European Journal of Medicinal Chemistry 46 (2011) 2530–2540

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Urea/thiourea derivatives of quinazolinone–lysine conjugates: Synthesis and structure–activity relationships of a new series of antimicrobials

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ARTICLE INFO

Article history:
Received 17 January 2011
Received in revised form
4 March 2011
Accepted 19 March 2011
Available online 8 April 2011

Keywords:
Quinazolinone–lysine conjugates
Urea
Thiourea
Potent microbe inhibitors

ABSTRACT

Synthesis of a series of urea/thiourea/acetamide/sulphonamide derivatives of quinazolinones conjugated lysine has been reported. Structures of the products have been determined by standard spectroscopical studies. All the compounds have been screened for their antibacterial studies and structure–activity relationship has been developed. The activity profile revealed that the compounds containing urea and thiourea functionalities along with fluoro group have exerted a highly potent activity. Thus, the title compounds represent a novel class of potent antimicrobial agents.

1. Introduction

Despite a number of antibiotics available for the treatment of bacterial infections, emergence of multi-drug resistant organisms has posed a great challenge to the scientists. There appears to be a need for the development of new drugs with improved efficacy and better toxicity profile [1]. One of the most frequently encountered heterocycle in medicinal chemistry is quinazolin-4(3*H*)-one and its derivatives are reported to possess diverse biological applications including antimicrobial [2], analgesic and anti-inflammatory [3], anti-convulsant [4], anti-cancer [5] and anti-tubercular [6] activities.

The therapeutical applications of essential amino acids have received a considerable attention in respiratory physiology, cardiology, renal failure, neurological disorders, and congenital defects. Amongst, lysine is pharmacologically and medicinally significant because lysine acetylsalicylate (lysine aspirin) and bendazac lysine (a lysine salt), both derivatives of lysine, have been investigated for their therapeutical effects on migraine headaches [7], acute respiratory infections [8] and rheumatoid arthritis [9]. Lysine has been used in the treatment of recurrent herpetic lesions and aphthous ulcers [10].

Urea is a functional moiety that is commonly found in the natural products and often displays a wide range of biological activities [11]. In particular; substituted ureas have attracted attention due to their range of applications as agricultural pesticides [12] and anti-convulsants [13]. An unsymmetrically substituted urea is a common structural feature of many biologically active compounds such as enzyme inhibitors and pseudopeptides [14]. Unsymmetrically substituted ureas at amino groups have also been shown to have a potent HIV-1 protease inhibitory activity [13,14] equipotent towards both wild and mutant types [14]. Sulfonylureas have been found to have applications as oral antidiabetic drugs and as herbicides. Some urea derivatives are useful as active ingredients in antimicrobial, antifungal and algaecides agents [15]. A series of ureas and thioureas was synthesized, and their inhibitory activities against NO^- production in lipopolysaccharide-activated macrophages were evaluated [[16] and references cited therein].

Prompted by the above observations and keeping in mind that amino acids are known to enhance the physiological effects of some other drugs when given in together [17] and also in continuation of our earlier work [2,18,19], we envisioned our approach towards the synthesis of a novel series of quinazolinone conjugated lysine and their urea/thiourea/acetamide and methyl sulphonamide derivatives followed by the biological evaluation.

2. Results and discussion

2.1. Chemistry

Quinazolinones were coupled to lysine using EDCI/HOBt as a coupling agent and DIEA as a base. The € amino group of lysine

Abbreviations: Boc, *t*-Butoxycarbonyl; DCM, Dichloromethane; DIEA, Diisopropylethylamine; EDCI, 1-(3-Dimethylaminopropyl)-3-ethyl-carbodiimide.HCl; HOBt, 1-Hydroxybenzotriazole; TFA, Trifluoro acetic acid.

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doi:10.1016/j.ejmech.2011.03.041

was converted to substituted urea, thiourea, acetamide and methyl sulphonamide derivatives using isocyanates, isothiocyanates, acetyl chloride and methyl sulphonyl chloride respectively. The yields of the synthesized compounds were found to be good and characterized by M.P., ^{1}H NMR, ^{13}C NMR and mass spectroscopical techniques. The physical and analytical data of the synthesized compounds are provided in Table 1. ^{1}H NMR of **4** and **5** showed the signal at δ 8.15–8.30 doublet (1H) indicating the formation of amide bond between heterocycle and lysine. The formation of urea/thiourea derivatives was confirmed by $\delta \sim$8.0–9.5 singlet (1H) and ~6.0–7.2 multiplet (1H) in the ^{1}H NMR spectra and all the aromatic protons exactly matching the structure. Deprotection of methyl ester resulted in the formation of COOH group which showed signal at δ 11.80–12.00 singlet (1H) and all other peaks exactly matching its structure. Further all the synthesized compounds were confirmed by mass spectra which are in accordance with their molecular formulae.

2.2. Biology

Antibacterial activity of the synthesized compounds were tested against different strains of both gram positive bacteria namely *Bacillus substilis* and gram negative bacteria like *Escherichia coli*, *Pseudomonas fluorescens*, *Xanthomonas campestris pvs.* and *Xanthomonas oryzae*. The results obtained as zone of inhibition (mm) are presented in Table 2. Streptomycin and tetracycline were used as standard drugs for the assay. The concentration used for the test compounds and that of the standard drugs remains the same.

It is observed from Table 2 that quinazolinone–lysine conjugates (**4**, **5**) have exhibited moderate activity. When *C* terminal protected methyl ester was deblocked (**8**, **9**) there is a slight enhancement in the activity. On the other hand, retaining of *C* terminal protection and deblocking of Boc group of Lys led to a slight decrease in the activity (**6**, **7**). When both the protecting groups were cleaved (**10**, **11**) it resulted in the scattered activity than their counter parts.

We took the advantage of € amino group of lysine to convert it into urea/thiourea/acetamide/sulphonamide derivatives as these functionalities were found to be essential in the lead pharmacophores like PNU-100480, linezolid etc [24–26]. Further, these functionalities were substituted with various groups like F, Cl, OMe and Me since in the earlier studies it has been shown that the presence of one or more of the aforesaid would lead to the improvement of the activity [[27] and references cited therein].

As a result, urea (**a–c of 13**, **14**, **15**, **16**) and thiourea (**a–c of 18**, **19**, **20**, **21**) containing compounds have exhibited a highly potent activity against all the five pathogens tested. But when the € amino group of Lys was acetylated (**23–26**) and sulphonated (**28–31**), there is a dramatic decrease in the activity. Hence, substitution by acetylation or sulphonation leads to reduction of the antibacterial activity. Earlier report [28] described that when O of urea was replaced by S, the antibacterial activity decreased. But in the

Table 1
Physical and analytical data of the synthesized compounds.

Entry	Appearance	Yield (%)	M.P. (°C)	Molecular Formula	Theoretical Mol. Wt.	Actual mass values (M^+)
4	White solid	87	160–162	$C_{23}H_{32}N_4O_6$	460.23	459.7 (M^-)
5	Off white solid	93	167–169	$C_{24}H_{34}N_4O_6$	474.25	473.7 (M^-)
6	Brownish gummy	86	–	$C_{20}H_{25}F_3N_4O_6$	474	361.3
7	Brownish gummy	88	–	$C_{21}H_{27}F_3N_4O_6$	488	375.4
8	Off white solid	85	150–152	$C_{22}H_{30}N_4O_6$	446.22	445.1 (M^-)
9	Off white solid	84	156–157	$C_{23}H_{32}N_4O_6$	460.23	459.1 (M^-)
10	Brownish gummy	87	–	$C_{19}H_{23}F_3N_4O_6$	460.16	347.3
11	Brownish gummy	86	–	$C_{20}H_{25}F_3N_4O_6$	474.17	359.3 (M^-)
13a	Off white solid	80	130–132	$C_{25}H_{28}ClN_5O_5$	513.18	515.2
13b	Off white solid	82	127–129	$C_{26}H_{31}N_5O_6$	509.23	510.8
13c	Off white solid	83	140–141	$C_{25}H_{28}FN_5O_5$	497.21	498.8
14a	Pale yellow solid	81	135–136	$C_{26}H_{30}ClN_5O_5$	527.19	529.2
14b	White solid	81	130–132	$C_{27}H_{33}N_5O_6$	523.24	524.4
14c	Off white solid	82	139–140	$C_{26}H_{30}FN_5O_5$	511.22	512.3
15a	Pale yellow solid	96	140–142	$C_{24}H_{26}ClN_5O_5$	499.16	501.3
15b	White solid	86	139–141	$C_{25}H_{29}N_5O_6$	495.21	494.1 (M^-)
15c	Off white solid	96	149–150	$C_{24}H_{26}FN_5O_5$	483.19	482.2 (M^-)
16a	Pale yellow solid	91	136–137	$C_{25}H_{28}ClN_5O_5$	513.18	515.2
16b	White solid	90	140–141	$C_{26}H_{31}N_5O_6$	509.23	510.1
16c	Off white solid	94	150–152	$C_{25}H_{28}FN_5O_5$	497.21	496.3 (M^-)
18a	Off white solid	83	165–167	$C_{26}H_{30}FN_5O_4S$	527.2	528.2
18b	White solid	85	157–158	$C_{26}H_{31}N_5O_4S$	509.21	510.1
18c	Off white solid	84	158–159	$C_{25}H_{28}FN_5O_4S$	513.18	514.7
19a	Off white solid	82	168–170	$C_{27}H_{32}FN_5O_4S$	541.22	542.2
19b	White solid	83	140–141	$C_{27}H_{33}N_5O_4S$	523.23	522.3 (M^-)
19c	Off white solid	82	150–152	$C_{26}H_{30}FN_5O_4S$	527.2	528.3
20a	Off white solid	92	163–165	$C_{25}H_{28}FN_5O_4S$	513.18	512.3 (M^-)
20b	Colourless gummy	95	–	$C_{25}H_{29}N_5O_4S$	495.19	494.1 (M^-)
20c	Colourless gummy	90	–	$C_{24}H_{26}FN_5O_4S$	499.17	498.2 (M^-)
21a	Off white solid	94	169–170	$C_{26}H_{30}FN_5O_4S$	527.20	528.2
21b	White solid	93	156–158	$C_{26}H_{31}N_5O_4S$	509.21	508.3 (M^-)
21c	Off white solid	90	167–169	$C_{25}H_{28}FN_5O_4S$	513.18	512.3 (M^-)
23	Colourless gummy	84	–	$C_{20}H_{26}N_4O_5$	402.19	403.3
24	Colourless gummy	82	–	$C_{21}H_{28}N_4O_5$	416.21	417.3
25	Pale yellow gummy	89	–	$C_{19}H_{24}N_4O_5$	388.17	389.2
26	Pale yellow gummy	88	–	$C_{20}H_{26}N_4O_5$	402.19	403.2
28	Off white solid	84	120–122	$C_{19}H_{26}N_4O_6S$	438.16	439.3
29	Off white solid	85	127–129	$C_{20}H_{28}N_4O_6S$	452.17	453.1
30	Brownish gummy	86	–	$C_{18}H_{24}N_4O_6S$	424.14	423.3 (M^-)
31	Brownish gummy	85	–	$C_{19}H_{26}N_4O_6S$	438.16	437.1 (M^-)

Table 2
Inhibitory zone (diameter) mm of the synthesized compounds against tested bacterial strains by disc diffusion method.

