO-d_6) δ: 11.44 (brs, 1H), 10.65 (brs, 1H), 7.86 (d, *J* = 9.3 Hz, 2H), 7.78 (brs, 2H), 7.07 (d, *J* = 9.2 Hz, 2H), 4.05 (t, *J* = 6.4 Hz, 2H), 2.59 (s, 3H), 2.51-248 (m, 6H), 2.42 (s, 3H), 2.00-1.20 (m, 10H); ^{13}C NMR (DMSO-d_6) δ: 165.4, 161.0, 156.3, 152.6, 147.7, 130.0, 128.1, 125.6, 115.5, 67.9, 54.0, 53.1, 28.4, 25.2, 23.1, 18.6, 18.5; MS (*m\z*); 428 (M^+, 100%); Anal. Calc. for: $C_{22}H_{32}N_6OS$ (428): C, 61.65; H, 7.53; N, 19.61%; Found: C, 61.87; H, 7.65; N, 19.54%.

4.1.7.29. 2-(1-(4-Methyl-2-(4-((5-(thiazolidin-3-yl)pentyl)oxy)phenyl)thiazol-5-yl)ethylidene) hydrazine-1-carboximidamide (91). Yellow solid (146 mg, 85%); mp = 135-138 °C; ^{1}H NMR (DMSO-d_6) δ: 7.86 (d, *J* = 9.1 Hz, 2H), 7.78 (brs, 4H), 7.07 (d, *J* = 9.1 Hz, 2H), 4.05 (t, *J* = 6.4 Hz, 2H), 3.29 (s, 2H), 2.59 (s, 3H), 2.51-248 (m, 4H), 2.42 (s, 3H), 2.00-1.20 (m, 8H); MS (*m\z*);

446 (M^+, 7.70%); Anal. Calc. for: $C_{21}H_{30}N_6OS_2$ (446): C, 56.47; H, 6.77; N, 18.82%; Found: C, 56.75; H, 6.94; N, 18.59%.

4.1.7.30. 2-(1-(2-(4-(5-(1*H*-Imidazol-1-yl)pentyl)oxy)phenyl)-4-methylthiazol-5-yl) ethylidene)hydrazine-1-carboximidamide (92). Yellow solid (151 mg, 87%); mp = 183-185 °C; ^{1}H NMR (DMSO-d_6) δ: 11.56 (brs, 1H), 9.20 (s, 1H), 7.85 (d, *J* = 8.7 Hz, 2H), 7.81 (s, 1H), 7.80 (brs, 3H), 7.69 (d, *J* = 5.7 Hz, 2H), 7.04 (d, *J* = 8.7 Hz, 1H), 4.23 (t, *J* = 6.6 Hz, 2H), 4.04 (t, *J* = 6.1 Hz, 2H), 2.58 (s, 3H), 2.43 (s, 3H), 1.91-1.87 (m, 2H), 1.79-1.75 (m, 2H), 1.49-1.40 (m, 2H); MS (*m*\z); 425 (M^+, 28.25%); Anal. Calc. for: $C_{21}H_{27}N_7OS$ (425): C, 59.27; H, 6.40; N, 23.04%; Found: C, 59.40; H, 6.58; N, 22.87%.

4.1.7.31. 2-(1-(4-Methyl-2-(4-((5-(piperidin-1-yl)pentyl)oxy)phenyl)thiazol-5-yl)ethylidene) hydrazine-1-carboximidamide (93). Yellow solid (167 mg, 97%); mp = 178-179 °C; ^{1}H NMR (DMSO-d_6) δ: 11.55 (brs, 1H), 10.40 (brs, 1H), 7.86 (d, *J* = 8.6 Hz, 2H), 7.77 (brs, 2H), 7.07 (d, *J* = 8.6 Hz, 2H), 4.05 (t, *J* = 7.6 Hz, 2H), 3.40-3.38 (m, 2H), 3.01-2.96 (m, 2H), 2.84-2.77 (m, 2H), 2.60 (s, 3H), 2.44 (s, 3H), 1.77-1.68 (m, 6H), 1.48-1.38 (m, 6H); ^{13}C NMR (DMSO-d_6) δ: 165.4, 161.0, 156.2, 152.7, 147.8, 130.0, 128.1, 125.7, 115.5, 67.8, 56.0, 52.3, 28.5, 23.2, 23.1, 22.8, 21.9, 18.5; MS (*m*\z); 442 (M^+, 100%); Anal. Calc. for: $C_{23}H_{34}N_6OS$ (442): C, 62.41; H, 7.74; N, 18.99%; Found: C, 62.59; H, 7.85; N, 18.73%.