Entry	Zone of inhibition[a] (mm) ± SD ($n = 3$)				
	B. substilis	*E. coli*	*P. fluorescens*	*X. campestris pvs.*	*X. oryzae*
4	8 ± 1.1	9 ± 1.3	11 ± 1.2	12 ± 1.1	12 ± 0.9
5	6 ± 1.2	8 ± 0.8	8 ± 0.8	7 ± 0.4	9 ± 0.5
6	6 ± 0.5	8 ± 0.4	10 ± 0.3	9 ± 0.5	10 ± 0.3
7	10 ± 1.0	9 ± 1.1	10 ± 1.2	12 ± 1.2	12 ± 1.3
8	10 ± 0.4	11 ± 0.5	14 ± 0.4	13 ± 0.6	14 ± 0.4
9	9 ± 1.1	10 ± 1.3	11 ± 1.4	12 ± 1.2	11 ± 1.1
10	8 ± 0.6	9 ± 0.7	10 ± 0.7	10 ± 0.4	9 ± 0.8
11	14 ± 0.8	10 ± 1.0	12 ± 1.2	13 ± 1.1	12 ± 1.2
13a	24 ± 0.6	28 ± 0.6	29 ± 0.8	28 ± 0.9	29 ± 0.9
13b	22 ± 0.8	23 ± 0.8	25 ± 0.9	26 ± 0.8	28 ± 0.7
13c	35 ± 1.1	36 ± 1.3	36 ± 1.2	37 ± 1.1	36 ± 0.9
14a	25 ± 0.8	26 ± 0.9	29 ± 0.6	28 ± 0.4	30 ± 0.5
14b	20 ± 1.1	21 ± 1.1	22 ± 0.9	24 ± 0.9	25 ± 0.8
14c	36 ± 1.2	35 ± 0.8	34 ± 0.8	36 ± 0.4	35 ± 0.5
15a	28 ± 0.8	30 ± 1.1	32 ± 1.2	30 ± 1.1	30 ± 1.3
15b	24 ± 0.7	25 ± 0.9	27 ± 0.8	28 ± 0.7	28 ± 0.8
15c	35 ± 0.4	35 ± 0.5	34 ± 0.4	33 ± 0.6	34 ± 0.4
16a	29 ± 0.6	28 ± 0.4	30 ± 0.5	28 ± 0.8	29 ± 0.7
16b	22 ± 1.1	24 ± 0.9	23 ± 1.0	25 ± 1.2	26 ± 1.1
16c	35 ± 1.1	36 ± 1.3	35 ± 1.4	34 ± 1.2	36 ± 1.1
18a	33 ± 0.6	32 ± 0.7	34 ± 0.9	33 ± 0.8	34 ± 1.2
18b	23 ± 0.4	22 ± 0.5	24 ± 0.8	27 ± 0.7	26 ± 1.1
18c	36 ± 0.5	38 ± 0.4	36 ± 0.3	38 ± 0.5	35 ± 0.3
19a	32 ± 1.2	33 ± 1.4	33 ± 1.4	30 ± 1.2	32 ± 1.4
19b	22 ± 1.4	23 ± 1.5	23 ± 1.3	25 ± 1.1	24 ± 1.5
19c	34 ± 1.0	35 ± 1.1	33 ± 1.2	34 ± 1.2	36 ± 1.3
20a	34 ± 1.1	33 ± 1.3	35 ± 1.1	34 ± 1.2	35 ± 1.4
20b	23 ± 1.2	23 ± 1.2	25 ± 1.0	28 ± 1.0	28 ± 1.1
20c	36 ± 0.6	38 ± 0.7	34 ± 0.7	36 ± 0.4	36 ± 0.8
21a	33 ± 1.0	34 ± 1.4	34 ± 1.2	32 ± 1.3	33 ± 1.0
21b	23 ± 1.0	24 ± 1.4	25 ± 1.2	26 ± 1.3	25 ± 1.0
21c	34 ± 0.8	32 ± 1.0	32 ± 1.2	33 ± 1.1	34 ± 1.2
23	9 ± 1.0	10 ± 1.2	12 ± 1.1	11 ± 1.0	12 ± 0.8
24	8 ± 1.1	9 ± 0.6	7 ± 0.9	6 ± 0.7	8 ± 0.6
25	11 ± 0.8	10 ± 0.4	13 ± 0.6	12 ± 0.9	14 ± 0.8
26	10 ± 1.3	11 ± 1.4	10 ± 1.5	14 ± 1.1	12 ± 1.2
28	8 ± 0.8	6 ± 0.9	9 ± 0.7	8 ± 0.6	11 ± 0.8
29	11 ± 1.0	9 ± 1.4	11 ± 1.2	12 ± 1.0	11 ± 1.3
30	9 ± 0.9	9 ± 0.8	12 ± 0.6	10 ± 0.6	10 ± 0.4
31	12 ± 0.8	11 ± 1.0	12 ± 1.2	11 ± 1.1	10 ± 1.2
Streptomycin	17 ± 0.5	21 ± 0.6	23 ± 0.8	–	–
Tetracyclin	–	–	–	19 ± 0.6	18 ± 0.5

[a] Values are mean of three determinations, the ranges of which are < 5% of the mean in all cases.

present investigation, it was found that the presence of S is also equally important which resulted in a highly potent activity. This may be due to more nucleophilic character of sulphur. The charge present in the molecule might help in penetrating through the bacterial cell wall easily there by arresting its growth.

Among the halogen substituted compounds, F containing molecules have shown more potent activity which is analogues to earlier study [27] compared to Cl containing molecules. This could be attributed to the high electronegative nature of F compared to Cl. Further, when an H atom of the phenyl ring was replaced by a methyl group (**18a**, **19a**, **20a**, **21a**) in F containing compounds, the activity was slightly decreased. On the other hand, both Me and OMe containing compounds of urea and thiourea derivatives have shown equipotency in arresting the growth of pathogens which could be due to their more electron donating effect. Thus, the order of activity based on the groups attached to the phenyl ring of ureido and thiouriedo derivatives was found to be F > F–Me > Cl > OMe ≈ Me.

When *C* terminal methyl ester of all the compounds is deblocked, the resultant COOH containing compounds showed an enhancement in the activity than their counter parts. This is due to the increase of the polarity of these compounds [2] which would help the molecules to interact or penetrate more through the cell membranes of microbes and there by inactivating them. This indicates that increase in the polarity has an impact on the activity. Also activity towards gram negative bacteria was more compared to gram positive microorganisms.

Further, increasing the alkyl chain length of quinazolinone moiety from 2 to 3 carbon atoms causes a slight decrease in the activity except **7**, **11**, **25 and 27**. Hence, the presence of a propyl group is found to be essential in exerting more activity compared to butyl chain which is in good agreement with our earlier reports [2,29] which describes the conjugation with peptides.

Quinazolinones when taken in isolation were inactive against the panel of organisms, but have shown enhanced activity when conjugated to Lys and in turn their urea/thiourea derivatives have exerted high potency revealing the latter's importance in arresting/inhibiting the microbial growth.

3. Conclusion

We have successfully synthesized a series of propyl and butyl groups containing quinazolinone–lysine conjugates and converted them to compounds containing C=O, C=S, NH–CO–CH_3 and NH–SO_2–CH_3 functional groups. The antibacterial activity of the synthesized compounds showed that the urea and thiourea moieties play a major role in enhancing the activity. Further, it is interesting to note that F attached to the phenyl ring of the conjugates acts as an active moiety in arresting the growth of the microbes. Thus the nature of the substituent was found to be crucial to improve the activity. Also, increasing the alkyl chain length of quinazolinones from two to three carbon atoms resulted in slight decrease in the activity. This study extends the knowledge of different substituents at phenyl ring which might be of interest for the identification of novel class of antimicrobials.

4. Experimental

4.1. Materials

All chemicals and reagents were obtained from Aldrich (USA), Spectrochem Pvt. Ltd. (India) and Rankem Pvt. Ltd. (India) and were used without further purification. Lysine used was of *L*-configuration and purchased from Advanced Chem. Tech. (Louisville, Kentucky, USA). Silica gel (100–200 mesh) for column chromatography was purchased from Sisco Research Laboratories Pvt. Ltd., (Mumbai, India). Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on 400 MHz Bruker FT-NMR Spectrometer. ^{13}C NMR spectra were recorded in DMSO-d_6 at 100 MHz. The chemical shifts were reported as parts per million (δ ppm) using TMS as an internal standard. Mass spectra were obtained on LCMSDTrap - XCT instrument. The progress of the reaction was monitored on pre-coated silica gel plates (Merck) using chloroform/methanol/acetic acid (8.7:1:0.3) as an eluent system. The bacterial strains used were obtained from Department of Studies in Biotechnology, University of Mysore, India. All the chemicals and reagents used for antimicrobial studies were of bacteriological grade unless otherwise indicated and were purchased from Hi-media chemicals (Mumbai, India).

4.2. Synthesis

The 3-(4-oxo-3,4-dihydroquinazolin-2-yl)propanoic acid **1** and 4-(4-oxo-3,4-dihydroquinazolin-2-yl)butanoic acid **2** were synthesized as previously reported using anthranilide, succinic

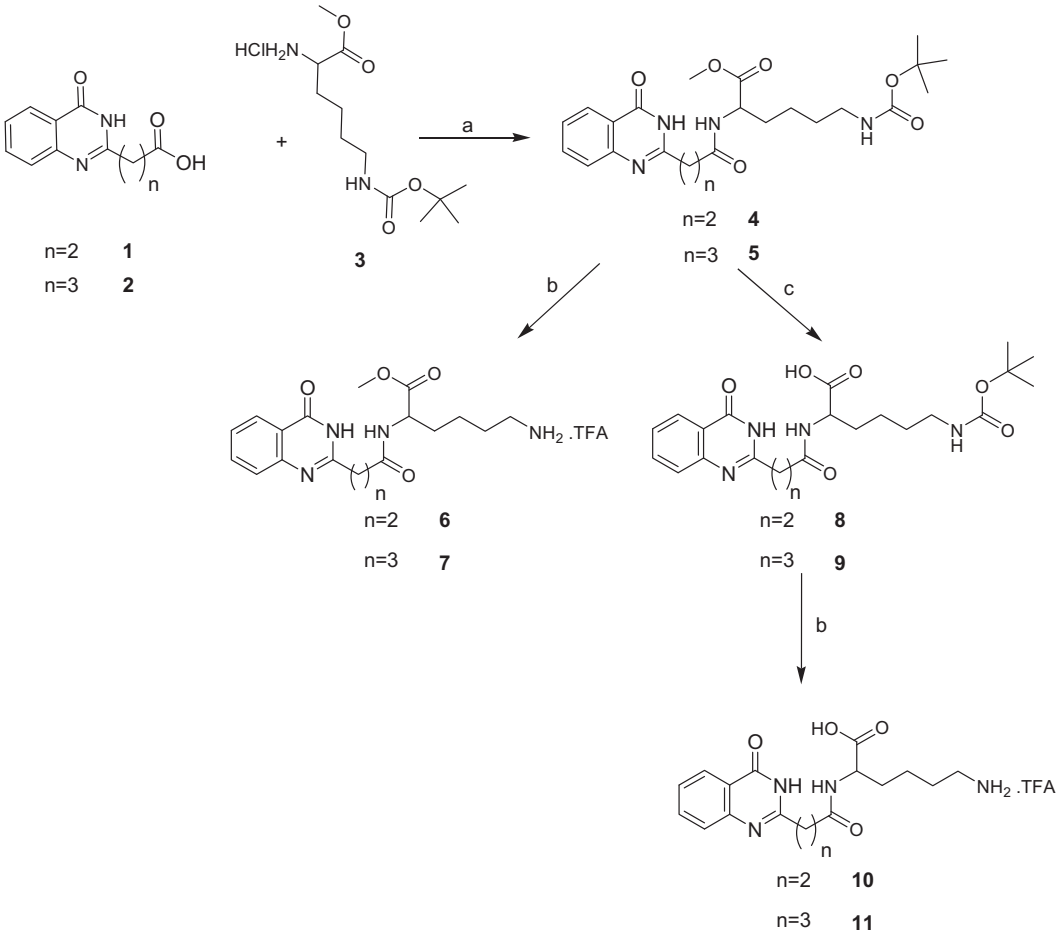
anhydride and dihydro-3*H*-pyran-2,6-dione [11,20,21]. Lysine **3** was coupled with aforesaid heterocyclic precursors **1** and **2** using EDCI/HOBt as a coupling agent and DIEA as a base to get **4** and **5**. The carboxylic group was protected by methyl ester and its removal was effected by hydrolysis using LiOH. The Boc group was used for temporary N^{α} protection and its removal was achieved with TFA. Urea **13** (**a**–**c**), **14** (**a**–**c**); thiourea **18** (**a**–**c**), **19** (**a**–**c**); acetamide (**23**, **24**) and methyl sulphonamide (**28**, **29**) derivatives of heterocyclic conjugates of lysine were synthesized by reacting **6** and **7** with isocyanates **12** (**a**–**c**), isothiocyanates **17** (**a**–**c**), acetyl chloride **22**, methyl sulphonyl chloride **27** respectively in presence of DIEA as a base [22]. The methyl ester group was removed by hydrolysing with LiOH to obtain respective free acids **15** (**a**–**c**), **16** (**a**–**c**); **20** (**a**–**c**), **21** (**a**–**c**); **25**, **26** and **30**, **31**. Synthetic structural frame works of heterocyclic conjugates of lysine and their derivatives such as urea, thiourea, acetamide and sulphonamide are presented in Scheme 1 and 2 respectively.

4.2.1. Methyl 6-(tert-butoxycarbonylamino)-2-(3-(4-oxo-3,4-dihydroquinazolin-2-yl)propanamido) hexanoate (*4*)

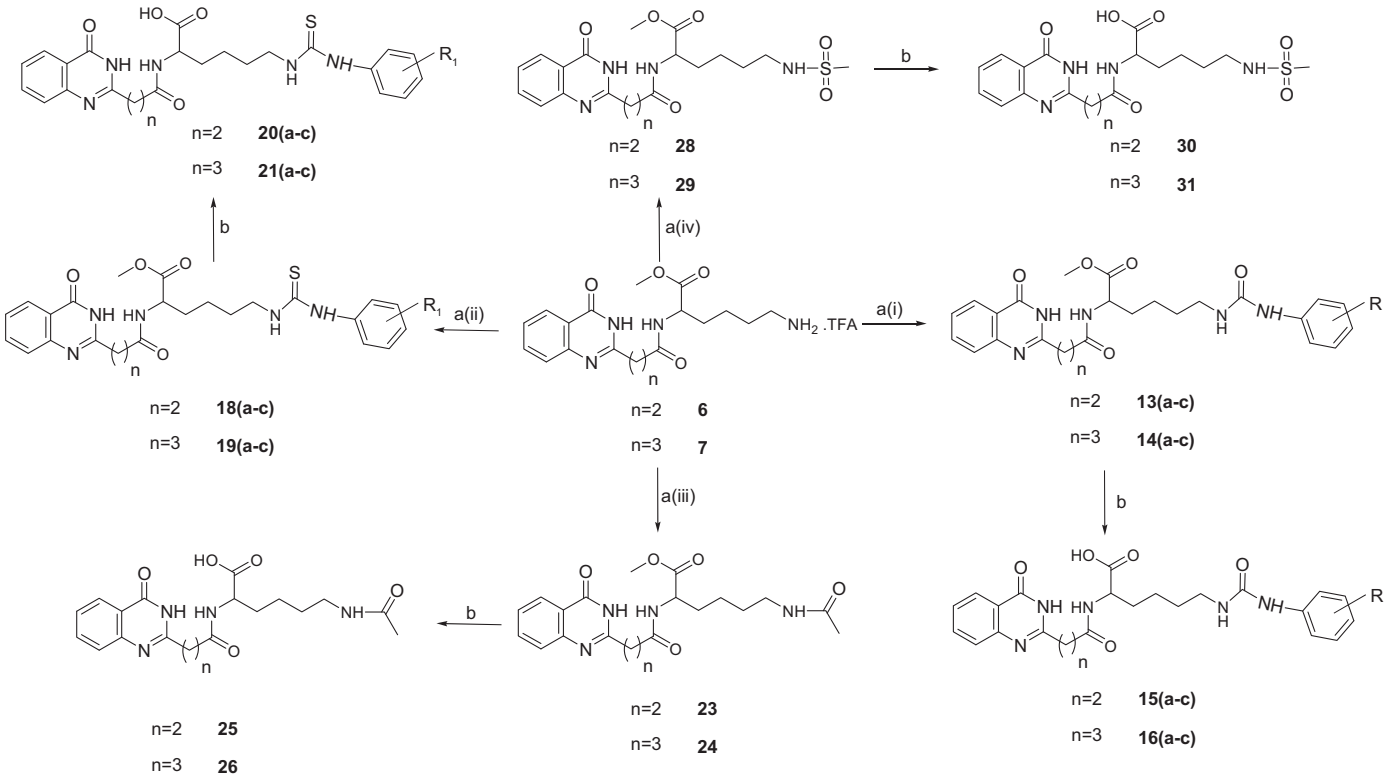
To a stirred solution of 3-(4-oxo-3,4-dihydroquinazolin-2-yl) propanoic acid (2.00 g, 9.17 mmol) in DMF (25 mL) cooled to 0 °C, a mixture of H-Lys(Boc)-OMe.HCl (2.71 g, 9.17 mmol), DIEA (6.5 mL, 36.7 mmol), HOBt (1.85 g, 13.76 mmol), EDCI (3.70 g, 19.2 mmol) and THF (25 mL) was added. The reaction mixture was stirred overnight while slowly warming to room temperature. The reaction mixture was quenched with H_2O (10 mL) and the solvent was evaporated. The residue was extracted with EtOAc (30 mL) and the organic layer was washed with 1*N* HCl (1 × 200 mL), water (1 × 200 mL), saturated $NaHCO_3$ solution (1 × 200 mL) and brine (1 × 200 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated at high vacuum. Chromatography (20% EtOAc-Hexane) over silica gel (100–200 mesh) provided compound **4** as white powder. ^{1}H NMR (DMSO-D_6, 400 MHz): δ 12.12 (s, 1H), 8.29–8.28 (d, 1H, J = 7.6 Hz), 8.06–8.04 (d, 1H, J = 8.0 Hz), 7.76–7.73 (t, 1H, J = 7.4 Hz), 7.55–7.53 (d, 1H, J = 8.0 Hz), 7.45–7.41 (t, 1H, J = 7.4 Hz), 6.71 (s, 1H), 4.21–4.16 (m, 1H), 3.57 (s, 3H), 2.84–2.81 (m, 4H), 2.67–2.65 (m, 2H), 1.65–1.50 (m, 2H), 1.34 (s, 9H), 1.32–1.30 (m, 2H), 1.24–1.22 (m, 2H). ^{13}C NMR (DMSO-D_6, 100 MHz): δ 173.2, 171.7, 171.0, 162.2, 158.5, 149.0, 134.6, 128.4, 127.6, 126.2, 126.0, 80.2, 52.5, 51.9, 40.4, 31.4, 31.1, 30.2, 30.0, 29.1, 23.9.

4.2.2. Methyl 6-(tert-butoxycarbonylamino)-2-(4-(4-oxo-3,4-dihydroquinazolin-2-yl)butanamido) hexanoate (*5*)

The compound **5** was synthesized by following the procedure described for the compound **4** using 4-(4-oxo-3,4-dihydroquinazolin-2-yl)butanoic acid (2.00 g, 8.62 mmol) in DMF (25 mL), H-Lys(Boc)-OMe.HCl (2.50 g, 8.62 mmol), DIEA (6.1 mL, 34.48 mmol), HOBt (1.75 g, 12.93 mmol), EDCI (3.50 g, 18.1 mmol) and THF (25 mL). ^{1}H NMR (DMSO-D_6, 400 MHz): δ 12.11 (s, 1H), 8.16–8.14 (d, 1H, J = 7.6 Hz), 8.07–8.05 (d, 1H, J = 7.2 Hz), 7.77–7.73 (t, 1H, J = 8.4 Hz), 7.59–7.57 (d, 1H, J = 8.4 Hz), 7.46–7.42 (t, 1H, J = 7.2 Hz), 6.71 (s, 1H), 4.19–4.13 (m, 1H), 3.59 (s, 3H), 2.87–2.85 (m, 2H), 2.61–2.57 (t, 2H, J = 7.4 Hz), 2.21–2.18 (t, 2H, J = 7.4 Hz), 1.95–1.92 (m, 2H), 1.64–1.49 (m, 2H), 1.33



Scheme 1. Synthesis of heterocyclic conjugates of lysine and their deprotection *Reagents and conditions*: (a) EDCI/HOBt, DIEA, 0 °C, overnight at rt (b) 50% TFA in DCM, 1 h, rt (c) LiOH/H_2O/MeOH/THF, overnight at rt.



Scheme 2. Synthesis of urea/thiourea/acetamide/sulphonamide derivatives of the conjugates **6** and **7** where R = 4-Cl, 4-OMe, 5-F and R_1 = 4-F+6-Me, 2-Me, 3-F; *Reagents and conditions*: (a) DIEA/THF, 8h, 0 °C to rt; (i) R–N=C=O, (ii) R_1–N=C=S, (iii) CH_3–CO–Cl, (iv) CH_3–SO_2–Cl, (b) LiOH/H_2O/MeOH/THF, overnight at rt.

(s, 9H), 1.32–1.30 (m, 2H), 1.24–1.22 (m, 2H). ^{13}C NMR (DMSO-D_6, 100 MHz): δ 173.4, 171.6, 169.9, 162.5, 158.0, 149.2, 134.3, 128.4, 127.5, 126.3, 126.0, 80.0, 52.2, 51.9, 40.5, 34.4, 34.3, 31.2, 29.7, 29.0, 23.2, 23.1.

*4.2.3. Methyl 6-amino-2-(3-(4-oxo-3,4-dihydroquinazolin-2-yl) propanamido)hexanoate trifluoro acetic acid salt (**6**)*

To a stirred solution of **4** (2.00 g, 4.34 mmol) in DCM (10 mL) cooled to 0 °C was added 50% TFA in DCM (15 mL) and stirred for 1 h at the same temperature. The reaction mixture was concentrated at high vacuum to get the product **6** as TFA salt which was then recrystallized using hexane and ethyl acetate.

*4.2.4. Methyl 6-amino-2-(4-(4-oxo-3,4-dihydroquinazolin-2-yl) butanamido)hexanoate trifluoro acetic acid salt (**7**)*

The compound **7** was synthesized by following the procedure described for the compound **6** using **5** (2.00 g, 4.21 mmol) in DCM (10 mL) and 50% TFA in DCM (15 mL).

*4.2.5. 6-(tert-Butoxycarbonylamino)-2-(3-(4-oxo-3,4-dihydroquinazolin-2-yl)propanamido) hexanoic acid (**8**)*

To a stirred solution of **4** (0.20 g, 0.42 mmol) in methanol (0.5 mL), water (0.5 mL) and THF (0.5 mL), LiOH (0.02 g, 0.84 mmol) was added. The reaction mixture was stirred for 24 h at room temperature and the solvent was evaporated under reduced pressure. The residue was dissolved in water and washed with ethyl acetate. The aqueous layer was acidified with 1*N* HCl, extracted with ethyl acetate, dried and evaporated under reduced pressure to afford **8** as solid which was recrystallized from hexane and ethyl acetate. ^{1}H NMR (DMSO-D_6, 400 MHz): δ 12.12 (s, 1H), 12.01 (s, 1H), 8.29–8.28 (d, 1H, J = 7.6 Hz), 8.06–8.04 (d, 1H, J = 8.0 Hz), 7.76–7.73 (t, 1H, J = 7.4 Hz), 7.55–7.53 (d, 1H, J = 8.0 Hz), 7.45–7.41 (t, 1H, J = 7.4 Hz), 6.71 (s, 1H), 4.21–4.16 (m, 1H), 2.84–2.81 (m, 4H), 2.67–2.65 (m, 2H), 1.65–1.50 (m, 2H), 1.34 (s, 9H), 1.32–1.30 (m, 2H), 1.24–1.22 (m, 2H). ^{13}C NMR (DMSO-D_6, 100 MHz): δ 175.6, 171.6, 171.2, 162.4, 158.3, 149.1, 134.5, 128.2, 127.5, 126.2, 126.0, 80.1, 52.6, 40.3, 31.3, 31.0, 30.3, 29.9, 29.0, 23.5.

*4.2.6. 6-(tert-Butoxycarbonylamino)-2-(4-(4-oxo-3,4-dihydroquinazolin-2-yl)butanamido) hexanoic acid (**9**)*

The compound **9** was synthesized by following the procedure described for compound **8** using **5** (0.20 g, 0.42 mmol) in methanol (0.5 mL), water (0.5 mL), THF (0.5 mL) and LiOH (0.02 g, 0.84 mmol). ^{1}H NMR (DMSO-D_6, 400 MHz): δ 12.11 (s, 1H), 12.01 (s, 1H), 8.16–8.14 (d, 1H, J = 7.6 Hz), 8.07–8.05 (d, 1H, J = 7.2 Hz), 7.77–7.73 (t, 1H, J = 8.4 Hz), 7.59–7.57 (d, 1H, J = 8.4 Hz), 7.46–7.42 (t, 1H, J = 7.2 Hz), 6.71 (s, 1H), 4.19–4.13 (m, 1H), 2.87–2.85 (m, 2H), 2.61–2.57 (t, 2H, J = 7.4 Hz), 2.21–2.18 (t, 2H, J = 7.4 Hz), 1.95–1.92 (m, 2H), 1.64–1.49 (m, 2H), 1.33 (s, 9H), 1.32–1.30 (m, 2H), 1.24–1.22 (m, 2H). ^{13}C NMR (DMSO-D_6, 100 MHz): δ 174.9, 171.5, 169.7, 162.3, 157.8, 149.2, 134.3, 128.3, 127.3, 126.1, 125.9, 80.4, 52.1, 40.3, 34.3, 34.0, 31.1, 29.7, 29.0, 23.2, 23.0.

*4.2.7. 6-Amino-2-(3-(4-oxo-3,4-dihydroquinazolin-2-yl) propanamido)hexanoic acid trifluoro acetic acid salt (**10**)*

The compound **10** was synthesized by following the procedure described for compound **6** using **8** (0.10 g, 0.22 mmol) in DCM (0.5 mL) and 50% TFA in DCM (1 mL).

*4.2.8. 6-Amino-2-(4-(4-oxo-3,4-dihydroquinazolin-2-yl) butanamido)hexanoic acid trifluoro acetic acid salt (**11**)*

The compound **11** was synthesized by following the procedure described for compound **6** using **9** (0.10 g, 0.21 mmol) with 50% TFA in DCM (1 mL).

*4.2.9. General procedure for the synthesis of uriedo derivatives **13a–c** and **14a–c***

To a solution of compound **6**/**7** (0.42 mmol) and DIEA (0.15 mL, 0.84 mmol) in dry THF (3 mL), the appropriate isocyanates: namely: 1-chloro-4-isocyanatobenzene, 1-isocyanato-4-methoxybenzene and 1-fluoro-3-isocyanatobenzene (0.63 mmol) was added respectively at 0 °C. The reaction mixture was stirred for 8 h slowly warming to room temperature. The solution was filtered and the solvent was evaporated. The residue was purified by chromatography (30% EtOAc-Hexane) over silica gel (100–200 mesh) to give solid **13a–c** and **14a–c**.

*4.2.10. General procedure for the synthesis of thiouriedo derivatives **18a–c** and **19a–c***

To a solution of compound **6**/**7** (0.42 mmol) and DIEA (0.15 mL, 0.84 mmol) in dry THF (3 mL), the appropriate isothiocyanates: namely: 4-fluoro-1-isothiocyanato-2-methylbenzene, 1-isothiocyanato-2-methylbenzene and 1-fluoro-3-isothiocyanatobenzene (0.63 mmol) was added respectively at 0 °C. The reaction mixture was stirred for 8 h slowly warming to room temperature. The solution was filtered and the solvent was evaporated. The residue was purified by chromatography (30% EtOAc-Hexane) over silica gel (100–200 mesh) to give solid **18a–c** and **19a–c**.

*4.2.11. General procedure for the synthesis of acetamide and sulphonamide derivatives **23**, **24**, **28** and **29***

To a stirred solution of **6**/**7** (0.42 mmol) in DCM (3 mL) were added DIEA (0.15 mL, 0.84 mmol) and acetyl chloride/sulphonyl chloride (0.42 mmol) at 0 °C. After stirring at room temperature for 1 h, saturated $NaHCO_3$ was added to the reaction mixture with vigorous stirring. After stirring for 30 min, the reaction mixture was then diluted with EtOAc and washed sequentially with brine, 1*N* HCl, brine, saturated $NaHCO_3$, and brine. The organic layer was dried over anhydrous $MgSO_4$. Removal of the volatiles *in vacuo* provided the compounds **23**, **24**, **28** and **29** respectively.

*4.2.12. General procedure for the synthesis of acids by hydrolysis **15** (**a–c**), **16**(**a–c**); **20**(**a–c**), **21**(**a–c**); **25**, **26**; **30** and **31***

To a stirred solution of **13**(**a–c**), **14**(**a–c**)/**18**(**a–c**), **19**(**a–c**)/**23**, **24**/**28**, **29** (0.42 mmol) in methanol (0.5 mL), water (0.5 mL) and THF (0.5 mL), LiOH (0.02 g, 0.84 mmol) was added. The reaction mixture was stirred for 24 h at room temperature and the solvent was evaporated under reduced pressure. The residue was dissolved in water and washed with ethyl acetate. The aqueous layer was acidified with 1*N* HCl, extracted with ethyl acetate, dried and evaporated under reduced pressure to afford **15**(**a–c**), **16**(**a–c**); **20** (**a–c**), **21**(**a–c**); **25, 26; 30** and **31** respectively which was recrystallized from hexane and ethyl acetate.

*4.2.13. Methyl 6-(3-(4-chlorophenyl)ureido)-2-(3-(4-oxo-3,4-dihydroquinazolin-2-yl) propanamido) hexanoate (**13a**)*

^{1}H NMR (DMSO-D_6, 400 MHz): δ 12.10 (s, 1H), 8.29–8.28 (d, 1H, *J* = 6.8 Hz), 8.05–8.03 (d, 1H, *J* = 8.0 Hz), 7.75–7.72 (t, 1H, *J* = 7.4 Hz), 7.54–7.52 (d, 1H, *J* = 8.0 Hz), 7.44–7.40 (t, 1H, *J* = 7.4 Hz), 7.33–7.31 (d, 2H, *J* = 8.0 Hz), 7.22–7.20 (d, 2H, *J* = 8.0 Hz), 6.28 (br, 1H), 5.90 (br,1H), 4.18 (br, 1H), 3.56 (s, 3H), 2.94–2.92 (d, 2H, *J* = 5.2 Hz), 2.81–2.80 (d, 2H, *J* = 6.8 Hz), 2.71–2.60 (m, 2H), 1.63–1.55 (m, 2H), 1.30–1.21 (m, 4H). ^{13}C NMR (DMSO-D_6, 100 MHz): δ 173.2, 171.7, 162.1, 160.0, 158.5, 149.2, 134.7, 131.4, 129.2, 128.6, 125.5, 127.2, 126.4, 126.1, 121.3, 52.3, 52.1, 42.6, 31.1, 31.1, 30.1, 30.0, 23.2.

*4.2.14. Methyl 6-(3-(4-methoxyphenyl)ureido)-2-(3-(4-oxo-3,4-dihydroquinazolin-2-yl) propanamido)hexanoate (**13b**)*

^{1}H NMR (DMSO-D_6, 400 MHz): δ 12.10 (s, 1H), 8.30–8.28 (d, 1H, *J* = 6.4 Hz), 8.05–8.03 (d, 2H, *J* = 5.7 Hz), 7.79 (s, 1H), 7.76–7.72 (t, 1H, *J* = 7.4 Hz), 7.54–7.52 (d, 1H, *J* = 8.0 Hz), 7.44–7.40 (t, 1H, *J* = 7.2 Hz), 6.91–6.89 (d, 1H, *J* = 7.2 Hz), 6.79 (s, 3H), 4.21–4.19 (d, 1H, *J* = 5.2 Hz), 3.79 (s, 3H), 3.56 (s, 3H), 2.99–2.81 (m, 2H), 2.80–2.71 (m, 2H), 2.70–2.58 (m, 2H), 1.66–1.57 (m, 2H), 1.36–1.29 (m, 4H). ^{13}C NMR (DMSO-D_6, 100 MHz): δ 173.2, 171.7, 162.1, 157.0, 155.6, 149.2, 134.7, 130.0, 127.2, 126.4, 126.2, 126.1, 121.2, 120.9, 118.3, 110.9, 56.1, 52.4, 52.2, 31.5, 31.3, 30.0, 29.7, 23.3.

*4.2.15. Methyl 6-(3-(3-fluorophenyl)ureido)-2-(3-(4-oxo-3,4-dihydroquinazolin-2-yl) propanamido) hexanoate (**13c**)*

^{1}H NMR (DMSO-D_6, 400 MHz): δ 12.10 (s, 1H), 8.58 (s, 1H), 8.30–8.29 (d, 1H, *J* = 7.2 Hz), 8.05–8.04 (d, 1H, *J* = 7.2 Hz), 7.76–7.72 (t, 1H, *J* = 7.2 Hz), 7.54–7.52 (d, 1H, *J* = 8.4 Hz), 7.42–7.39 (m, 2H), 7.21–7.15 (m, 1H), 6.98–6.96 (d, 1H, *J* = 8.0 Hz), 6.65–6.61 (t, 1H, *J* = 7.2 Hz), 6.14 (s, 1H), 4.20–4.19 (d, 1H, *J* = 5.2 Hz), 3.56 (s, 3H), 3.01–3.00 (d, 2H, *J* = 6.0 Hz), 2.81–2.80 (d, 2H, *J* = 7.2 Hz), 2.68–2.60 (m, 2H), 1.66–1.60 (m, 2H), 1.37–1.21 (m, 4H). ^{13}C NMR (DMSO-D_6, 100 MHz): δ 172.8, 171.3, 163.7, 156.6, 155.0, 148.8, 134.3, 130.2, 130.2, 126.8, 126.0, 125.7, 120.9, 113.3, 107.3, 107.1, 104.4, 104.1, 52.0, 51.8, 31.1, 30.7, 29.6, 29.3, 22.8.

*4.2.16. Methyl 6-(3-(4-chlorophenyl)ureido)-2-(4-(4-oxo-3,4-dihydroquinazolin-2-yl) butanamido) hexanoate (**14a**)*

^{1}H NMR (DMSO-D_6, 400 MHz): δ 12.10 (s, 1H), 8.29–8.28 (d, 1H, *J* = 6.8 Hz), 8.05–8.03 (d, 1H, *J* = 8.0 Hz), 7.75–7.72 (t, 1H, *J* = 7.4 Hz), 7.54–7.52 (d, 1H, *J* = 8.0 Hz), 7.44–7.40 (t, 1H, *J* = 7.4 Hz), 7.33–7.31 (d, 2H, *J* = 8.0 Hz), 7.22–7.20 (d, 2H, *J* = 8.0 Hz), 6.28 (br, 1H), 5.90 (br,1H), 4.18 (br, 1H), 3.56 (s, 3H), 2.94–2.92 (d, 2H, *J* = 5.2 Hz), 2.81–2.80 (d, 2H, *J* = 6.8 Hz), 2.71–2.60 (m, 2H), 1.97–1.93 (m, 2H), 1.63–1.55 (m, 2H), 1.30–1.21 (m, 4H). ^{13}C NMR (DMSO-D_6, 100 MHz): δ 173.3, 171.5, 162.2, 155.8, 151.2, 149.0, 134.3, 129.9, 127.4, 126.4, 126.3, 126.2, 121.3, 120.7, 118.3, 110.8, 56.1, 52.3, 52.2, 34.4, 34.1, 31.0, 29.7, 23.3, 23.0.

*4.2.17. Methyl 6-(3-(4-methoxyphenyl)ureido)-2-(4-(4-oxo-3,4-dihydroquinazolin-2-yl) butanamido) hexanoate (**14b**)*

^{1}H NMR (DMSO-D_6, 400 MHz): δ 12.10 (s, 1H), 8.17–8.15 (d, 1H, *J* = 7.2 Hz), 8.06–8.03 (m, 2H), 7.79 (s, 1H), 7.76–7.72 (t, 1H, *J* = 7.2 Hz), 7.58–7.56 (d, 1H, *J* = 8.4 Hz), 7.45–7.41 (t, 1H, *J* = 7.2 Hz), 6.92–6.90 (d, 1H, *J* = 7.6 Hz), 6.84–6.77 (m, 3H), 4.19–4.15 (m, 1H), 3.79 (s, 3H), 3.59 (s, 3H), 3.03–3.02 (m, 2H), 2.60–2.56 (t, 2H, *J* = 7.6 Hz), 2.21–2.17 (t, 2H, *J* = 7.6 Hz), 1.95–1.91 (m, 2H), 1.68–1.53 (m, 2H), 1.38–1.30 (m, 4H). ^{13}C NMR (DMSO-D_6, 100 MHz): δ 173.3, 172.4, 162.2, 157.4, 155.6, 149.3, 134.7, 130.0, 127.3, 126.4, 126.1, 121.3, 120.9, 118.3, 110.9, 56.1, 52.4, 52.2, 34.5, 34.2, 31.0, 29.8, 23.3, 23.1.

*4.2.18. Methyl 6-(3-(3-fluorophenyl)ureido)-2-(4-(4-oxo-3,4-dihydroquinazolin-2-yl) butanamido) hexanoate (**14c**)*

^{1}H NMR (DMSO-D_6, 400 MHz): δ 12.10 (s, 1H), 8.58 (s, 1H), 8.17–8.15 (d, 1H, *J* = 6.8 Hz), 8.06–8.04 (d, 1H, *J* = 7.6 Hz), 7.76–7.72 (t, 1H, *J* = 8.1 Hz), 7.58–7.56 (d, 1H, *J* = 8.0 Hz), 7.45–7.41 (m, 2H), 7.21–7.16 (q, 1H, *J* = 7.8 Hz), 6.98–6.96 (d, 1H, *J* = 8.0 Hz), 6.66–6.62 (t, 1H, *J* = 8.4 Hz), 6.17–6.14 (t, 1H, *J* = 5.4 Hz), 4.21–4.15 (m, 1H), 3.59 (s, 3H), 3.06–3.01 (m, 2H), 2.60–2.56 (t, 2H, *J* = 7.6 Hz), 2.21–2.17 (t, 2H, *J* = 7.6 Hz), 1.95–1.89 (m, 2H), 1.69–1.54 (m, 2H), 1.40–1.34 (m, 2H), 1.29–1.27 (m, 2H). ^{13}C NMR (DMSO-D_6, 100 MHz): δ 172.9, 171.3, 163.8, 156.7, 149.9, 148.7, 134.3, 130.1, 130.1, 126.9, 126.0, 125.8, 120.9, 113.4, 107.4, 107.2, 104.4, 104.2, 52.0, 51.9, 34.4, 34.1, 29.9, 29.8, 23.2, 23.0.

*4.2.19. 6-(3-(4-Chlorophenyl)ureido)-2-(3-(4-oxo-3,4-dihydroquinazolin-2-yl)propanamido) hexanoic acid (**15a**)*

^{1}H NMR (DMSO-D_6, 400 MHz): δ 12.10 (s, 1H), 11.90 (s, 1H), 8.29–8.28 (d, 1H, *J* = 6.8 Hz), 8.05–8.03 (d, 1H, *J* = 8.0 Hz), 7.75–7.72 (t, 1H, *J* = 7.4 Hz), 7.54–7.52 (d, 1H, *J* = 8.0 Hz), 7.44–7.40

(t, 1H, J = 7.4 Hz), 7.33–7.31 (d, 2H, J = 8.0 Hz), 7.22–7.20 (d, 2H, J = 8.0 Hz), 6.28 (br, 1H), 5.90 (br,1H), 4.18 (br, 1H), 2.94–2.92 (d, 2H, J = 5.2 Hz), 2.81–2.80 (d, 2H, J = 6.8 Hz), 2.71–2.60 (m, 2H), 1.63–1.55 (m, 2H), 1.30–1.21 (m, 4H). ^{13}C NMR (DMSO-D_6, 100 MHz): δ 175.3, 171.8, 162.2, 160.1, 158.4, 149.2, 134.5, 131.3, 129.1, 128.5, 128.4, 127.1, 126.3, 126.0, 121.2, 52.3, 42.8, 31.2, 31.2, 30.2, 30.1, 23.2.

*4.2.20. 6-(3-(4-Methoxyphenyl)ureido)-2-(3-(4-oxo-3,4-dihydroquinazolin-2-yl)propanamido) hexanoic acid (**15b**)*

^{1}H NMR (DMSO-D_6, 400 MHz): δ 12.10 (s, 1H), 12.04 (s, 1H), 8.30–8.28 (d, 1H, J = 6.4 Hz), 8.05–8.03 (d, 2H, J = 5.7 Hz), 7.79 (s, 1H), 7.76–7.72 (t, 1H, J = 7.4 Hz), 7.54–7.52 (d, 1H, J = 8.0 Hz), 7.44–7.40 (t, 1H, J = 7.2 Hz), 6.91–6.89 (d, 1H, J = 7.2 Hz), 6.79 (s, 3H), 4.21–4.19 (d, 1H, J = 5.2 Hz), 3.79 (s, 3H), 2.99–2.81 (m, 2H), 2.80–2.71 (m, 2H), 2.70–2.58 (m, 2H), 1.66–1.57 (m, 2H), 1.36–1.29 (m, 4H). ^{13}C NMR (DMSO-D_6, 100 MHz): δ 175.0, 171.7, 162.0, 157.1, 155.5, 149.0, 134.8, 129.2, 127.1, 126.5, 126.3, 126.2, 121.0, 120.7, 118.4, 110.7, 56.2, 52.3, 31.4, 31.2, 29.9, 29.7, 23.3.

*4.2.21. 6-(3-(3-Fluorophenyl)ureido)-2-(3-(4-oxo-3,4-dihydroquinazolin-2-yl)propanamido) hexanoic acid (**15c**)*

^{1}H NMR (DMSO-D_6, 400 MHz): δ 12.10 (s, 1H), 12.00 (s, 1H), 8.58 (s, 1H), 8.30–8.29 (d, 1H, J = 7.2 Hz), 8.05–8.04 (d, 1H, J = 7.2 Hz), 7.76–7.72 (t, 1H, J = 7.2 Hz), 7.54–7.52 (d, 1H, J = 8.4 Hz), 7.42–7.39 (m, 2H), 7.21–7.15 (m, 1H), 6.98–6.96 (d, 1H, J = 8.0 Hz), 6.65–6.61 (t, 1H, J = 7.2 Hz), 6.14 (s, 1H), 4.20–4.19 (d, 1H, J = 5.2 Hz), 3.01–3.00 (d, 2H, J = 6.0 Hz), 2.81–2.80 (d, 2H, J = 7.2 Hz), 2.68–2.60 (m, 2H), 1.66–1.60 (m, 2H), 1.37–1.21 (m, 4H). ^{13}C NMR (DMSO-D_6, 100 MHz): δ 174.9, 171.2, 163.9, 156.7, 149.9, 148.8, 134.2, 130.2, 130.2, 126.7, 126.0, 125.5, 120.8, 113.1, 107.4, 107.2, 104.4, 104.2, 52.0, 31.0, 30.6, 29.5, 29.2, 22.8.

*4.2.22. 6-(3-(4-Chlorophenyl)ureido)-2-(4-(4-oxo-3,4-dihydroquinazolin-2-yl)butanamido) hexanoic acid (**16a**)*

^{1}H NMR (DMSO-D_6, 400 MHz): δ 12.10 (s, 1H), 11.90 (s, 1H), 8.29–8.28 (d, 1H, J = 6.8 Hz), 8.05–8.03 (d, 1H, J = 8.0 Hz), 7.75–7.72 (t, 1H, J = 7.4 Hz), 7.54–7.52 (d, 1H, J = 8.0 Hz), 7.44–7.40 (t, 1H, J = 7.4 Hz), 7.33–7.31 (d, 2H, J = 8.0 Hz), 7.22–7.20 (d, 2H, J = 8.0 Hz), 6.28 (br, 1H), 5.90 (br,1H), 4.18 (br, 1H), 2.94–2.92 (d, 2H, J = 5.2 Hz), 2.81–2.80 (d, 2H, J = 6.8 Hz), 2.71–2.60 (m, 2H), 1.97–1.93 (m, 2H), 1.63–1.55 (m, 2H), 1.30–1.21 (m, 4H). ^{13}C NMR (DMSO-D_6, 100 MHz): δ 175.2, 171.3, 162.0, 155.7, 151.1, 149.1, 134.2, 129.8, 127.3, 126.4, 126.2, 126.1, 121.2, 120.6, 118.2, 110.7, 56.0, 52.3, 34.3, 34.1, 31.1, 29.8, 23.2, 23.1.

*4.2.23. 6-(3-(4-Methoxyphenyl)ureido)-2-(4-(4-oxo-3,4-dihydroquinazolin-2-yl)butanamido) hexanoic acid (**16b**)*

^{1}H NMR (DMSO-D_6, 400 MHz): δ 12.10 (s, 1H), 12.06 (s, 1H), 8.17–8.15 (d, 1H, J = 7.2 Hz), 8.06–8.03 (m, 2H), 7.79 (s, 1H), 7.76–7.72 (t, 1H, J = 7.2 Hz), 7.58–7.56 (d, 1H, J = 8.4 Hz), 7.45–7.41 (t, 1H, J = 7.2 Hz), 6.92–6.90 (d, 1H, J = 7.6 Hz), 6.84–6.77 (m, 3H), 4.19–4.15 (m, 1H), 3.79 (s, 3H), 3.03–3.02 (m, 2H), 2.60–2.56 (t, 2H, J = 7.6 Hz), 2.21–2.17 (t, 2H, J = 7.6 Hz), 1.95–1.91 (m, 2H), 1.68–1.53 (m, 2H), 1.38–1.30 (m, 4H). ^{13}C NMR (DMSO-D_6, 100 MHz): δ 174.8, 172.3, 162.3, 157.3, 155.5, 149.2, 134.6, 129.9, 127.3, 126.4, 126.0, 121.3, 121.2, 120.8, 118.2, 110.8, 56.1, 52.3, 34.4, 34.1, 31.0, 29.7, 23.2, 23.0.

*4.2.24. 6-(3-(3-Fluorophenyl)ureido)-2-(4-(4-oxo-3,4-dihydroquinazolin-2-yl)butanamido) hexanoic acid (**16c**)*

^{1}H NMR (DMSO-D_6, 400 MHz): δ 12.10 (s, 1H), 11.80 (s, 1H), 8.58 (s, 1H), 8.17–8.15 (d, 1H, J = 6.8 Hz), 8.06–8.04 (d, 1H, J = 7.6 Hz), 7.76–7.72 (t, 1H, J = 8.1 Hz), 7.58–7.56 (d, 1H, J = 8.0 Hz), 7.45–7.41 (m, 2H), 7.21–7.16 (q, 1H, J = 7.8 Hz), 6.98–6.96 (d, 1H, J = 8.0 Hz), 6.66–6.62 (t, 1H, J = 8.4 Hz), 6.17–6.14 (t, 1H, J = 5.4 Hz), 4.21–4.15 (m, 1H), 3.06–3.01 (m, 2H), 2.60–2.56 (t, 2H, J = 7.6 Hz), 2.21–2.17 (t, 2H, J = 7.6 Hz), 1.95–1.89 (m, 2H), 1.69–1.54 (m, 2H), 1.40–1.34 (m, 2H), 1.29–1.27 (m, 2H). ^{13}C NMR (DMSO-D_6, 100 MHz): δ 175.3, 171.2, 163.7, 156.6, 150.0, 148.7, 134.2, 130.2, 130.2, 126.8, 126.1, 125.7, 120.8, 113.3, 107.5, 107.1, 104.3, 104.1, 52.0, 34.3, 34.0, 29.9, 29.7, 23.1, 22.9.

*4.2.25. Methyl 6-(3-(4-fluoro-2-methylphenyl)thioureido)-2-(3-(4-oxo-3,4-dihydroquinazolin-2-yl)propanamido) hexanoate (**18a**)*

^{1}H NMR (DMSO-D_6, 400 MHz): δ 12.11 (s, 1H), 8.90 (s, 1H), 8.17–8.15 (d, 1H, J = 7.2 Hz), 8.06–8.04 (d, 1H, J = 7.6 Hz), 7.76–7.72 (t, 1H, J = 7.6 Hz), 7.58–7.56 (d, 1H, J = 8.0 Hz), 7.45–7.41 (t, 1H, J = 7.6 Hz), 7.41–7.36 (m, 1H), 7.16–7.12 (m, 1H), 7.07–7.04 (m, 1H), 6.98–6.94 (t, 1H, J = 8.4 Hz), 4.17–4.16 (m, 1H), 3.59 (s, 3H), 3.41–3.36 (m, 2H), 2.61–2.57 (t, 2H, J = 7.2 Hz), 2.21–2.18 (t, 2H, J = 7.6 Hz), 2.12 (s, 3H), 1.64–1.61 (m, 1H), 1.58–1.55 (m, 1H), 1.48–1.45 (m, 2H), 1.27–1.21 (m, 2H). ^{13}C NMR (DMSO-D_6, 100 MHz): δ 180.3, 173.1, 171.9, 162.0, 159.9, 157.2, 149.3, 141.7, 134.7, 130.4, 127.2, 126.4, 126.1, 121.2, 120.8, 118.3, 52.3, 52.1, 44.1, 31.4, 31.3, 29.9, 28.4, 23.3, 17.8.

*4.2.26. Methyl 2-(3-(4-oxo-3,4-dihydroquinazolin-2-yl) propanamido)-6-(3-o-tolylthioureido) hexanoate (**18b**)*

^{1}H NMR (DMSO-D_6, 400 MHz): δ 12.11 (s, 1H), 8.94 (s, 1H), 8.17–8.15 (d, 1H, J = 7.2 Hz), 8.06–8.04 (d, 1H, J = 7.6 Hz), 7.76–7.72 (t, 1H, J = 8.2 Hz), 7.58–7.56 (d, 1H, J = 8.0 Hz), 7.45–7.41 (t, 1H, J = 7.2 Hz), 7.28–7.28 (m, 1H), 7.21–7.12 (m, 4H), 4.19–4.14 (m, 1H), 3.59 (s, 3H), 3.38–3.32 (m, 2H), 2.61–2.57 (t, 2H, J = 7.2 Hz), 2.21–2.18 (t, 2H, J = 6.8 Hz), 2.13 (s, 3H), 1.68–1.53 (m, 2H), 1.51–1.44 (m, 2H), 1.27–1.21 (m, 2H). ^{13}C NMR (DMSO-D_6, 100 MHz): δ 180.1, 172.9, 171.8, 161.9, 160.0, 157.3, 149.4, 141.6, 134.8, 130.3, 127.3, 126.4, 126.0, 121.2, 120.9, 118.4, 52.3, 52.0, 44.0, 31.5, 31.3, 30.0, 28.4, 23.4, 18.0.

*4.2.27. Methyl 6-(3-(3-fluorophenyl)thioureido)-2-(3-(4-oxo-3,4-dihydroquinazolin-2-yl) propanamido) hexanoate (**18c**)*

^{1}H NMR (DMSO-D_6, 400 MHz): δ 12.11 (s, 1H), 9.54 (s, 1H), 8.31–8.30 (d, 1H, J = 7.2 Hz), 8.05–8.04 (d, 1H, J = 7.2 Hz), 7.85 (br, 1H), 7.76–7.72 (t, 1H, J = 7.2 Hz), 7.55–7.47 (m, 2H), 7.44–7.40 (t, 1H, J = 7.2 Hz), 7.32–7.26 (q, 1H, J = 7.6 Hz), 7.13–7.11 (d, 1H, J = 7.6 Hz), 6.87–6.84 (t, 1H, J = 8.0 Hz), 4.22–4.20 (m, 1H), 3.57 (s, 3H), 3.40 (br, 2H), 2.82–2.80 (m, 2H), 2.69–2.62 (m, 2H), 1.67–1.58 (m, 2H), 1.51–1.47 (m, 2H), 1.31–1.29 (m, 2H). ^{13}C NMR (DMSO-D_6, 100 MHz): δ 180.5, 173.2, 171.7, 162.1, 160.0, 157.3, 149.2, 141.8, 134.7, 130.5, 127.2, 126.4, 126.2, 121.3, 120.9, 118.4, 52.4, 52.2, 44.0, 31.5, 31.2, 30.0, 28.4, 23.3.

*4.2.28. Methyl 6-(3-(4-fluoro-2-methylphenyl)thioureido)-2-(4-(4-oxo-3,4-dihydroquinazolin-2-yl)butanamido) hexanoate (**19a**)*

^{1}H NMR (DMSO-D_6, 400 MHz): δ 12.11 (s, 1H), 8.90 (s, 1H), 8.17–8.15 (d, 1H, J = 7.2 Hz), 8.06–8.04 (d, 1H, J = 7.6 Hz), 7.76–7.72 (t, 1H, J = 7.6 Hz), 7.58–7.56 (d, 1H, J = 8.0 Hz), 7.45–7.41 (t, 1H, J = 7.6 Hz), 7.41–7.36 (m, 1H), 7.16–7.12 (m, 1H), 7.07–7.04 (m, 1H), 6.98–6.94 (t, 1H, J = 8.4 Hz), 4.17–4.16 (m, 1H), 3.59 (s, 3H), 3.41–3.36 (m, 2H), 2.61–2.57 (t, 2H, J = 7.2 Hz), 2.21–2.18 (t, 2H, J = 7.6 Hz), 2.12 (s, 3H), 1.97–1.91 (m, 2H), 1.64–1.61 (m, 1H), 1.58–1.55 (m, 1H), 1.48–1.45 (m, 2H), 1.27–1.21 (m, 2H). ^{13}C NMR (DMSO-D_6, 100 MHz): δ 180.4, 173.3, 172.4, 162.2, 159.6, 157.4, 149.3, 141.8, 134.7, 130.3, 127.3, 126.4, 126.1, 121.3, 120.8, 118.8, 110.9, 52.4, 52.2, 43.9, 34.5, 34.2, 31.1, 28.7, 23.3, 23.1, 18.1.

*4.2.29. Methyl 2-(4-(4-oxo-3,4-dihydroquinazolin-2-yl) butanamido)-6-(3-o-tolylthioureido) hexanoate (**19b**)*

^{1}H NMR (DMSO-D_6, 400 MHz): δ 12.11 (s, 1H), 8.94 (s, 1H), 8.17–8.15 (d, 1H, J = 7.2 Hz), 8.06–8.04 (d, 1H, J = 7.6 Hz), 7.76–7.72

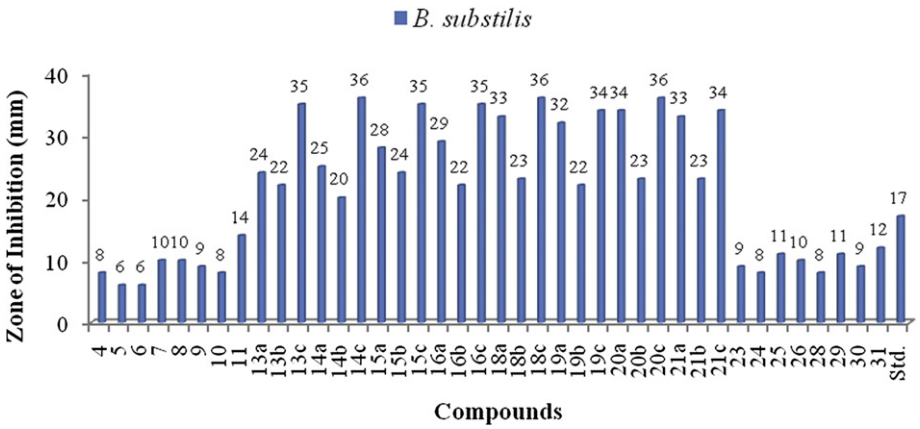


Fig. 1. Diagramatic representation of antibacterial activity of the compounds against *B. substilis*.

(t, 1H, J = 8.2 Hz), 7.58–7.56 (d, 1H, J = 8.0 Hz), 7.45–7.41 (t, 1H, J = 7.2 Hz), 7.28–7.28 (m, 1H), 7.21–7.12 (m, 4H), 4.19–4.14 (m, 1H), 3.59 (s, 3H), 3.38–3.32 (m, 2H), 2.61–2.57 (t, 2H, J = 7.2 Hz), 2.21–2.18 (t, 2H, J = 6.8 Hz), 2.13 (s, 3H), 1.97–1.90 (m, 2H), 1.68–1.53 (m, 2H), 1.51–1.44 (m, 2H), 1.27–1.21 (m, 2H). ^{13}C NMR (DMSO-D_6, 100 MHz): δ 180.3, 173.2, 172.4, 162.1, 159.6, 157.0, 149.2, 141.7, 134.6, 130.0, 127.5, 126.3, 126.0, 121.1, 120.9, 118.5, 110.7, 52.5, 52.2, 43.9, 34.3, 34.2, 31.1, 28.6, 23.2, 23.0, 17.7.

*4.2.30. Methyl 6-(3-(3-fluorophenyl)thioureido)-2-(4-(4-oxo-3,4-dihydroquinazolin-2-yl) butanamido) hexanoate (**19c**)*

^{1}H NMR (DMSO-D_6, 400 MHz): δ 12.10 (s, 1H), 9.54 (s, 1H), 8.18–8.17 (d, 1H, J = 6.8 Hz), 8.06–8.04 (d, 1H, J = 7.2 Hz), 7.86 (br, 1H), 7.76–7.73 (t, 1H, J = 7.2 Hz), 7.58–7.56 (d, 1H, J = 8.4 Hz), 7.50–7.41 (m, 2H), 7.32–7.26 (q, 1H, J = 8.2 Hz), 7.12–7.10 (d, 1H, J = 7.6 Hz), 6.87–6.84 (t, 1H, J = 7.2 Hz), 4.22–4.16 (m, 1H), 3.60 (s, 3H), 3.41 (br, 2H), 2.61–2.57 (t, 2H, J = 7.2 Hz), 2.22–2.18 (t, 2H, J = 7.6 Hz), 1.97–1.90 (m, 2H), 1.68–1.54 (m, 2H), 1.52–1.47 (m, 2H), 1.31–1.29 (m, 2H). ^{13}C NMR (DMSO-D_6, 100 MHz): δ 180.0, 173.3, 172.3, 162.0, 159.7, 157.2, 149.2, 141.6, 139.5, 129.9, 127.4, 126.3, 121.2, 120.7, 118.2, 110.9, 52.4, 52.3, 43.8, 34.2, 34.1, 31.0, 28.5, 23.1, 22.9.

*4.2.31. 6-(3-(4-Fluoro-2-methylphenyl)thioureido)-2-(3-(4-oxo-3,4-dihydroquinazolin-2-yl) propanamido)hexanoic acid (**20a**)*

^{1}H NMR (DMSO-D_6, 400 MHz): δ 12.11 (s, 1H), 11.91 (s, 1H), 8.90 (s, 1H), 8.17–8.15 (d, 1H, J = 7.2 Hz), 8.06–8.04 (d, 1H, J = 7.6 Hz), 7.76–7.72 (t, 1H, J = 7.6 Hz), 7.58–7.56 (d, 1H, J = 8.0 Hz), 7.45–7.41 (t, 1H, J = 7.6 Hz), 7.41–7.36 (m, 1H), 7.16–7.12 (m, 1H), 7.07–7.04 (m, 1H), 6.98–6.94 (t, 1H, J = 8.4 Hz), 4.17–4.16 (m, 1H), 3.41–3.36 (m, 2H), 2.61–2.57 (t, 2H, J = 7.2 Hz), 2.21–2.18 (t, 2H, J = 7.6 Hz), 2.12 (s, 3H), 1.64–1.61 (m, 1H), 1.58–1.55 (m, 1H), 1.48–1.45 (m, 2H), 1.27–1.21 (m, 2H). ^{13}C NMR (DMSO-D_6, 100 MHz): δ 180.3, 175.2, 171.8, 162.0, 159.8, 157.1, 149.4, 141.8, 134.6, 130.5, 127.1, 126.4, 126.1, 121.1, 120.7, 118.2, 52.4, 44.0, 31.3, 31.1, 30.0, 28.3, 23.2, 17.9.

*4.2.32. 2-(3-(4-Oxo-3,4-dihydroquinazolin-2-yl)propanamido)-6-(3-o-tolylthioureido)hexanoic acid (**20b**)*

^{1}H NMR (DMSO-D_6, 400 MHz): δ 12.11 (s, 1H), 12.01 (s, 1H), 8.94 (s, 1H), 8.17–8.15 (d, 1H, J = 7.2 Hz), 8.06–8.04 (d, 1H, J = 7.6 Hz), 7.76–7.72 (t, 1H, J = 8.2 Hz), 7.58–7.56 (d, 1H, J = 8.0 Hz), 7.45–7.41 (t, 1H, J = 7.2 Hz), 7.28–7.28 (m, 1H), 7.21–7.12 (m, 4H), 4.19–4.14 (m, 1H), 3.38–3.32 (m, 2H), 2.61–2.57 (t, 2H, J = 7.2 Hz), 2.21–2.18 (t, 2H, J = 6.8 Hz), 2.13 (s, 3H), 1.68–1.53 (m, 2H), 1.51–1.44 (m, 2H), 1.27–1.21 (m, 2H). ^{13}C NMR (DMSO-D_6, 100 MHz): δ 180.1, 174.8, 171.7, 161.8, 159.9, 157.4, 149.3, 141.5, 134.9, 130.2, 127.2, 126.3, 126.0, 121.1, 120.8, 118.5, 52.1, 44.3, 31.4, 31.0, 30.0, 28.3, 23.3, 17.9.

*4.2.33. 6-(3-(3-Fluorophenyl)thioureido)-2-(3-(4-oxo-3,4-dihydroquinazolin-2-yl)propanamido) hexanoic acid (**20c**)*

^{1}H NMR (DMSO-D_6, 400 MHz): δ 12.11 (s, 1H), 12.01 (s, 1H), 9.54 (s, 1H), 8.31–8.30 (d, 1H, J = 7.2 Hz), 8.05–8.04 (d, 1H, J = 7.2 Hz), 7.85 (br, 1H), 7.76–7.72 (t, 1H, J = 7.2 Hz), 7.55–7.47 (m, 2H), 7.44–7.40 (t, 1H, J = 7.2 Hz), 7.32–7.26 (q, 1H, J = 7.6 Hz), 7.13–7.11 (d, 1H, J = 7.6 Hz), 6.87–6.84 (t, 1H, J = 8.0 Hz), 4.22–4.20 (m, 1H), 3.40 (br, 2H), 2.82–2.80 (m, 2H), 2.69–2.62 (m, 2H), 1.67–1.58 (m, 2H), 1.51–1.47 (m, 2H), 1.31–1.29 (m, 2H). ^{13}C NMR (DMSO-D_6,

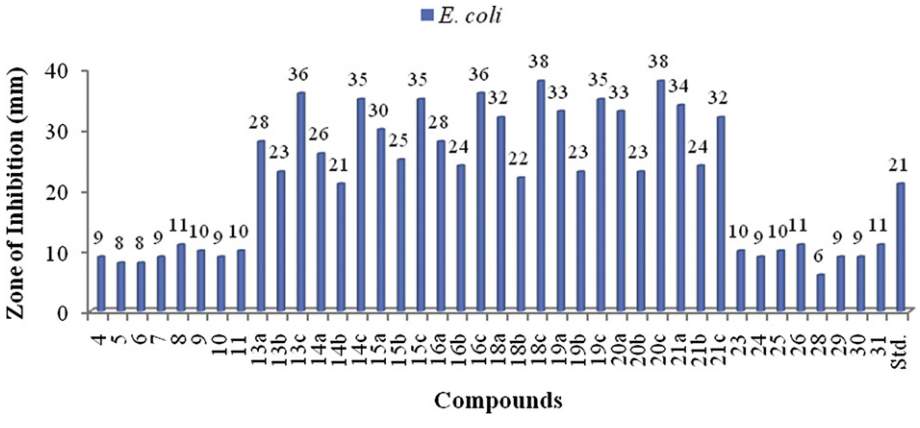


Fig. 2. Diagramatic representation of antibacterial activity of the compounds against *E. coli*.

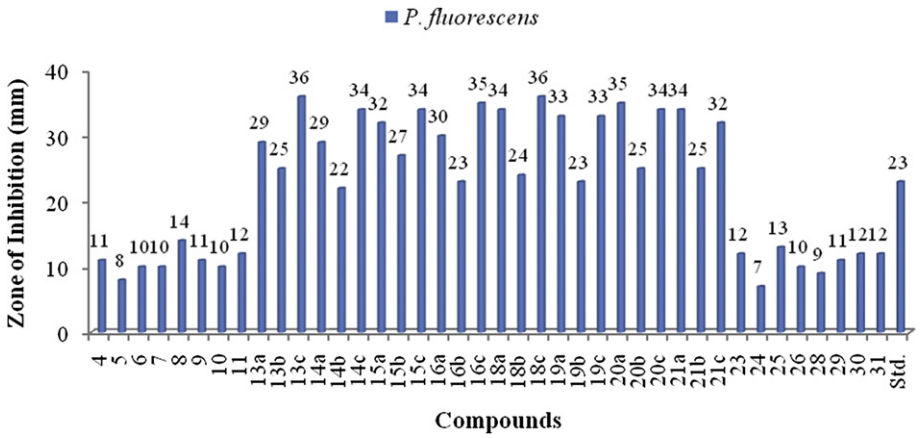


Fig. 3. Diagramatic representation of antibacterial activity of the compounds against *P. fluorescens*.

100 MHz): δ 180.5, 173.2, 171.6, 162.0, 159.9, 157.3, 149.1, 141.6, 134.8, 130.6, 127.3, 126.4, 126.1, 121.3, 120.8, 118.6, 52.3, 44.1, 31.6, 31.1, 30.2, 28.3, 23.2.

*4.2.34. 6-(3-(4-Fluoro-2-methylphenyl)thioureido)-2-(4-(4-oxo-3,4-dihydroquinazolin-2-yl) butanamido)hexanoic acid (**21a**)*

^{1}H NMR (DMSO-D$_6$, 400 MHz): δ 12.11 (s, 1H), 12.01 (s, 1H), 8.90 (s, 1H), 8.17–8.15 (d, 1H, *J* = 7.2 Hz), 8.06–8.04 (d, 1H, *J* = 7.6 Hz), 7.76–7.72 (t, 1H, *J* = 7.6 Hz), 7.58–7.56 (d, 1H, *J* = 8.0 Hz), 7.45–7.41 (t, 1H, *J* = 7.6 Hz), 7.41–7.36 (m, 1H), 7.16–7.12 (m, 1H), 7.07–7.04 (m, 1H), 6.98–6.94 (t, 1H, *J* = 8.4 Hz), 4.17–4.16 (m, 1H), 3.41–3.36 (m, 2H), 2.61–2.57 (t, 2H, *J* = 7.2 Hz), 2.21–2.18 (t, 2H, *J* = 7.6 Hz), 2.12 (s, 3H), 1.97–1.91 (m, 2H), 1.64–1.61 (m, 1H), 1.58–1.55 (m, 1H), 1.48–1.45 (m, 2H), 1.27–1.21 (m, 2H). ^{13}C NMR (DMSO-D$_6$, 100 MHz): δ 180.6, 175.4, 172.3, 162.0, 159.8, 157.3, 149.2, 141.7, 134.5, 130.2, 127.2, 126.1, 126.0, 121.5, 120.9, 118.5, 110.2, 52.3, 43.6, 34.3, 34.0, 31.6, 28.5, 23.2, 23.0, 17.8.

*4.2.35. 2-(4-(4-Oxo-3,4-dihydroquinazolin-2-yl)butanamido)-6-(3-o-tolylthioureido)hexanoic acid (**21b**)*

^{1}H NMR (DMSO-D$_6$, 400 MHz): δ 12.11 (s, 1H), 11.81 (s, 1H), 8.94 (s, 1H), 8.17–8.15 (d, 1H, *J* = 7.2 Hz), 8.06–8.04 (d, 1H, *J* = 7.6 Hz), 7.76–7.72 (t, 1H, *J* = 8.2 Hz), 7.58–7.56 (d, 1H, *J* = 8.0 Hz), 7.45–7.41 (t, 1H, *J* = 7.2 Hz), 7.28–7.28 (m, 1H), 7.21–7.12 (m, 4H), 4.19–4.14 (m, 1H), 3.38–3.32 (m, 2H), 2.61–2.57 (t, 2H, *J* = 7.2 Hz), 2.21–2.18 (t, 2H, *J* = 6.8 Hz), 2.13 (s, 3H), 1.97–1.90 (m, 2H), 1.68–1.53 (m, 2H), 1.51–1.44 (m, 2H), 1.27–1.21 (m, 2H). ^{13}C NMR (DMSO-D$_6$, 100 MHz): δ 180.2, 175.1, 172.4, 162.1, 159.8, 157.0, 149.1, 141.6, 134.5, 129.9, 127.4, 126.4, 126.1, 121.0, 120.8, 118.4, 110.6, 52.4, 44.2, 34.2, 34.1, 31.3, 28.9, 23.1, 22.9, 18.0.

*4.2.36. 6-(3-(3-Fluorophenyl)thioureido)-2-(4-(4-oxo-3,4-dihydroquinazolin-2-yl)butanamido) hexanoic acid (**21c**)*

^{1}H NMR (DMSO-D$_6$, 400 MHz): δ 12.10 (s, 1H), 12.00 (s, 1H), 9.54 (s, 1H), 8.18–8.17 (d, 1H, *J* = 6.8 Hz), 8.06–8.04 (d, 1H, *J* = 7.2 Hz), 7.86 (br, 1H), 7.76–7.73 (t, 1H, *J* = 7.2 Hz), 7.58–7.56 (d, 1H, *J* = 8.4 Hz), 7.50–7.41 (m, 2H), 7.32–7.26 (q, 1H, *J* = 8.2 Hz), 7.12–7.10 (d, 1H, *J* = 7.6 Hz), 6.87–6.84 (t, 1H, *J* = 7.2 Hz), 4.22–4.16 (m, 1H), 3.41 (br, 2H), 2.61–2.57 (t, 2H, *J* = 7.2 Hz), 2.22–2.18 (t, 2H, *J* = 7.6 Hz), 1.97–1.90 (m, 2H), 1.68–1.54 (m, 2H), 1.52–1.47 (m, 2H), 1.31–1.29 (m, 2H). ^{13}C NMR (DMSO-D$_6$, 100 MHz): δ 180.1, 175.5, 172.2, 161.9, 159.3, 157.0, 149.1, 141.5, 139.7, 130.0, 127.3, 126.2, 126.2, 121.4, 120.6, 118.4, 110.7, 52.3, 43.5, 34.1, 34.0, 31.3, 28.1, 23.0, 22.6.

*4.2.37. Methyl 6-acetamido-2-(3-(4-oxo-3,4-dihydroquinazolin-2-yl)propanamido)hexanoate (**23**)*

^{1}H NMR (DMSO-D$_6$, 400 MHz): δ 12.11 (s, 1H), 9.34 (s, 1H), 8.30–8.28 (d, 1H, *J* = 7.2 Hz), 8.06–8.04 (d, 1H, *J* = 6.8 Hz), 7.76–7.72 (t, 1H, *J* = 7.8 Hz), 7.54–7.52 (d, 1H, *J* = 8.0 Hz), 7.44–7.40 (t, 1H, *J* = 7.6 Hz), 4.20–4.16 (m, 1H), 3.57 (s, 3H), 3.13–3.08 (q, 2H, *J* = 6.2 Hz), 2.83–2.80 (t, 2H, *J* = 6.8 Hz), 2.68–2.62 (q, 2H, *J* = 8.0 Hz), 2.06 (s, 3H), 1.67–1.54 (m, 2H), 1.31–1.21 (m, 4H). ^{13}C NMR (DMSO-D$_6$, 100 MHz): δ 173.3, 171.6, 171.2, 162.4, 158.4, 149.1, 134.5, 128.5, 127.4, 126.4, 126.2, 52.3, 52.0, 40.4, 31.3, 31.2, 30.2, 30.0, 23.9, 23.2.

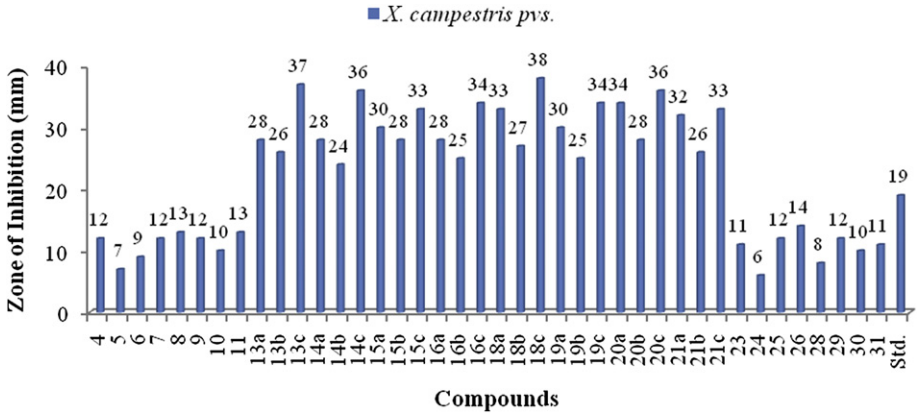


Fig. 4. Diagramatic representation of antibacterial activity of the compounds against *X. campestris pvs.*

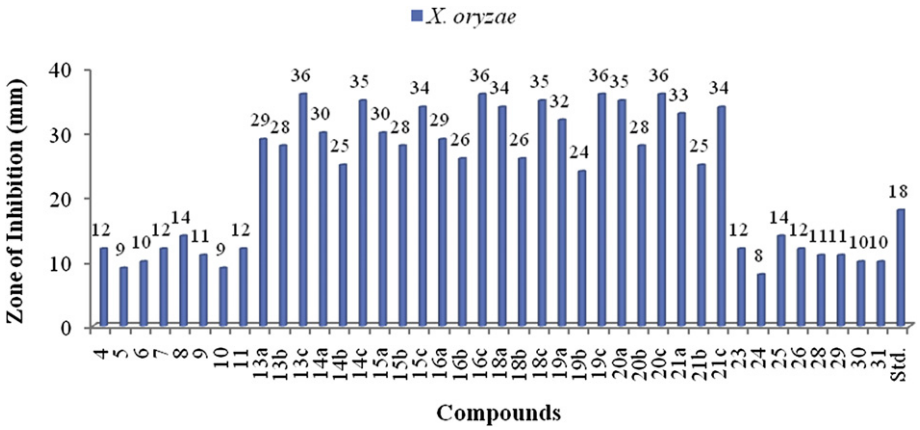


Fig. 5. Diagramatic representation of antibacterial activity of the compounds against *X. oryzae*.

*4.2.38. Methyl 6-acetamido-2-(4-(4-oxo-3,4-dihydroquinazolin-2-yl)butanamido)hexanoate (**24**)*

^{1}H NMR (DMSO-D$_6$, 400 MHz): δ 12.10 (s, 1H), 9.34 (s, 1H), 8.17–8.14 (t, 1H, J = 7.8 Hz), 8.06–8.04 (d, 1H, J = 7.6 Hz), 7.76–7.73 (t, 1H, J = 7.0 Hz), 7.58–7.56 (d, 1H, J = 8.0 Hz), 7.45–7.41 (t, 1H, J = 7.4 Hz), 4.18–4.15 (m, 1H), 3.59 (s, 3H), 3.56–3.51 (m, 2H), 2.61–2.57 (t, 2H, J = 7.4 Hz), 2.28 (s, 3H), 2.24–2.19 (t, 2H, J = 10.0 Hz), 1.97–1.91 (m, 2H), 1.67–1.53 (m, 2H), 1.27–1.21 (m, 4H). ^{13}C NMR (DMSO-D$_6$, 100 MHz): δ 173.1, 171.5, 171.0, 162.3, 158.3, 149.0, 134.5, 128.5, 127.5, 126.4, 126.1, 52.2, 51.9, 40.5, 34.4, 34.3, 31.2, 29.7, 23.2, 23.1, 22.8.

*4.2.39. 6-Acetamido-2-(3-(4-oxo-3,4-dihydroquinazolin-2-yl) propanamido)hexanoic acid (**25**)*

^{1}H NMR (DMSO-D$_6$, 400 MHz): δ 12.11 (s, 1H), 11.91 (s, 1H), 9.34 (s, 1H), 8.30–8.28 (d, 1H, J = 7.2 Hz), 8.06–8.04 (d, 1H, J = 6.8 Hz), 7.76–7.72 (t, 1H, J = 7.8 Hz), 7.54–7.52 (d, 1H, J = 8.0 Hz), 7.44–7.40 (t, 1H, J = 7.6 Hz), 4.20–4.16 (m, 1H), 3.13–3.08 (q, 2H, J = 6.2 Hz), 2.83–2.80 (t, 2H, J = 6.8 Hz), 2.68–2.62 (q, 2H, J = 8.0 Hz), 2.06 (s, 3H), 1.67–1.54 (m, 2H), 1.31–1.21 (m, 4H). ^{13}C NMR (DMSO-D$_6$, 100 MHz): δ 175.3, 171.5, 171.0, 162.3, 158.4, 149.0, 134.5, 128.6, 127.4, 126.3, 126.1, 52.4, 40.5, 31.4, 31.3, 30.2, 29.9, 23.9, 23.3.

*4.2.40. 6-Acetamido-2-(4-(4-oxo-3,4-dihydroquinazolin-2-yl) butanamido)hexanoic acid (**26**)*

^{1}H NMR (DMSO-D$_6$, 400 MHz): δ 12.10 (s, 1H), 11.90 (s, 1H), 9.34 (s, 1H), 8.17–8.14 (t, 1H, J = 7.8 Hz), 8.06–8.04 (d, 1H, J = 7.6 Hz), 7.76–7.73 (t, 1H, J = 7.0 Hz), 7.58–7.56 (d, 1H, J = 8.0 Hz), 7.45–7.41 (t, 1H, J = 7.4 Hz), 4.18–4.15 (m, 1H), 3.56–3.51 (m, 2H), 2.61–2.57 (t, 2H, J = 7.4 Hz), 2.28 (s, 3H), 2.24–2.19 (t, 2H, J = 10.0 Hz), 1.97–1.91 (m, 2H), 1.67–1.53 (m, 2H), 1.27–1.21 (m, 4H). ^{13}C NMR (DMSO-D$_6$, 100 MHz): δ 175.0, 171.5, 169.9, 162.4, 158.3, 149.1, 134.6, 128.3, 127.4, 126.4, 126.3, 52.4, 41.1, 34.8, 34.3, 31.3, 29.8, 23.3, 23.1, 22.6.

*4.2.41. Methyl 6-(methylsulfonamido)-2-(3-(4-oxo-3,4-dihydroquinazolin-2-yl)propanamido) hexanoate (**28**)*

^{1}H NMR (DMSO-D$_6$, 400 MHz): δ 12.11 (s, 1H), 9.33 (s, 1H), 8.30–8.28 (d, 1H, J = 7.2 Hz), 8.06–8.04 (d, 1H, J = 6.8 Hz), 7.76–7.72 (t, 1H, J = 8.2 Hz), 7.54–7.52 (d, 1H, J = 8.4 Hz), 7.44–7.41 (t, 1H, J = 7.2 Hz), 4.22–4.16 (m, 1H), 3.56 (s, 3H), 3.13–3.08 (q, 2H, J = 6.4 Hz), 2.83–2.80 (t, 2H, J = 6.8 Hz), 2.68–2.62 (q, 2H, J = 7.8 Hz), 2.47 (s, 3H), 1.67–1.54 (m, 2H), 1.33–1.21 (m, 4H). ^{13}C NMR (DMSO-D$_6$, 100 MHz): δ 173.5, 171.6, 171.0, 162.3, 158.5, 149.4, 134.5, 128.3, 127.5, 126.4, 126.3, 52.4, 51.8, 44.3, 40.5, 31.4, 30.3, 30.2, 23.8.

*4.2.42. Methyl 6-(methylsulfonamido)-2-(4-(4-oxo-3,4-dihydroquinazolin-2-yl)butanamido) hexanoate (**29**)*

^{1}H NMR (DMSO-D$_6$, 400 MHz): δ 12.11 (s, 1H), 9.34 (s, 1H), 8.17–8.15 (d, 1H, J = 7.6 Hz), 8.06–8.04 (d, 1H, J = 7.2 Hz), 7.77–7.73 (t, 1H, J = 8.0 Hz), 7.58–7.56 (d, 1H, J = 8.0 Hz), 7.45–7.41 (t, 1H, J = 7.6 Hz), 4.21–4.19 (m, 1H), 3.59 (s, 3H), 3.14–3.12 (m, 2H), 2.61–2.57 (t, 2H, J = 7.4 Hz), 2.48 (s, 3H), 2.21–2.17 (t, 2H, J = 7.6 Hz), 1.95–1.91 (m, 2H), 1.69–1.54 (m, 2H), 1.29–1.24 (m, 4H). ^{13}C NMR (DMSO-D$_6$, 100 MHz): δ 173.4, 171.8, 171.2, 162.6, 158.5, 149.1, 134.4, 128.2, 127.6, 126.3, 126.3, 52.4, 51.5, 44.6, 40.7, 34.6, 34.5, 31.1, 29.8, 23.3, 22.6.

*4.2.43. 6-(Methylsulfonamido)-2-(3-(4-oxo-3,4-dihydroquinazolin-2-yl)propanamido)hexanoic acid (**30**)*

^{1}H NMR (DMSO-D$_6$, 400 MHz): δ 12.11 (s, 1H), 11.91 (s, 1H), 9.33 (s, 1H), 8.30–8.28 (d, 1H, J = 7.2 Hz), 8.06–8.04 (d, 1H, J = 6.8 Hz), 7.76–7.72 (t, 1H, J = 8.2 Hz), 7.54–7.52 (d, 1H, J = 8.4 Hz), 7.44–7.41 (t, 1H, J = 7.2 Hz), 4.22–4.16 (m, 1H), 3.13–3.08 (q, 2H, J = 6.4 Hz), 2.83–2.80 (t, 2H, J = 6.8 Hz), 2.68–2.62 (q, 2H, J = 7.8 Hz), 2.47 (s, 3H), 1.67–1.54 (m, 2H), 1.33–1.21 (m, 4H). ^{13}C NMR (DMSO-D$_6$, 100 MHz): δ 175.3, 171.4, 170.8, 162.2, 157.4, 149.3, 134.7, 128.3, 127.5, 126.2, 126.3, 52.3, 44.4, 40.3, 31.3, 30.2, 30.0, 23.7.

*4.2.44. 6-(Methylsulfonamido)-2-(4-(4-oxo-3,4-dihydroquinazolin-2-yl)butanamido)hexanoic acid (**31**)*

^{1}H NMR (DMSO-D$_6$, 400 MHz): δ 12.11 (s, 1H), 12.01 (s, 1H), 9.34 (s, 1H), 8.17–8.15 (d, 1H, J = 7.6 Hz), 8.06–8.04 (d, 1H, J = 7.2 Hz), 7.77–7.73 (t, 1H, J = 8.0 Hz), 7.58–7.56 (d, 1H, J = 8.0 Hz), 7.45–7.41 (t, 1H, J = 7.6 Hz), 4.21–4.19 (m, 1H), 3.14–3.12 (m, 2H), 2.61–2.57 (t, 2H, J = 7.4 Hz), 2.48 (s, 3H), 2.21–2.17 (t, 2H, J = 7.6 Hz), 1.95–1.91 (m, 2H), 1.69–1.54 (m, 2H), 1.29–1.24 (m, 4H). ^{13}C NMR (DMSO-D$_6$, 100 MHz): δ 175.1, 171.6, 171.0, 162.5, 158.4, 149.0, 134.3, 128.1, 127.4, 126.2, 126.2, 52.2, 44.8, 40.5, 34.5, 34.4, 31.1, 29.8, 23.2, 22.5.

4.3. Antibacterial activity

In vitro antibacterial assay was performed against *B. substilis* (Fig. 1), *E. coli* (Fig. 2), *P. fluorescens* (Fig. 3), *X. campestris pvs*. (Fig. 4) and *X. oryzae* (Fig. 5) by using the disc diffusion method [23]. The bacterial strains were maintained on LB agar medium at 28 °C. The bacteria were grown in LB broth and centrifuged at 10,000 rpm for 5 min. The pellet was dissolved in double distilled water and used to inoculate the plates. The paper discs containing streptomycin and tetracycline were used as positive control and DMSO as a negative control. Each disc contained 10 μg of standard drugs and 10 μg of synthesized compounds. The plates were maintained at

4 °C for 2 h to allow the diffusion of drugs and then incubated at 28 °C. All the compounds were tested in triplicate and inhibition zones were measured in mm after 24 h of incubation.

Acknowledgements

One of the authors RS gratefully acknowledges Lady Tata Memorial Trust, Mumbai for the award of Junior Research Scholarship.

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