4.1.7.32. 2-(1-(4-Methyl-2-(4-((5-(2-methylpiperidin-1-yl)pentyl)oxy)phenyl)thiazol-5-yl) ethylidene)hydrazine-1-carboximidamide (94). Yellow solid (161 mg, 94%); mp = 89-91 °C; ^{1}H NMR (DMSO-d_6) δ: 7.82 (d, *J* = 9.2 Hz, 2H), 7.02 (d, *J* = 9.2 Hz, 2H), 5.74- 5.60 (brs, 4H), 4.01 (t, *J* = 7.2 Hz, 2H), 2.77-2.75 (m, 1H), 2.55 (s, 3H), 2.30 (s, 3H), 2.22-2.19 (m, 2H), 2.05-2.02 (m, 2H), 1.75- 1.72 (m, 2H), 1.55- 1.18 (m, 10H), 0.98 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 165.4, 161.0, 156.3, 152.6, 147.7, 134.6, 128.1, 125.7, 119.6, 115.5, 67.9, 58.6,

52.0, 51.2, 31.3, 30.2, 28.6, 23.3, 22.9, 22.2, 18.6, 17.6; MS (*m*\z); 456 (M^+, 7.66%); Anal. Calc. for: $C_{24}H_{36}N_6OS$ (456): C, 63.12; H, 7.95; N, 18.40%; Found: C, 63.31; H, 8.17; N, 18.63%.

4.1.7.33. 2-(1-(4-Methyl-2-(4-((5-(3-methylpiperidin-1-yl)pentyl)oxy)phenyl)thiazol-5-yl) ethylidene)hydrazine-1-carboximidamide (95). Yellow solid (162 mg, 95%); mp = 130-133 °C; ^{1}H NMR (DMSO-d_6) δ: 11.41 (brs, 1H), 10.35 (brs, 1H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.71 (brs, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 4.06 (t, *J* = 6.2 Hz, 2H), 3.47-3.30 (m, 4H), 3.00- 2.90 (m, 2H), 2.59 (s, 3H), 2.42 (s, 3H), 2.00- 1.89 (m, 2H), 1.87- 1.71 (m, 7H), 1.55-1.45 (m, 2H), 0.89 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 165.4, 161.0, 156.3, 152.6, 147.8, 130.0, 128.1, 125.7, 115.5, 67.8, 57.7, 56.3, 51.9, 30.5, 29.0, 28.5, 23.1, 22.7, 19.0, 18.6, 18.5; MS (*m*\z); 456 (M^+, 20.74%); Anal. Calc. for: $C_{24}H_{36}N_6OS$ (456): C, 63.12; H, 7.95; N, 18.40%; Found: C, 63.29; H, 8.19; N, 18.23%.

4.1.7.34. 2-(1-(4-Methyl-2-(4-((5-(4-methylpiperidin-1-yl)pentyl)oxy)phenyl)thiazol-5-yl) ethylidene)hydrazine-1-carboximidamide (96). Yellow solid (164 mg, 96%); mp = 138-139 °C; ^{1}H NMR (DMSO-d_6) δ: 7.82 (d, *J* = 7.2 Hz, 2H), 7.01 (d, *J* = 7.2 Hz, 2H), 5.74 (brs, 2H), 5.62 (brs, 2H), 4.02-3.97 (m, 2H), 2.80 (t, *J* = 9.6 Hz, 2H), 2.56 (s, 3H), 2.31 (s, 3H), 2.23-1.72 (m, 8H), 1.56-1.07 (m, 7H), 0.88 (d, *J* = 6 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ: 162.7, 160.5, 160.0, 147.9, 143.2, 134.6, 127.7, 126.3, 115.3, 68.1, 58.6, 53.9, 34.5, 30.9, 29.0, 26.7, 24.0, 22.3, 18.6, 16.5; MS (*m*\z); 456 (M^+, 100%); Anal. Calc. for: $C_{24}H_{36}N_6OS$ (456): C, 63.12; H, 7.95; N, 18.40%; Found: C, 63.40; H, 7.69; N, 18.17%.

4.1.7.35. 2-(1-(4-Methyl-2-(4-((5-(4-methylpiperazin-1-yl)pentyl)oxy)phenyl)thiazol-5-yl) ethylidene)hydrazine-1-carboximidamide (97). Yellow solid (156 mg, 91%); mp = 180-183 °C; ^{1}H NMR (DMSO-d_6) δ: 7.81 (d, *J* = 5.7 Hz, 2H), 7.01 (d, *J* = 5.7 Hz, 2H), 5.74-5.59 (brs, 4H), 4.01 (t, *J* = 6.6 Hz, 2H), 2.55 (s, 3H), 2.38- 2.23 (m, 10H), 2.29 (s, 3H), 2.21 (s, 3H) 1.75-

1.71 (m, 2H), 1.45- 1.41 (m, 4H); ^{13}C NMR (DMSO-d_6) δ: 162.7, 160.5, 160.0, 147.9, 143.2, 134.6, 127.7, 126.3, 115.3, 68.1, 58.6, 55.2, 53.2, 46.2, 28.9, 26.5, 23.9, 18.6, 16.5; MS (*m*\z); 457 (M^+, 22.25%); Anal. Calc. for: $C_{23}H_{35}N_7OS$ (457): C, 60.36; H, 7.71; N, 21.42%; Found: C, 60.49; H, 7.85; N, 21.27%.

4.1.7.36. 2-(1-(4-Methyl-2-(4-((5-morphlinopentyl)oxy)phenyl)thiazol-5-yl)ethylidene) hydrazine-1-carboximidamide (98). Yellow solid (160 mg, 93%); mp = 181-183 °C; ^{1}H NMR (DMSO-d_6) δ: 7.85 (d, *J* = 7.9 Hz, 2H), 7.01 (d, *J* = 7.9 Hz, 2H), 5.78-5.59 (brs, 4H), 4.02 (t, *J* = 6.2 Hz, 2H), 3.55-3.50 (m, 4H), 3.47-3.40 (m, 6H), 2.58 (s, 3H), 2.26 (s, 3H), 1.79-1.45 (m, 6H); ^{13}C NMR (DMSO-d_6) δ: 162.7, 160.4, 160.0, 147.9, 143.2, 134.6, 127.7, 126.3, 115.3, 68.0, 66.6, 58.6, 53.8, 28.9, 26.1, 23.8, 18.6, 16.5; MS (*m*\z); 444 (M^+, 100%); Anal. Calc. for: $C_{22}H_{32}N_6O_2S$ (444): C, 59.43; H, 7.25; N, 18.90%; Found: C, 59.70; H, 7.41; N, 19.13%.

4.1.7.37. 2-(1-(4-Methyl-2-(4-((5-thiomorphlinopentyl)oxy)phenyl)thiazol-5-yl)ethylidene) hydrazine-1-carboximidamide (99). Orange solid (139 mg, 81%); mp = 119-121 °C; ^{1}H NMR (DMSO-d_6) δ: 7.81 (d, *J* = 7.8 Hz, 2H), 7.01 (d, *J* = 7.8 Hz, 2H), 5.73-5.59 (brs, 4H), 4.01 (t, *J* = 6.3 Hz, 2H), 2.58 (s, 3H), 2.55-2.49 (m, 8H), 2.29 (s, 3H), 1.75-1.70 (m, 4H), 1.48-1.44 (m, 4H); ^{13}C NMR (DMSO-d_6) δ: 162.7, 160.5, 160.0, 147.9, 143.2, 134.6, 127.7, 126.3, 115.3, 68.1, 58.8, 55.1, 28.9, 27.6, 26.1, 23.8, 18.6, 16.5; MS (*m*\z); 460 (M^+, 100%); Anal. Calc. for: $C_{22}H_{32}N_6OS_2$ (460): C, 57.36; H, 7.00; N, 18.24%; Found: C, 57.59; H, 7.16; N, 18.05%.

4.1.7.38. 2-(1-(2-(4-((5-(Azepan-1-yl)pentyl)oxy)phenyl)-4-methylthiazol-5-yl)ethylidene) hydrazine-1-carboximidamide (100). White solid (145 mg, 85%); mp = 181-182 °C; ^{1}H NMR (DMSO-d_6) δ: 7.81 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 5.74-5.63 (brs, 4H), 4.01 (t, *J* = 6.4 Hz, 2H), 2.55 (s, 3H), 2.54-2.51 (m, 4H), 2.40 (t, *J* = 6.8 Hz, 2H), 2.29 (s, 3H), 1.74-1.42 (m, 10H), 1.43-1.42 (m, 4H); ^{13}C NMR (DMSO-d_6) δ: 162.7, 160.5, 160.0, 147.9, 143.2, 134.6,

127.7, 126.3, 115.3, 68.1, 57.9, 55.3, 29.0, 28.4, 27.4, 27.0, 23.8, 18.6, 16.5; MS (*m*\z); 456 (M^+, 11.46%); Anal. Calc. for: $C_{24}H_{36}N_6OS$ (45): C, 63.12; H, 7.95; N, 18.40%; Found: C, 63.26; H, 8.13; N, 18.19%.

4.1.7.39. 2-(1-(4-Methyl-2-(4-((5-(octahydroisoquinolin-2(1*H*)pentyl)oxy)phenyl)thiazol-5-yl)ethylidene)hydrazine-1-carboximidamide (101). Orange solid (147 mg, 87%); mp = 72-74 °C; ^{1}H NMR (DMSO-d_6) δ: 7.82 (d, *J* = 8.7 Hz, 2H), 7.02 (d, *J* = 8.7 Hz, 2H), 6.05-5.97 (brs, 4H), 4.02 (t, *J* = 6.3 Hz, 2H), 2.95-2.77 (m, 2H), 2.56 (s, 3H), 2.34-2.29 (m, 2H), 2.31 (s, 3H), 2.05- 1.95 (m, 2H), 1.76-0.87 (m, 18H); ^{13}C NMR (DMSO-d_6) δ: 163.4, 160.6, 159.9, 149.1, 144.4, 133.4, 127.8, 126.2, 115.3, 68.0, 59.9, 58.2, 54.0, 41.5, 32.8, 30.4, 29.2, 26.4, 26.1, 23.8, 22.5, 18.6, 17.1; MS (*m*\z); 496 (M^+, 100%); Anal. Calc. for: $C_{27}H_{40}N_6OS$ (496): C, 65.29; H, 8.12; N, 16.92%; Found: C, 65.43; H, 8.24; N, 6.53%.

4.2. Microbiological assays

4.2.1. Bacterial strains, mammalian cell lines, antibiotics and compounds. Bacterial strains used in this study were obtained from Biodefense and Emerging Infections Research Resources Repository (BEI Resources) and the American Type Culture Collection (ATCC). Human colorectal adenocarcinoma (Caco-2) cell line and murine macrophage (J774) cells were purchased from American Type Culture Collection (ATCC). Linezolid (Chem-impex International, Wood Dale, IL, USA) and vancomycin hydrochloride (Gold Biotechnology, St. Louis, MO, USA), were purchased from commercial vendors. Phenylthiazole compounds were prepared in a stock concentration of 10 mg/mL in DMSO.

4.2.2. Determination of the antibacterial activity (MICs and MBCs) of the new phenylthiazole compounds against *Staphylococcus aureus* and other multidrug-resistant Gram-positive bacterial species. The broth microdilution method was utilized to test the

antibacterial activity of the new phenylthiazole compounds against a panel of clinically-important *S. aureus* strains and Gram-positive bacteria according to the guidelines outlined by the Clinical and Laboratory Standards Institute (CLSI) [36], see SI for more details.

4.2.3. *In vivo* Pharmacokinetics. Pharmacokinetic studies were performed in male naïve Sprague−Dawley (SD) rats, (three animals) following Institutional Animal Care and Use Committee guidelines. Oral dosing (50 mg/kg) was administered by oral gavage in a vehicle containing 40% PEG 400, and 60% water. Blood samples were collected over a 24-hour period post dose into Vacutainer tubes containing EDTA-K2. Plasma was isolated, and the concentration of tested compound in plasma was determined with LC/MS/MS after protein precipitation with acetonitrile. Non-compartmental pharmacokinetic analysis was performed on plasma concentration data to calculate pharmacokinetic parameters as described in a previous report [37].

4.2.4. Killing kinetics of compounds 6, 9, 11 and 12 against MRSA. The test was performed against MRSA USA400, as described previously [23]. Briefly, logarithmic phase bacterial cells were diluted, and drugs were added at 5 × MIC (in triplicates). At the corresponding time intervals, bacterial cells were diluted and plated on Tryptic soy agar plates to determine the viable colony forming unit (CFU)/mL.

4.2.5. *In vitro* cytotoxicity analysis against human colorectal cells. Tested phenylthiazoles were assayed for potential cytotoxicity against a human colorectal adenocarcinoma (Caco-2) cell line, as described previously [38]. Briefly, tested compounds were incubated with caco-2 cells for 2 and 24 hours. Then, cells were incubated with MTS 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium) reagent for 3-4 hours before measuring absorbance values (OD_{490}).

4.2.6. MRSA biofilm eradication assessment. Tested compounds were examined for their ability to eradicate pre-formed, well established mature staphylococcal biofilm using the microtiter plate biofilm formation assay as described in previous reports [39, 40].

4.2.5. Intracellular infection of J774 cells with MRSA. The ability of tested compounds **8**, **9** and vancomycin (at 2 × MIC and 4 × MIC) to reduce the burden of intracellular MRSA USA400 inside murine macrophage (J774) cells was evaluated as reported elsewhere [41, 42].

Supporting information. The supporting information is available free of charge on the journal website. The experimental details of *In vitro* cytotoxicity assessment against J774 cells and in vivo PK, and ^{1}H and ^{13}C NMR spectra of all new described compounds.

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- The lead compounds **1b** and **1c** are obese with bad physicochemical properties and poor PK profiles
- Derivatives with small cyclic amines at the lipophilic part are with good physicochemical properties
- Compound **8** is a good candidate for biofilm-related infections (*S. epidermidis* and *S. aureus*)
- At non-toxic concentrations, compound **8** generated 98% reduction of intracellular MRSA
- Compound **8** is well absorbed, and maintained a therapeutic plasma concentration for more than 12 h

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: