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Original article

Synthesis of uriedo and thiouriedo derivatives of peptide conjugated heterocycles – A new class of promising antimicrobials

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ABSTRACT

Forty five new derivatives of ureas and thioureas were synthesized by the reaction of peptide conjugated heterocycles with isocyanates and isothiocyanates respectively. All the compounds have been characterized by IR, ^{1}H NMR, mass and elemental analysis. The compounds were evaluated for their ability to inhibit the growth of a panel of microorganisms and all the synthesized compounds displayed an excellent antimicrobial activity. From structure–activity relationship studies, it was apparent that thioureas infact is slightly more active than ureas. Also, substituents on the phenyl ring of the title compounds play a key role in the activity. Further, compound **40** is nearly twenty times more potent than the standard used. These results present a platform for the further studies in this line.

1. Introduction

The increasing incidence of infection caused by the rapid development of bacterial resistance to most of the known antibiotics is a serious health problem [1]. While many factors may be responsible for mutations in microbial genomes, it has been widely demonstrated that the incorrect use of antibiotics can greatly increase the development of resistant genotypes [2]. As multidrug-resistant bacterial strains proliferate, the necessity for effective therapy has stimulated research into the design and synthesis of novel antimicrobial molecules.

Peptides are among the most versatile bioactive molecules e.g. many peptide hormones and shorter peptides analogous exert their action by binding to membrane receptors [3]. Peptides and their derivatives exhibit a broad spectrum of biological activities such as antimicrobial [4], antiviral, and anticancer activities [5]. These novel compounds open up new perspectives in drug design by providing an entire range of highly specific and non-toxic pharmaceuticals. With growing application on their synthesis and bioactivity, chemists and biologists in recent years have directed considerable attention on the research of peptide-based derivatives [6,7]. Taking the advantage of low toxicity, biocompatibility and likeliness/structural diversity of amino acid residues with the biological system, currently there is huge tendency of conjugating amino acid/peptide residues with small bioactive heterocyclic motifs in the field of biomedical research [8].

Urea derivatives have been used for the treatment of a wide range of solid tumours [9,10]. Urea-based prodrugs have been reported as candidates for melanocyte-directed enzyme prodrug therapy (MDEPT), in which they release the drug upon exposure to tyrosinase [11]. Some related urea derivatives also have been reported as protein tyrosine kinases (PTKs) inhibitors, and have become an important class of potential anticancer drugs [12]. The urea and the thiourea derivatives have also been used for brain cancer treatment and as potent inhibitors of human DNA-topoisomerase II [13]. Moreover, other properties were attributed to urea derivatives such as HIV-1 protease and cholesterol acyltransferase (ACAT) inhibitory activities. They are also promising therapeutic agents for hypercholesteromia and atherosclerosis [14,15]. Urea/thiourea derivatives display a wide range of biological activities including antibacterial, antifungal, antitubercular, antithyroid, antihelmintic, rodenticidal, insecticidal, herbicidal, and plant growth regulator properties [16–21]. For these reasons, the synthesis of urea and their functionalized derivatives is of high interest.

Thus, due to the important properties presented by urea and thiourea derivatives involving particularly antimicrobial activity, and in continuation of our programme on development of novel antimicrobial agents [22–26], in this work we report the synthesis

Abbreviations: Boc, *t*-Butoxycarbonyl; NMM, *N*-Methyl morpholine; TFA, Trifluoroacetic acid.

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of ureas and thioureas of elastin-based peptide conjugated heterocycles and their activity against various strains of human pathogens.

2. Results and discussion

2.1. Chemistry

The uriedo and thiouriedo derivatives were synthesized by reacting peptide conjugated heterocycles with isocyanates and isothiocyanates respectively using NMM as base. All the derivatives were obtained in high yields. The evidence for the formation of compounds was obtained from IR, ^{1}H NMR, mass and elemental analysis. IR spectrum of the ureas and thioureas exhibited peaks at ν ~1640 cm^{-1} (C=O) and ν ~2040 cm^{-1} (C=S) respectively along with ν ~3280 cm^{-1} for NH. ^{1}H NMR spectra showed singlet for one proton (NH) at δ ~8.10, multiplet for NH at δ ~8.01 for urea derivatives. On the other hand, δ singlet at ~8.9 (NH) and multiplet at δ ~8.11 (NH) for thiourea derivatives. Further, all the other peaks are exactly matching the structure. Also % of each element (C, H, N and S) of the synthesized compounds was confirmed by elemental analysis and the values are found to be within ±0.4% of the calculated ones. The physical and mass data of the derivatives are presented in Table 1.

2.2. Biology

The synthesized ureas and thioureas were evaluated for their ability to inhibit the growth of different strains of human pathogens of both gram negative organisms like *Escherichia coli* and *Xanthomonas oryzae* and gram positive bacteria namely *Klebsiella pneumoniae* and *Coagulase positive staphylococcus* and antifungal studies against *Aspergillus niger*, *Aspergillus flavus* and *Fusarium oxysporum*. The results obtained as zone of inhibition (mm) and minimum inhibitory concentration (μg/mL) are presented in Tables 2 and 3 respectively. Amoxicillin and bavistin served as standard drugs for antibacterial and antifungal studies respectively.

In our earlier article [24,25], we discussed the synthesis and biological activity of amino acid/peptide conjugated heterocycles. Also, in another article [26], our group aimed at the synthesis of ureas/thioureas of lysine-quinazolinone conjugates. Prompted by the results obtained in these studies, the present work involved the synthesis and antimicrobial screening of a series of urea/thiourea derivatives of peptide conjugated 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (Heterocycle 1) and 1-(2,3-dichlorophenyl)piperazine (Heterocycle 2).

Among the derivatives synthesized, compounds containing thiourea group (**23**–**34**, **59**–**67**, **41**–**42** and **74**–**75**) have exhibited enhanced activity compared to urea derivatives (**11**–**22**, **53**–**58**, **40** and **73**). This would be due to the electronegativity and larger size of S which could alter the binding affinity of thioureas in the interacting site/s. This is supported by the earlier works [26,28]. Also, S and O atoms in the molecules are likely to act as hydrogen bond acceptors [28]. Due to these reasons, the synthesized ureas and thioureas might have exerted highly potent activity.

The results of the derivatives appeared to be related to the nature of the substituent group on the phenyl ring of ureas/thioureas. The compounds with electron withdrawing groups were more active with low MIC values. However, electron donating group did not present significant results as the latter did. In addition, it should be noted that the fluoro containing molecules are better than Cl, while the methoxy is comparable. This may be due to electronic effects [26,29]. This trend was observed in all the compounds used herein whether they were ureas or thioureas.

Table 1
Physical and mass data of the synthesized compounds.

Entry	R_f^a	R_f^b	Yield (%)	M.P. (°C)	Mol. For.	Mass (M^++Na)
11	0.54	0.61	87.4	155–157	$C_{30}H_{27}F_2N_5O_3$	566.5128
12	0.34	0.41	87.7	90–92	$C_{35}H_{43}ClFN_7O_6$	734.6298
13	0.33	0.45	90.6	96–98	$C_{36}H_{46}FN_7O_7$	730.2593
14	0.39	0.52	91.4	66–69	$C_{37}H_{39}F_2N_7O_6$	738.4692
15	0.41	0.48	92.3	109–111	$C_{37}H_{39}ClFN_7O_6$	754.6092
16	0.41	0.50	91.8	62–65	$C_{38}H_{42}FN_7O_7$	750.1095
17	0.32	0.50	91.3	175–178	$C_{38}H_{48}F_2N_8O_7$	789.7337
18	0.35	0.50	85.9	180–182	$C_{38}H_{48}ClFN_8O_7$	805.2267
19	0.31	0.47	92.8	130–132	$C_{39}H_{51}FN_8O_8$	801.7054
20	0.33	0.51	88.5	110–112	$C_{46}H_{48}F_2N_8O_7$	885.5691
21	0.34	0.46	90.8	85–87	$C_{46}H_{48}ClFN_8O_7$	901.3265
22	0.40	0.50	93.0	80–83	$C_{47}H_{51}FN_8O_8$	897.7008
23	0.50	0.58	91.3	Gum	$C_{30}H_{27}F_2N_5O_2S$	582.5493
24	0.35	0.43	91.5	110–112	$C_{35}H_{43}ClFN_7O_5S$	750.4167
25	0.34	0.46	90.3	55–57	$C_{36}H_{46}FN_7O_6S$	746.4637
26	0.42	0.48	88.6	94–96	$C_{37}H_{39}F_2N_7O_5S$	754.3367
27	0.40	0.49	90.6	140–142	$C_{37}H_{39}ClFN_7O_5S$	770.0956
28	0.40	0.51	92.3	65–68	$C_{38}H_{42}FN_7O_6S$	766.6413
29	0.31	0.48	89.0	195–197	$C_{38}H_{48}F_2N_8O_6S$	805.5963
30	0.37	0.52	91.5	109–111	$C_{38}H_{48}ClFN_8O_6S$	821.2460
31	0.34	0.49	92.5	80–82	$C_{39}H_{51}FN_8O_7S$	817.4638
32	0.35	0.49	87.6	80–82	$C_{46}H_{48}F_2N_8O_6S$	901.9367
33	0.38	0.47	86.4	105–107	$C_{46}H_{48}ClFN_8O_6S$	917.4269
34	0.42	0.54	94.8	67–70	$C_{47}H_{51}FN_8O_7S$	913.7763
40	0.42	0.52	90.2	125–127	$C_{159}H_{211}FN_{32}O_{35}$	*
41	0.38	0.50	91.8	133–135	$C_{159}H_{211}ClFN_{32}O_{35}S$	*
42	0.43	0.54	86.3	166–168	$C_{160}H_{214}FN_{32}O_{36}S$	*
53	0.51	0.58	92.2	107–109	$C_{28}H_{26}Cl_2FN_5O_2$	576.3267
54	0.36	0.43	87.6	163–164	$C_{33}H_{42}Cl_2FN_7O_5$	728.4168
55	0.44	0.51	89.5	209–211	$C_{35}H_{43}ClFN_7O_6$	734.2005
56	0.40	0.50	92.7	127–129	$C_{36}H_{46}FN_7O_7$	730.3691
57	0.37	0.50	93.3	135–137	$C_{36}H_{47}Cl_2FN_8O_6$	799.8792
58	0.39	0.51	87.9	98–100	$C_{44}H_{47}Cl_2FN_8O_6$	895.6374
59	0.52	0.60	93.4	109–111	$C_{28}H_{26}Cl_2FN_5OS$	592.3691
60	0.39	0.53	89.1	89–91	$C_{35}H_{42}Cl_3N_7O_4S$	740.0254
61	0.39	0.50	90.0	111–112	$C_{34}H_{45}Cl_2N_7O_5S$	756.6934
62	0.42	0.52	86.3	159–162	$C_{35}H_{43}ClFN_7O_5S$	750.0951
63	0.42	0.52	91.7	80–82	$C_{36}H_{46}FN_7O_6S$	746.5593
64	0.36	0.49	88.7	159–161	$C_{36}H_{47}Cl_3N_8O_5S$	831.4467
65	0.40	0.51	88.1	144–146	$C_{37}H_{50}Cl_2N_8O_6S$	824.7265
66	0.40	0.52	94.1	110–112	$C_{44}H_{47}Cl_3N_8O_5S$	927.6314
67	0.38	0.50	91.7	129–130	$C_{45}H_{50}Cl_2N_8O_6S$	923.4496
73	0.41	0.52	88.4	111–113	$C_{157}H_{211}Cl_2FN_{33}O_{35}$	*
74	0.40	0.53	86.5	122–124	$C_{157}H_{211}Cl_3N_{33}O_{35}S$	*
75	0.40	0.52	88.8	141–143	$C_{158}H_{214}Cl_2N_{33}O_{36}S$	*

*Confirmed by elemental analysis.

This reveals that substituent on the aromatic ring has an impact on the activity.

Among the derivatives of two heterocycles 1 and 2, compounds containing piperidine nucleus (**11**–**34**, **40**–**42**) have shown slight enhancement in the activity over the piperazine analogues (**53**–**67**, **73**–**75**). The reason could be more lipophilic nature of piperidine moiety [30] along with the presence of benzisoxazole and fluoro groups. Whereas in piperazine, it contains only Cl groups attached to phenyl ring. This clearly demonstrates the importance of lipophilicity for the antimicrobial activity.

Further, it has been reported in our earlier papers that [23–25] as the length and hydrophobicity of the peptide chain increases, activity also increases. This trend has been observed in the current investigation also.

Based on the primary growth inhibition activity, compounds that showed potent effects were selected to determine the minimum inhibitory inhibition (MIC). As a result, the derivatives of peptide conjugates have exhibited very high activity compared to peptide conjugates devoid of ureas/thioureas [24,25]. Particularly it is interesting to note that derivatives of tricosamer conjugates (**40**–**42** and **73**–**75**) have inhibited the growth of fungal species at

Table 2
Inhibitory zone (diameter) mm of the synthesized derivatives against tested bacterial and fungal strains by agar well diffusion method.

Entry	Antibacterial activity				Antifungal activity		
	Zone of inhibition[a] (mm) ± SD ($n = 3$)						
	E. coli	*X. oryzae*	*K. pneumoniae*	*C. positive staphylococcus*	*A. niger*	*A. flavus*	*F. oxysporum*
11	11 ± 0.40	11 ± 0.35	08 ± 0.05	08 ± 0.20	12 ± 0.11	09 ± 0.28	08 ± 0.32
12	26 ± 0.26	22 ± 0.35	18 ± 0.37	19 ± 0.30	27 ± 0.49	24 ± 0.10	26 ± 0.26
13	22 ± 0.40	17 ± 0.30	16 ± 0.36	14 ± 0.20	23 ± 0.37	19 ± 0.32	21 ± 0.23
14	31 ± 0.36	29 ± 0.40	27 ± 0.23	25 ± 0.40	34 ± 0.36	29 ± 0.23	31 ± 0.40
15	28 ± 0.51	25 ± 0.45	23 ± 0.26	21 ± 0.50	31 ± 0.36	26 ± 0.32	28 ± 0.35
16	26 ± 0.55	24 ± 0.40	19 ± 0.34	17 ± 0.41	27 ± 0.36	20 ± 0.36	23 ± 0.30
17	34 ± 0.25	35 ± 0.50	33 ± 0.20	30 ± 0.32	36 ± 0.10	32 ± 0.25	33 ± 0.06
18	30 ± 0.55	26 ± 0.52	29 ± 0.28	27 ± 0.32	33 ± 0.38	29 ± 0.49	32 ± 0.34
19	26 ± 0.40	33 ± 0.15	27 ± 0.45	23 ± 0.25	30 ± 0.10	27 ± 0.26	27 ± 0.41
20	39 ± 0.41	40 ± 0.25	36 ± 0.32	34 ± 0.37	40 ± 0.30	35 ± 0.34	39 ± 0.11
21	34 ± 0.35	35 ± 0.51	33 ± 0.20	31 ± 0.30	38 ± 0.23	31 ± 0.52	35 ± 0.42
22	30 ± 0.37	30 ± 0.41	30 ± 0.32	28 ± 0.40	35 ± 0.51	29 ± 0.21	32 ± 0.44
23	13 ± 0.32	12 ± 0.35	09 ± 0.26	09 ± 0.26	13 ± 0.45	10 ± 0.20	07 ± 0.26
24	28 ± 0.56	25 ± 0.32	21 ± 0.30	21 ± 0.21	29 ± 0.52	27 ± 0.36	29 ± 0.36
25	24 ± 0.56	20 ± 0.36	14 ± 0.20	16 ± 0.25	26 ± 0.28	22 ± 0.32	24 ± 0.35
26	32 ± 0.41	30 ± 0.30	28 ± 0.20	26 ± 0.25	35 ± 0.26	30 ± 0.25	32 ± 0.32
27	30 ± 0.45	27 ± 0.36	26 ± 0.23	24 ± 0.30	33 ± 0.49	29 ± 0.21	31 ± 0.25
28	24 ± 0.43	22 ± 0.35	21 ± 0.41	19 ± 0.36	28 ± 0.46	23 ± 0.26	25 ± 0.25
29	35 ± 0.40	36 ± 0.17	35 ± 0.55	31 ± 0.47	37 ± 0.31	33 ± 0.20	35 ± 0.26
30	31 ± 0.32	32 ± 0.20	30 ± 0.25	28 ± 0.15	34 ± 0.57	30 ± 0.25	31 ± 0.46
31	28 ± 0.56	28 ± 0.23	26 ± 0.26	24 ± 0.30	31 ± 0.32	26 ± 0.49	26 ± 0.58
32	41 ± 0.30	41 ± 0.34	37 ± 0.36	36 ± 0.32	41 ± 0.41	36 ± 0.15	40 ± 0.30
33	35 ± 0.10	36 ± 0.50	34 ± 0.37	32 ± 0.25	39 ± 0.35	32 ± 0.30	36 ± 0.37
34	31 ± 0.26	31 ± 0.55	31 ± 0.37	29 ± 0.43	36 ± 0.45	30 ± 0.15	33 ± 0.35
40	24 ± 0.30	21 ± 0.45	22 ± 0.36	22 ± 0.30	46 ± 0.35	43 ± 0.44	44 ± 0.40
41	21 ± 0.30	17 ± 0.26	19 ± 0.26	17 ± 0.36	45 ± 0.21	40 ± 0.34	41 ± 0.35
42	17 ± 0.30	14 ± 0.51	16 ± 0.05	15 ± 0.30	43 ± 0.25	38 ± 0.23	39 ± 0.40
53	09 ± 0.35	09 ± 0.30	10 ± 0.20	11 ± 0.30	10 ± 0.36	11 ± 0.30	07 ± 0.20
54	29 ± 0.40	26 ± 0.25	23 ± 0.20	24 ± 0.15	32 ± 0.40	28 ± 0.30	30 ± 0.32
55	27 ± 0.60	24 ± 0.28	22 ± 0.17	20 ± 0.32	30 ± 0.17	25 ± 0.36	27 ± 0.45
56	25 ± 0.40	23 ± 0.15	18 ± 0.20	16 ± 0.06	26 ± 0.36	19 ± 0.32	22 ± 0.32
57	33 ± 0.49	34 ± 0.52	32 ± 0.37	29 ± 0.36	35 ± 0.06	31 ± 0.31	32 ± 0.15
58	37 ± 0.40	38 ± 0.15	35 ± 0.30	33 ± 0.31	39 ± 0.43	34 ± 0.35	34 ± 0.35
59	10 ± 0.45	10 ± 0.41	11 ± 0.35	12 ± 0.20	11 ± 0.46	12 ± 0.40	06 ± 0.11
60	27 ± 0.45	24 ± 0.30	20 ± 0.47	22 ± 0.35	28 ± 0.41	26 ± 0.49	28 ± 0.34
61	23 ± 0.30	19 ± 0.41	13 ± 0.17	18 ± 0.11	25 ± 0.40	21 ± 0.32	23 ± 0.40
62	29 ± 0.45	26 ± 0.41	25 ± 0.20	23 ± 0.25	32 ± 0.28	28 ± 0.06	30 ± 0.36
63	23 ± 0.32	21 ± 0.36	20 ± 0.43	18 ± 0.34	29 ± 0.23	22 ± 0.40	24 ± 0.47
64	29 ± 0.61	31 ± 0.35	24 ± 0.45	26 ± 0.25	32 ± 0.42	24 ± 0.26	29 ± 0.36
65	27 ± 0.11	26 ± 0.52	22 ± 0.36	22 ± 0.35	29 ± 0.29	23 ± 0.32	24 ± 0.25
66	32 ± 0.43	33 ± 0.51	32 ± 0.20	30 ± 0.20	34 ± 0.15	30 ± 1.00	31 ± 0.75
67	29 ± 0.47	28 ± 0.47	29 ± 0.32	26 ± 0.23	32 ± 0.30	28 ± 0.42	29 ± 0.23
73	22 ± 0.50	19 ± 0.47	21 ± 0.28	20 ± 0.49	48 ± 0.26	42 ± 0.41	43 ± 0.25
74	19 ± 0.50	16 ± 0.32	18 ± 0.20	16 ± 0.41	44 ± 0.20	39 ± 0.32	40 ± 0.31
75	15 ± 0.32	13 ± 0.37	15 ± 0.25	14 ± 0.17	42 ± 0.43	37 ± 0.43	38 ± 0.17
Amoxicillin	12 ± 0.57	09 ± 0.26	08 ± 0.26	08 ± 0.25	–	–	–
Bavistin	–	–	–	–	12 ± 0.31	09 ± 0.26	10 ± 0.20

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

a concentration of 1–3 μg/mL which is nearly 10–25 fold greater than the standard antibiotic used.

3. Conclusion

In conclusion, we prepared a series of urea and thiourea derivatives of peptide conjugated heterocycles and evaluated their inhibitory activities on the growth of pathogenic bacteria and fungi. These have exhibited highly promising activity. Introduction of S in place of O in the ureas has led to enhanced results. Presence of electron withdrawing substituents particularly F is found to be essential for potent activity compared to electron donating group. Among the analogues of two heterocyclic conjugates, piperidine nucleus bearing compounds have shown more activity compared to piperazine moiety containing derivatives. The most striking feature of this study is that F and Cl containing urea/thiourea derivatives of tricosamer conjugates **40** (1.25 μg/mL) and **41** (1.75 μg/mL) have nearly 20–25 fold greater activity than the standard used in the assay. Thus, the present findings provide new opportunity for the development of novel antimicrobials to overcome the ever-increasing problem of drug resistance.

4. Experimental

4.1. Materials

All the amino acids used except glycine were of L-configuration unless otherwise mentioned. TFA was purchased from Advanced Chem. Tech. (Louisville, Kentucky, USA). NMM and phenyl-isocyanate/isothiocyanate were purchased from Sigma Chemical Co. (St. Louis, MO). All solvents and reagents used for the synthesis were of analytical grade. All the chemicals and reagents used for antimicrobial studies were of bacteriological grade unless otherwise indicated. Nutrient broth and nutrient agar were purchased

Table 3
Minimum inhibitory concentration (MIC) in μg/mL of the synthesized derivatives against tested bacterial and fungal strains by microdilution method.

Entry	Antibacterial activity				Antifungal activity		
	Minimum inhibitory concentration (MIC) in μg/mL[a]						
	E. coli	*X. oryzae*	*K. pneumoniae*	*C. positive staphylococcus*	*A. niger*	*A. flavus*	*F. oxysporum*
14	12	09	09	11	09	13	14
17	7.75	6.75	5.25	6.75	5.00	5.75	7.00
18	9.25	8.50	6.75	8.75	6.50	7.50	8.50
20	5.00	5.00	3.25	4.25	3.25	4.75	4.25
21	6.25	6.50	4.75	6.00	4.75	6.25	6.00
26	11.50	8.50	8.25	10.25	8.50	12.25	13.25
29	7.25	6.25	5.00	6.25	4.75	5.50	6.75
30	8.75	8.00	6.50	8.00	6.00	6.75	8.00
32	4.75	4.75	3.00	4.00	3.00	4.50	4.00
33	6.00	6.25	4.50	5.75	4.50	6.00	5.75
40	–	–	–	–	1.25	1.25	1.50
41	–	–	–	–	1.75	1.75	2.50
42	–	–	–	–	2.00	2.00	2.00
54	13	10	10	12	11	14	15
57	8.25	7.25	6.00	7.25	5.50	6.25	7.50
58	5.50	5.75	4.00	5.00	4.00	5.25	5.00
64	9.50	8.75	7.00	9.00	6.75	7.75	8.75
66	6.75	6.75	5.00	6.25	5.00	6.50	6.25
73	–	–	–	–	2.00	1.75	2.00
74	–	–	–	–	2.50	2.50	3.00
75	–	–	–	–	2.75	2.75	3.25
Amoxicillin	24	19	20	23	–	–	–
Bavistin	–	–	–	–	22	26	25

'–' = not determined.
[a] Values are median of three determinations.

from Hi-media chemicals (Mumbai, India). The pathogens used for the microbial studies were obtained from a local hospital. The progress of the reaction was monitored by TLC using silica gel coated on glass plates with the solvent system comprising chloroform/methanol/acetic acid in the ratio 95:5:3 (R_f^a)/90:10:3 (R_f^b) throughout the study and the compounds on TLC plates were detected by iodine vapours. Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. FT-IR was performed in Jasco Spectrometer. ^{1}H NMR spectra were obtained on VARIAN 400 MHz instrument using $CDCl_3$ and the chemical shifts are reported as parts per million (δ ppm) using TMS as an internal standard. Electrospray ionization mass spectrometry (ESI-MS) was performed on a Bruker electrospray mass spectrometer. Elemental analysis was performed by using VARIO EL III Elementar and the values are within ±0.4% of the calculated ones.

4.2. Synthesis

All the amino acid/peptide conjugates were prepared according to the procedure described in our earlier reports [24,25]. The γ-carboxyl group of Glu was protected by cyclohexyl ester and removed by treatment with polymer supported $HCOO^-NH_3^+$, 10% Pd–C [27]. The Boc group was used for temporary N^{α} protection and its removal was achieved with TFA. These were converted into urea and thiourea derivatives of the conjugates by reacting with isocyanates and isothiocyanates respectively in presence of NMM as a base. The procedure followed for the synthesis of derivatives of heterocycle 1 conjugates are presented in Scheme 1 and 2 where as that of the derivatives of heterocycle 2 conjugates are given in Scheme 3 and 4 respectively.

4.3. General procedure for the deblocking of conjugated compounds

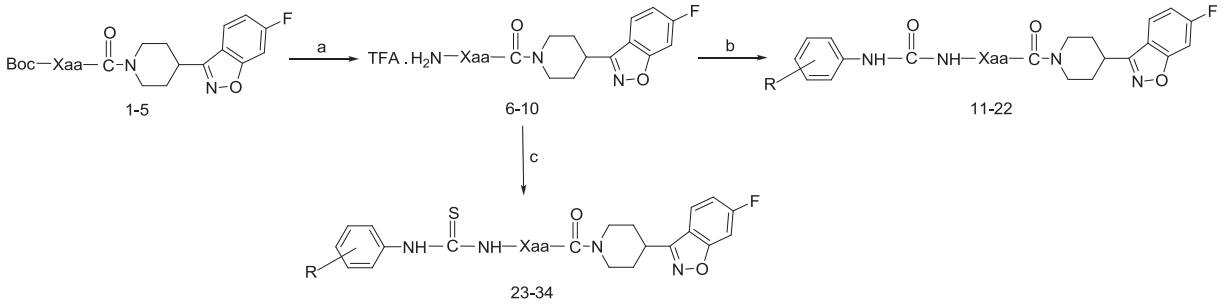
100 mg of Boc-Xaa-Heterocycle 1/2 (**1**–**5**/**35**/**43**–**47**/**68**) was stirred with 1.0 mL of TFA for 1 h at room temperature. After the completion of the reaction monitored by TLC, the reaction mixture was concentrated at high vacuum to get TFA·H-Xaa-Heterocycle 1/2 (**6**–**10**/**36**/**48**–**52**/**69**) which was then triturated with dry ether, filtered, washed with ether and dried under vacuum (Yield: 100%).

4.4. General procedure for the synthesis of uriedo derivatives (*11*–*22*, *53*–*58*, *37* and *70*)

To a solution of TFA·H-Xaa-Heterocycle 1/2 (0.001 mol) in DMF (10 mL/g of compound), cooled to 0 °C was added NMM (0.219 mL, 0.002 mol). To this solution respective isocyanate like 2F-phenyl isocyanate, 4Cl-phenyl isocyanate and 4OMe-phenyl isocyanate (0.0012 mol) was added dropwise maintaining the temperature at 0 °C. The reaction mixture was stirred for 8 h slowly warming to room temperature. DMF was evaporated under high vacuum and the residue was poured into about 20 mL ice-cold 90% saturated $KHCO_3$ solution and stirred for 15 min. The precipitated compound was extracted with ethyl acetate and washed sequentially with 5% $NaHCO_3$ solution (2 × 20 mL), water (2 × 20 mL), 0.1 N HCl (2 × 20 mL) followed by brine solution. The organic layer was dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure, triturated with hexane and dried under vacuum.

4.5. General procedure for the synthesis of thiouriedo derivatives (*23*–*34*, *59*–*67*, *38*–*39* and *71*–*72*)

To a solution of TFA·H-Xaa-Heterocycle 1/2 (0.001 mol) in DMF (10 mL/g of compound), cooled to 0 °C was added NMM (0.219 mL, 0.002 mol). To this solution respective isothiocyanates like 2F-phenyl isothiocyanate, 4Cl-phenyl isothiocyanate and 4OMe-phenyl isothiocyanate (0.0012 mol) was added dropwise maintaining the temperature at 0 °C. The reaction mixture was stirred for 8 h slowly warming to room temperature. DMF was evaporated under high vacuum and the residue was poured into about 20 mL ice-cold 90% saturated $KHCO_3$ solution and stirred for 15 min. The precipitated compound was extracted with ethyl acetate and washed sequentially with 5% $NaHCO_3$ solution (2 × 20 mL), water



Scheme 1. Schematic representation of the synthesis of uriedo/thiouriedo derivatives of amino acid/peptides conjugated heterocycle 1. Reagents and conditions: (a) TFA, 40 min, rt (b) R–N=C=O, NMM/DMF, 8 h, 0 °C to rt (c) R–N=C=S, NMM/DMF, 8 h, 0 °C to rt where Xaa = Trp, GGIP, GGFP, GVGVP, GFGFP; R = 2F, 4Cl, 4OMe.

(2 × 20 mL), 0.1 N HCl (2 × 20 mL) followed by brine solution. The organic layer was dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure, triturated with hexane and dried under vacuum.

4.6. Deprotection of OcHx of Glu of the derivatives

To a solution of the derivatives **37**–**39** and **70**–**72** (0.001 mol) in methanol (10 mL/g of compound), 10% Pd–C (100 mg) and polymer supported formate (1 g) were added and the mixture was stirred at room temperature for 8 h. After completion of the reaction monitored by TLC, catalyst and the polymer were filtered, washed with methanol. The solvent was evaporated under reduced pressure and the product was taken into $CHCl_3$, washed with saturated NaCl and the solvent was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and triturated with ether and dried to get side chain deprotected derivatives **40**–**42** and **73**–**75** respectively.

4.6.1. 2F-Urea derivative of Trp-Heterocycle 1 (*11*)

IR ν_{max} (nujol): 1604 (CO), 3305 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Urea = 8.22 (1H, s, NH), 8.13 (1H, m, NH), 7.06–7.85 (4H, m, ArH); Trp = 3.57–3.73 (2H, d, $-^{\beta}CH_2$), 4.65 (1H, t, $-^{\alpha}CH$), 6.99 (1H, s, –CH of indole), 7.06–7.85 (4H, m, ArH), Exchanged (–NH of indole); Heterocycle = 1.93–1.96 (4H, m, $-CH_2$), 2.97 (1H, m, –CH), 3.80–3.87 (4H, m, $-CH_2$), 7.06–7.85 (3H, m, ArH); Elemental Analysis: Calc. C = 66.29, H = 5.01, N = 12.88, Found C = 66.25, H = 5.04, N = 12.86.

4.6.2. 4Cl-Urea derivative of $G^1G^2I^3P^4$-Heterocycle 1 (*12*)

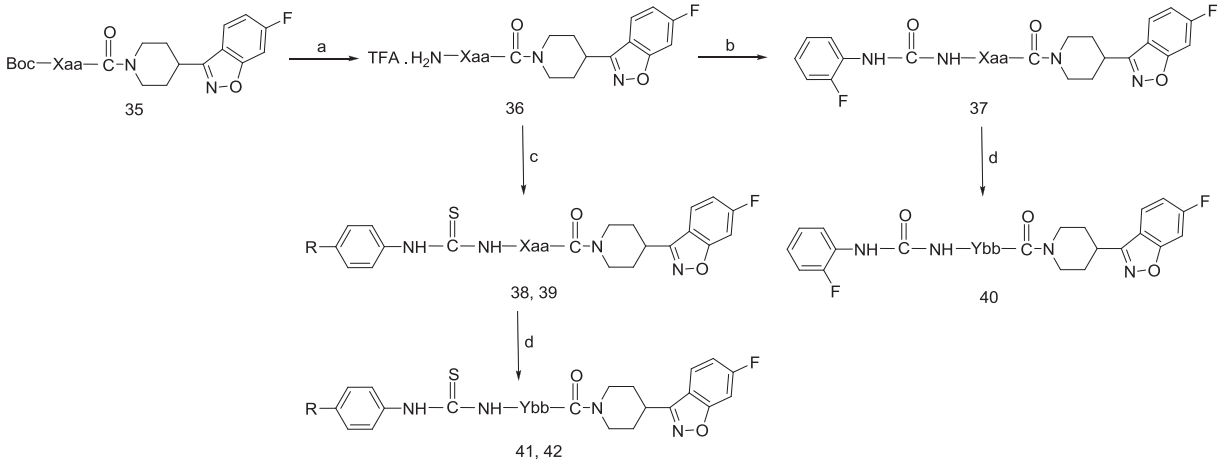
IR ν_{max} (nujol): 1644 (CO), 3324 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Urea = 8.15 (1H, s, NH), 7.94 (1H, m, NH), 7.05–7.88 (4H, m, ArH); –NH = 8.05–8.14 (2H, m); Gly^1 = 3.90 (2H, s, $-^{\alpha}CH$); Gly^2 = 4.18 (2H, s, $-^{\alpha}CH$); Ile^3 = 0.89–1.04 (6H, m, $-(CH_3)_2$), 1.44 (2H, m, $-^{\gamma}CH_2$), 2.14 (1H, m, $-^{\beta}CH$), 4.68 (1H, m, $-^{\alpha}CH$); Pro^4 = 1.93–3.60 (6H, m, $-CH_2$), 4.61 (1H, m, $-^{\alpha}CH$); Heterocycle = 1.84,1.95 (4H, m, $-CH_2$), 2.87 (1H, m, –CH), 3.65 (4H, m, $-CH_2$), 7.05–7.88 (3H, m, ArH); Elemental Analysis: Calc. C = 59.02, H = 6.09, N = 13.77, Found C = 59.05, H = 6.11, N = 13.74.

4.6.3. 4OMe-Urea derivative of $G^1G^2I^3P^4$-Heterocycle 1 (*13*)

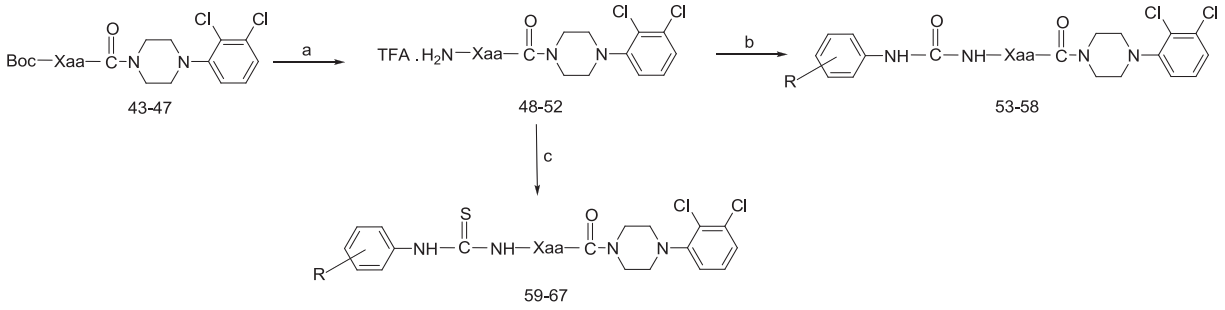
IR ν_{max} (nujol): 1615 (CO), 3312 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Urea = 8.10 (1H, s, NH), 7.90 (1H, m, NH), 7.00–7.81 (4H, m, ArH), 3.60 (3H, s, OMe); –NH = 8.01–8.08 (2H, m); Gly^1 = 3.94 (2H, s, $-^{\alpha}CH$); Gly^2 = 4.20 (2H, s, $-^{\alpha}CH$); Ile^3 = 0.92–1.01 (6H, m, $-(CH_3)_2$), 1.47 (2H, m, $-^{\gamma}CH_2$), 2.18 (1H, m, $-^{\beta}CH$), 4.69 (1H, m, $-^{\alpha}CH$); Pro^4 = 1.89–3.58 (6H, m, $-CH_2$), 4.64 (1H, m, $-^{\alpha}CH$); Heterocycle = 1.88,1.97 (4H, m, $-CH_2$), 2.81 (1H, m, –CH), 3.68 (4H, m, $-CH_2$), 7.00–7.81 (3H, m, ArH); Elemental Analysis: Calc. C = 61.09, H = 6.55, N = 13.85, Found C = 61.04, H = 6.52, N = 13.44.

4.6.4. 2F-Urea derivative of $G^1G^2F^3P^4$-Heterocycle 1 (*14*)

IR ν_{max} (nujol): 1629 (CO), 3278 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Urea = 8.05 (1H, s, NH), 7.69 (1H, m, NH), 6.95–7.97 (4H, m, ArH); –NH = 8.10–8.53 (2H, s); Gly^1 = 3.82 (2H, s, $-^{\alpha}CH$); Gly^2 = 4.07 (2H, s, $-^{\alpha}CH$); Phe^3 = 3.60, 3.71 (2H, d, $-^{\beta}CH_2$), 4.95 (1H, t, $-^{\alpha}CH$); 6.95–7.97 (5H, m, ArH); Pro^4 = 2.00–3.95 (6H, m, $-CH_2$), 4.65 (1H, m, $-^{\alpha}CH$); Heterocycle = 1.90–1.97 (4H, m, $-CH_2$), 2.93



Scheme 2. Schematic representation of the synthesis of uriedo/thiouriedo derivatives of tricosamer conjugated heterocycle 1. Reagents and conditions: (a) TFA, 40 min, rt (b) 2F–Ph–N=C=O, NMM/DMF, 8 h, 0 °C to rt (c) R–N=C=S, NMM/DMF, 8 h, 0 °C to rt (d) Polymer supported $HCOO^-NH_3^+$/10% Pd–C; R = Cl, OMe where Xaa = GE(OcHx)GFP GVGVP GVGVP GVGVP GFGFP GFGFP, Ybb = GEGFP GVGVP GVGVP GVGVP GFGFP GFGFP.



Scheme 3. Schematic representation of the synthesis of uriedo/thiouriedo derivatives of amino acid/peptides conjugated heterocycle 2. Reagents and conditions: (a) TFA, 40 min, rt (b) R–N═C═O, NMM/DMF, 8 h, 0 °C to rt (c) R–N═C═S, NMM/DMF, 8 h, 0 °C to rt where Xaa = Trp, GGIP, GGFP, GVGVP, GFGFP; R = 2F, 4Cl, 4OMe.

(1H, m, –CH), 3.50, 3.56 (4H, m, $-CH_2$), 6.95–7.97 (3H, m, ArH); Elemental Analysis: Calc. C = 62.09, H = 5.49, N = 13.70, Found C = 61.94, H = 5.40, N = 13.65.

*4.6.5. 4Cl-Urea derivative of $G^1G^2F^3P^4$-Heterocycle 1 (**15**)*

IR ν_{max} (nujol): 1636 (CO), 3294 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Urea = 8.00 (1H, s, NH), 7.73 (1H, m, NH), 6.90–7.92 (4H, m, ArH); –NH = 8.09–8.49 (2H, s); Gly^1 = 3.86 (2H, s, $-^{\alpha}CH$); Gly^2 = 4.11 (2H, s, $-^{\alpha}CH$); Phe^3 = 3.58, 3.69 (2H, d, $-^{\beta}CH_2$), 4.92 (1H, t, $-^{\alpha}CH$); 6.90–7.92 (5H, m, ArH); Pro^4 = 2.06–3.91 (6H, m, $-CH_2$), 4.63 (1H, m, $-^{\alpha}CH$); Heterocycle = 1.94–2.00 (4H, m, $-CH_2$), 2.92 (1H, m, –CH), 3.48, 3.59 (4H, m, $-CH_2$), 6.90–7.92 (3H, m, ArH); Elemental Analysis: Calc. C = 60.69, H = 5.37, N = 13.39, Found C = 60.72, H = 5.30, N = 13.36.

*4.6.6. 4OMe-Urea derivative of $G^1G^2F^3P^4$-Heterocycle 1 (**16**)*

IR ν_{max} (nujol): 1638 (CO), 3304 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Urea = 8.03 (1H, s, NH), 7.79 (1H, m, NH), 6.94–7.99 (4H, m, ArH), 3.66 (3H, s, OMe); –NH = 8.14–8.44 (2H, s); Gly^1 = 3.90 (2H, s, $-^{\alpha}CH$); Gly^2 = 4.14 (2H, s, $-^{\alpha}CH$); Phe^3 = 3.49, 3.60 (2H, d, $-^{\beta}CH_2$), 4.90 (1H, t, $-^{\alpha}CH$); 6.92–7.94 (5H, m, ArH); Pro^4 = 2.01–3.94 (6H, m, $-CH_2$), 4.64 (1H, m, $-^{\alpha}CH$); Heterocycle = 1.96–2.04 (4H, m, $-CH_2$), 2.95 (1H, m, –CH), 3.42, 3.56 (4H, m, $-CH_2$), 6.94–7.99 (3H, m, ArH); Elemental Analysis: Calc. C = 62.71, H = 5.82, N = 13.47, Found C = 62.75, H = 5.80, N = 13.51.

*4.6.7. 2F-Urea derivative of $G^1V^2G^3V^4P^5$-Heterocycle 1 (**17**)*

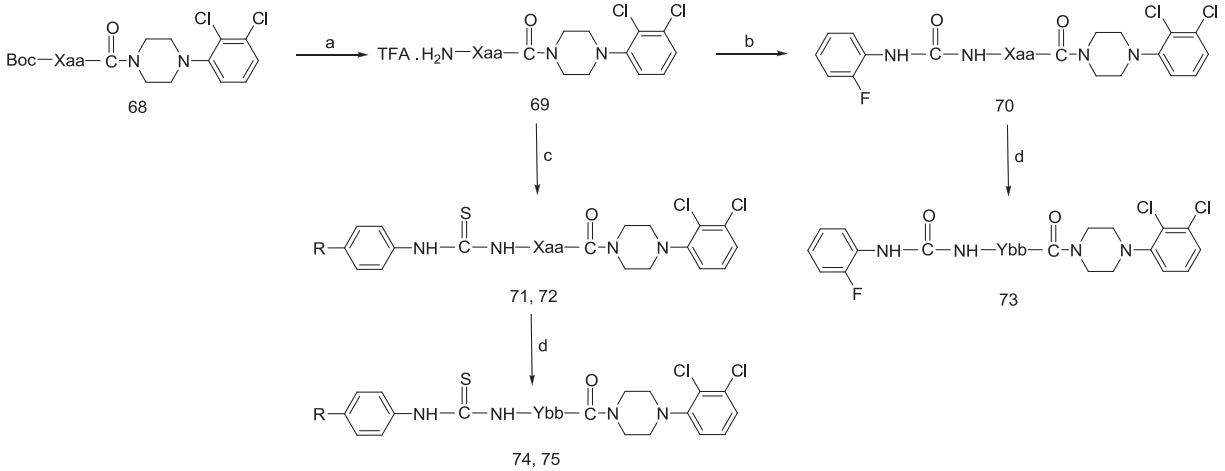
IR ν_{max} (nujol): 1698 (CO), 3300 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Urea = 8.07 (1H, s, NH), 7.59 (1H, m, NH), 6.77–7.68 (4H, m, ArH); –NH = 8.02–8.05 (3H, s); Gly^1 = 3.84 (2H, s, $-^{\alpha}CH$); Val^2 = 0.97 (6H, m, $-(CH_3)_2$), 2.79 (1H, m, $-^{\beta}CH$), 4.70 (1H, s, $-^{\alpha}CH$); Gly^3 = 4.10 (2H, s, $-^{\alpha}CH$); Val^4 = 0.99 (6H, m, $-(CH_3)_2$), 2.93 (1H, m, $-^{\beta}CH$), 4.90 (1H, s, $-^{\alpha}CH$); Pro^5 = 2.15–3.46 (6H, m, $-CH_2$), 4.32 (1H, m, $-^{\alpha}CH$); Heterocycle = 1.92–2.09 (4H, m, $-CH_2$), 2.81 (1H, m, –CH), 3.62, 3.73 (4H, m, $-CH_2$), 6.77–7.68 (3H, m, ArH); Elemental Analysis: Calc. C = 59.52, H = 6.31, N = 14.61, Found C = 59.52, H = 6.29, N = 14.63.

*4.6.8. 4Cl-Urea derivative of $G^1V^2G^3V^4P^5$-Heterocycle 1 (**18**)*

IR ν_{max} (nujol): 1654 (CO), 3301 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Urea = 8.06 (1H, s, NH), 7.57 (1H, m, NH), 6.82–7.77 (4H, m, ArH); –NH = 8.00–8.06 (3H, s); Gly^1 = 3.82 (2H, s, $-^{\alpha}CH$); Val^2 = 0.98 (6H, m, $-(CH_3)_2$), 2.69 (1H, m, $-^{\beta}CH$), 4.75 (1H, s, $-^{\alpha}CH$); Gly^3 = 4.13 (2H, s, $-^{\alpha}CH$); Val^4 = 0.97 (6H, m, $-(CH_3)_2$), 2.96 (1H, m, $-^{\beta}CH$), 4.95 (1H, s, $-^{\alpha}CH$); Pro^5 = 2.10–3.44 (6H, m, $-CH_2$), 4.30 (1H, m, $-^{\alpha}CH$); Heterocycle = 1.90–2.10 (4H, m, $-CH_2$), 2.85 (1H, m, –CH), 3.60, 3.74 (4H, m, $-CH_2$), 6.82–7.77 (3H, m, ArH); Elemental Analysis: Calc. C = 58.27, H = 6.18, N = 14.31, Found C = 58.25, H = 6.15, N = 14.33.

*4.6.9. 4OMe-Urea derivative of $G^1V^2G^3V^4P^5$-Heterocycle 1 (**19**)*

IR ν_{max} (nujol): 1624 (CO), 3299 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Urea = 8.02 (1H, s, NH), 7.68 (1H, m, NH), 6.75–7.66 (4H, m, ArH), 3.69 (3H, s, OMe); –NH = 8.02 (3H, s); Gly^1 = 3.87 (2H, s, $-^{\alpha}CH$); Val^2 = 1.07 (6H, m, $-(CH_3)_2$), 2.86 (1H, m, $-^{\beta}CH$), 4.63 (1H, s, $-^{\alpha}CH$); Gly^3 = 4.08 (2H, s, $-^{\alpha}CH$); Val^4 = 1.09 (6H, m, $-(CH_3)_2$), 2.96 (1H, m, $-^{\beta}CH$), 4.88 (1H, s, $-^{\alpha}CH$); Pro^5 = 2.14–3.42 (6H, m, $-CH_2$), 4.31 (1H, m, $-^{\alpha}CH$); Heterocycle = 1.97–2.07 (4H, m, $-CH_2$), 2.86



Scheme 4. Schematic representation of the synthesis of uriedo/thiouriedo derivatives of tricosamer conjugated heterocycle 2. Reagents and conditions: (a) TFA, 40 min, rt (b) 2F–Ph–N═C═O, NMM/THF, 8 h, 0 °C to rt (c) R–N═C═S, NMM/THF, 8 h, 0 °C to rt (d) Polymer supported $HCOO^-NH_3^+$/10% Pd–C; R = Cl, OMe where Xaa = GE(OcHx)GFP GVGVP GVGFP GFGFP GVGVP GVGFP; Ybb = GEGFP GVGVP GVGFP GFGFP GVGVP GVGFP.

(1H, m, –CH), 3.65, 3.75 (4H, m, $-CH_2$), 6.75–7.66 (3H, m, ArH); Elemental Analysis: Calc. C = 60.14, H = 6.60, N = 14.39, Found C = 60.17, H = 6.57, N = 14.37.

*4.6.10. 2F-Urea derivative of $G^1F^2G^3F^4P^5$-Heterocycle 1 (**20**)*

IR ν_{max} (nujol): 1634 (CO), 3280 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Urea = 8.18 (1H, s, NH), 7.97 (1H, m, NH), 7.13–7.90 (4H, m, ArH); –NH = 8.04–8.12 (3H, s); Gly^1 = 3.81 (2H, s, $-^{\alpha}CH$); Phe^2 = 3.50, 3.60 (2H, m, $-^{\beta}CH_2$), 4.53 (1H, s, $-^{\alpha}CH$), 7.13–7.90 (5H, m, ArH); Gly^3 = 4.28 (2H, s, $-^{\alpha}CH$); Phe^4 = 3.33, 3.72 (2H, m, $-^{\beta}CH_2$), 4.84 (1H, s, $-^{\alpha}CH$), 7.13–7.90 (5H, m, ArH); Pro^5 = 2.11–3.68 (6H, m, $-CH_2$), 4.36 (1H, m, $-^{\alpha}CH$); Heterocycle = 1.86 (4H, m, $-CH_2$), 2.89 (1H, m, –CH), 3.77, 3.92 (4H, m, $-CH_2$), 7.13–7.90 (3H, m, ArH); Elemental Analysis: Calc. C = 64.03, H = 5.61, N = 12.99, Found C = 64.02, H = 5.58, N = 12.98.

*4.6.11. 4Cl-Urea derivative of $G^1F^2G^3F^4P^5$-Heterocycle 1 (**21**)*

IR ν_{max} (nujol): 1635 (CO), 3294 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Urea = 8.20 (1H, s, NH), 7.92 (1H, m, NH), 7.09–7.78 (4H, m, ArH); –NH = 8.00–8.14 (3H, s); Gly^1 = 3.85 (2H, s, $-^{\alpha}CH$); Phe^2 = 3.55, 3.62 (2H, m, $-^{\beta}CH_2$), 4.49 (1H, s, $-^{\alpha}CH$), 7.09–7.78 (5H, m, ArH); Gly^3 = 4.26 (2H, s, $-^{\alpha}CH$); Phe^4 = 3.31, 3.70 (2H, m, $-^{\beta}CH_2$), 4.80 (1H, s, $-^{\alpha}CH$), 7.09–7.78 (5H, m, ArH); Pro^5 = 2.09–3.72 (6H, m, $-CH_2$), 4.39 (1H, m, $-^{\alpha}CH$); Heterocycle = 1.84 (4H, m, $-CH_2$), 2.90 (1H, m, –CH), 3.72, 3.90 (4H, m, $-CH_2$), 7.09–7.78 (3H, m, ArH); Elemental Analysis: Calc. C = 62.83, H = 5.50, N = 12.74, Found C = 62.81, H = 5.48, N = 12.75.

*4.6.12. 4OMe-Urea derivative of $G^1F^2G^3F^4P^5$-Heterocycle 1 (**22**)*

IR ν_{max} (nujol): 1634 (CO), 3296 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Urea = 8.15 (1H, s, NH), 7.96 (1H, m, NH), 7.10–7.82 (4H, m, ArH), 3.65 (3H, s, OMe); –NH = 8.04–8.13 (3H, s); Gly^1 = 3.86 (2H, s, $-^{\alpha}CH$); Phe^2 = 3.52, 3.60 (2H, m, $-^{\beta}CH_2$), 4.44 (1H, s, $-^{\alpha}CH$), 7.10–7.82 (5H, m, ArH); Gly^3 = 4.25 (2H, s, $-^{\alpha}CH$); Phe^4 = 3.33, 3.65 (2H, m, $-^{\beta}CH_2$), 4.78 (1H, s, $-^{\alpha}CH$), 7.10–7.82 (5H, m, ArH); Pro^5 = 2.12–3.73 (6H, m, $-CH_2$), 4.40 (1H, m, $-^{\alpha}CH$); Heterocycle = 1.82 (4H, m, $-CH_2$), 2.93 (1H, m, –CH), 3.69, 3.88 (4H, m, $-CH_2$), 7.10–7.82 (3H, m, ArH); Elemental Analysis: Calc. C = 64.52, H = 5.88, N = 12.81, Found C = 64.55, H = 5.83, N = 12.83.

*4.6.13. 2F-Thiourea derivative of Trp-Heterocycle 1 (**23**)*

IR ν_{max} (nujol): 1614 (CO), 2119 (CS), 3307 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Thiourea = 8.79 (1H, s, NH), 8.03 (1H, m, NH), 7.10–7.89 (4H, m, ArH); Trp = 3.59–3.73 (2H, d, $-^{\beta}CH_2$), 4.64 (1H, t, $-^{\alpha}CH$), 7.00 (1H, s, –CH of indole), 7.06–7.85 (4H, m, ArH), Exchanged (–NH of indole); Heterocycle = 1.95–1.99 (4H, m, $-CH_2$), 2.99 (1H, m, –CH), 3.84–3.88 (4H, m, $-CH_2$), 7.10–7.89 (3H, m, ArH); Elemental Analysis: Calc. C = 64.39, H = 4.86, N = 12.51, S = 5.73, Found C = 64.41, H = 4.90, N = 12.48, S = 5.73.

*4.6.14. 4Cl-Thiourea derivative of $G^1G^2I^3P^4$-Heterocycle 1 (**24**)*

IR ν_{max} (nujol): 1644 (CO), 2139 (CS), 3301 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Thiourea = 8.85 (1H, s, NH), 8.04 (1H, m, NH), 7.02–7.87 (4H, m, ArH); –NH = 7.95–8.02 (2H, m); Gly^1 = 3.97 (2H, s, $-^{\alpha}CH$); Gly^2 = 4.22 (2H, s, $-^{\alpha}CH$); Ile^3 = 0.90–1.00 (6H, m, $-(CH_3)_2$), 1.41 (2H, m, $-^{\gamma}CH_2$), 2.17 (1H, m, $-^{\beta}CH$), 4.71 (1H, m, $-^{\alpha}CH$); Pro^4 = 1.94–3.67 (6H, m, $-CH_2$), 4.65 (1H, m, $-^{\alpha}CH$); Heterocycle = 1.87,1.99 (4H, m, $-CH_2$), 2.83 (1H, m, –CH), 3.66 (4H, m, $-CH_2$), 7.02–7.87 (3H, m, ArH); Elemental Analysis: Calc. C = 57.72, H = 5.95, N = 13.46, S = 4.40, Found C = 57.75, H = 5.98, N = 13.43, S = 4.42.

*4.6.15. 4OMe-Thiourea derivative of $G^1G^2I^3P^4$-Heterocycle 1 (**25**)*

IR ν_{max} (nujol): 1605 (CO), 2125 (CS), 3286 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Thiourea = 8.79 (1H, s, NH), 8.02 (1H, m, NH), 7.10–7.90 (4H, m, ArH), 3.65 (3H, s, OMe); –NH = 8.04–8.14 (2H, m); Gly^1 = 3.90 (2H, s, $-^{\alpha}CH$); Gly^2 = 4.24 (2H, s, $-^{\alpha}CH$); Ile^3 = 0.95–1.07 (6H, m, $-(CH_3)_2$), 1.49 (2H, m, $-^{\gamma}CH_2$), 2.20 (1H, m, $-^{\beta}CH$), 4.72 (1H, m, $-^{\alpha}CH$); Pro^4 = 1.92–3.62 (6H, m, $-CH_2$), 4.70 (1H, m, $-^{\alpha}CH$); Heterocycle = 1.90,2.03 (4H, m, $-CH_2$), 2.85 (1H, m, –CH), 3.70 (4H, m, $-CH_2$), 7.10–7.90 (3H, m, ArH); Elemental Analysis: Calc. C = 59.73, H = 6.41, N = 13.55, S = 4.43, Found C = 59.70, H = 6.38, N = 13.53, S = 4.45.

*4.6.16. 2F-Thiourea derivative of $G^1G^2F^3P^4$-Heterocycle 1 (**26**)*

IR ν_{max} (nujol): 1641 (CO), 2027 (CS), 3281 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Thiourea = 8.88 (1H, s, NH), 8.02 (1H, m, NH), 6.97–7.95 (4H, m, ArH); –NH = 8.11–8.50 (2H, s); Gly^1 = 3.80 (2H, s, $-^{\alpha}CH$); Gly^2 = 4.07 (2H, s, $-^{\alpha}CH$); Phe^3 = 3.57, 3.70 (2H, d, $-^{\beta}CH_2$), 4.91 (1H, t, $-^{\alpha}CH$); 6.97–7.95 (5H, m, ArH); Pro^4 = 2.01–3.98 (6H, m, $-CH_2$), 4.62 (1H, m, $-^{\alpha}CH$); Heterocycle = 1.88–1.96 (4H, m, $-CH_2$), 2.96 (1H, m, –CH), 3.49, 3.57 (4H, m, $-CH_2$), 6.97–7.95 (3H, m, ArH); Elemental Analysis: Calc. C = 60.73, H = 5.37, N = 13.40, S = 4.38, Found C = 60.59, H = 5.35, N = 13.37, S = 4.35.

*4.6.17. 4Cl-Thiourea derivative of $G^1G^2F^3P^4$-Heterocycle 1 (**27**)*

IR ν_{max} (nujol): 1618 (CO), 2039 (CS), 3280 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Thiourea = 8.86 (1H, s, NH), 8.07 (1H, m, NH), 6.94–7.92 (4H, m, ArH); –NH = 8.08–8.49 (2H, s); Gly^1 = 3.79 (2H, s, $-^{\alpha}CH$); Gly^2 = 4.10 (2H, s, $-^{\alpha}CH$); Phe^3 = 3.52, 3.74 (2H, d, $-^{\beta}CH_2$), 4.95 (1H, t, $-^{\alpha}CH$); 6.94–7.92 (5H, m, ArH); Pro^4 = 2.04–3.96 (6H, m, $-CH_2$), 4.65 (1H, m, $-^{\alpha}CH$); Heterocycle = 1.82–1.91 (4H, m, $-CH_2$), 2.94 (1H, m, –CH), 3.45, 3.53 (4H, m, $-CH_2$), 6.94–7.92 (3H, m, ArH); Elemental Analysis: Calc. C = 59.39, H = 5.25, N = 13.10, S = 4.29, Found C = 59.36, H = 5.18, N = 13.14, S = 4.30.

*4.6.18. 4OMe-Thiourea derivative of $G^1G^2F^3P^4$-Heterocycle 1 (**28**)*

IR ν_{max} (nujol): 1625 (CO), 2041 (CS), 3275 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Thiourea = 8.80 (1H, s, NH), 8.09 (1H, m, NH), 6.96–7.94 (4H, m, ArH), 3.61 (3H, s, OMe); –NH = 8.06–8.42 (2H, s); Gly^1 = 3.83 (2H, s, $-^{\alpha}CH$); Gly^2 = 4.14 (2H, s, $-^{\alpha}CH$); Phe^3 = 3.50, 3.77 (2H, d, $-^{\beta}CH_2$), 4.94 (1H, t, $-^{\alpha}CH$); 6.96–7.94 (5H, m, ArH); Pro^4 = 2.00–3.91 (6H, m, $-CH_2$), 4.64 (1H, m, $-^{\alpha}CH$); Heterocycle = 1.80–1.94 (4H, m, $-CH_2$), 2.99 (1H, m, –CH), 3.44, 3.58 (4H, m, $-CH_2$), 6.96–7.94 (3H, m, ArH); Elemental Analysis: Calc. C = 61.36, H = 5.69, N = 13.18, S = 4.31, Found C = 61.40, H = 5.68, N = 13.20, S = 4.30.

*4.6.19. 2F-Thiourea derivative of $G^1V^2G^3V^4P^5$-Heterocycle 1 (**29**)*

IR ν_{max} (nujol): 1633 (CO), 2134 (CS), 3285 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Thiourea = 8.79 (1H, s, NH), 8.13 (1H, m, NH), 6.89–7.72 (4H, m, ArH); –NH = 8.01–8.09 (3H, s); Gly^1 = 3.86 (2H, s, $-^{\alpha}CH$); Val^2 = 1.02 (6H, m, $-(CH_3)_2$), 2.78 (1H, m, $-^{\beta}CH$), 4.72 (1H, s, $-^{\alpha}CH$); Gly^3 = 4.14 (2H, s, $-^{\alpha}CH$); Val^4 = 1.00 (6H, m, $-(CH_3)_2$), 2.96 (1H, m, $-^{\beta}CH$), 4.95 (1H, s, $-^{\alpha}CH$); Pro^5 = 2.10–3.47 (6H, m, $-CH_2$), 4.37 (1H, m, $-^{\alpha}CH$); Heterocycle = 1.90–2.11 (4H, m, $-CH_2$), 2.85 (1H, m, –CH), 3.59, 3.72 (4H, m, $-CH_2$), 6.89–7.72 (3H, m, ArH); Elemental Analysis: Calc. C = 58.30, H = 6.18, N = 14.31, S = 4.10, Found C = 58.34, H = 6.15, N = 14.33, S = 4.11.

*4.6.20. 4Cl-Thiourea derivative of $G^1V^2G^3V^4P^5$-Heterocycle 1 (**30**)*

IR ν_{max} (nujol): 1648 (CO), 2129 (CS), 3272 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Thiourea = 8.82 (1H, s, NH), 8.14 (1H, m, NH), 6.86–7.70 (4H, m, ArH); –NH = 8.02–8.11 (3H, s); Gly^1 = 3.88 (2H, s, $-^{\alpha}CH$); Val^2 = 1.01 (6H, m, $-(CH_3)_2$), 2.74 (1H, m, $-^{\beta}CH$), 4.70 (1H, s, $-^{\alpha}CH$); Gly^3 = 4.10 (2H, s, $-^{\alpha}CH$); Val^4 = 0.99 (6H, m, $-(CH_3)_2$), 2.95 (1H, m, $-^{\beta}CH$), 4.94 (1H, s, $-^{\alpha}CH$); Pro^5 = 2.13–3.49 (6H, m,

$-CH_2$), 4.34 (1H, m, $-^{\alpha}CH$); Heterocycle = 1.89–2.10 (4H, m, $-CH_2$), 2.81 (1H, m, −CH), 3.57, 3.75 (4H, m, $-CH_2$), 6.86–7.70 (3H, m, ArH); Elemental Analysis: Calc. C = 57.10, H = 6.05, N = 14.02, S = 4.01, Found C = 57.10, H = 6.04, N = 14.05, S = 4.02.

4.6.21. 4OMe-Thiourea derivative of $G^1V^2G^3V^4P^5$-Heterocycle 1 (**31**)

IR ν_{max} (nujol): 1630 (CO), 2119 (CS), 3265 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Thiourea = 8.80 (1H, s, NH), 8.12 (1H, m, NH), 6.80–7.74 (4H, m, ArH), 3.62 (3H, s, OMe); −NH = 8.03–8.10 (3H, s); Gly^1 = 3.84 (2H, s, $-^{\alpha}CH$); Val^2 = 0.98 (6H, m, $-(CH_3)_2$), 2.71 (1H, m, $-^{\beta}CH$), 4.74 (1H, s, $-^{\alpha}CH$); Gly^3 = 4.14 (2H, s, $-^{\alpha}CH$); Val^4 = 1.00 (6H, m, $-(CH_3)_2$), 2.94 (1H, m, $-^{\beta}CH$), 4.92 (1H, s, $-^{\alpha}CH$); Pro^5 = 2.10–3.52 (6H, m, $-CH_2$), 4.33 (1H, m, $-^{\alpha}CH$); Heterocycle = 1.90–2.12 (4H, m, $-CH_2$), 2.84 (1H, m, −CH), 3.60, 3.72 (4H, m, $-CH_2$), 6.80–7.74 (3H, m, ArH); Elemental Analysis: Calc. C = 58.93, H = 6.47, N = 14.10, S = 4.03, Found C = 58.97, H = 6.44, N = 14.12, S = 4.06.

4.6.22. 2F-Thiourea derivative of $G^1F^2G^3F^4P^5$-Heterocycle 1 (**32**)

IR ν_{max} (nujol): 1628 (CO), 2028 (CS), 3280 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Thiourea = 8.74 (1H, s, NH), 8.10 (1H, m, NH), 7.11–7.85 (4H, m, ArH); −NH = 8.01–8.10 (3H, s); Gly^1 = 3.79 (2H, s, $-^{\alpha}CH$); Phe^2 = 3.51, 3.60 (2H, m, $-^{\beta}CH_2$), 4.56 (1H, s, $-^{\alpha}CH$), 7.11–7.85 (5H, m, ArH); Gly^3 = 4.29 (2H, s, $-^{\alpha}CH$); Phe^4 = 3.33, 3.78 (2H, m, $-^{\beta}CH_2$), 4.87 (1H, s, $-^{\alpha}CH$), 7.11–7.85 (5H, m, ArH); Pro^5 = 2.16–3.68 (6H, m, $-CH_2$), 4.38 (1H, m, $-^{\alpha}CH$); Heterocycle = 1.82 (4H, m, $-CH_2$), 2.88 (1H, m, −CH), 3.79, 3.90 (4H, m, $-CH_2$), 7.11–7.85 (3H, m, ArH); Elemental Analysis: Calc. C = 62.86, H = 5.50, N = 12.75, S = 3.65, Found C = 62.85, H = 5.48, N = 12.95, S = 3.74.

4.6.23. 4Cl-Thiourea derivative of $G^1F^2G^3F^4P^5$-Heterocycle 1 (**33**)

IR ν_{max} (nujol): 1620 (CO), 2044 (CS), 3310 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Thiourea = 8.80 (1H, s, NH), 8.12 (1H, m, NH), 7.22–7.79 (4H, m, ArH); −NH = 8.04–8.12 (3H, s); Gly^1 = 3.83 (2H, s, $-^{\alpha}CH$); Phe^2 = 3.54, 3.62 (2H, m, $-^{\beta}CH_2$), 4.52 (1H, s, $-^{\alpha}CH$), 7.22–7.79 (5H, m, ArH); Gly^3 = 4.25 (2H, s, $-^{\alpha}CH$); Phe^4 = 3.30, 3.72 (2H, m, $-^{\beta}CH_2$), 4.84 (1H, s, $-^{\alpha}CH$), 7.22–7.79 (5H, m, ArH); Pro^5 = 2.11–3.72 (6H, m, $-CH_2$), 4.39 (1H, m, $-^{\alpha}CH$); Heterocycle = 1.84 (4H, m, $-CH_2$), 2.85 (1H, m, −CH), 3.73, 3.89 (4H, m, $-CH_2$), 7.22–7.79 (3H, m, ArH); Elemental Analysis: Calc. C = 61.70, H = 5.40, N = 12.51, S = 3.58, Found C = 61.73, H = 5.38, N = 12.83, S = 3.59.

4.6.24. 4OMe-Thiourea derivative of $G^1F^2G^3F^4P^5$-Heterocycle 1 (**34**)

IR ν_{max} (nujol): 1638 (CO), 2021 (CS), 3254 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Thiourea = 8.78 (1H, s, NH), 8.14 (1H, m, NH), 7.05–7.68 (4H, m, ArH), 3.67 (3H, s, OMe); −NH = 8.00–8.12 (3H, s); Gly^1 = 3.87 (2H, s, $-^{\alpha}CH$); Phe^2 = 3.50, 3.69 (2H, m, $-^{\beta}CH_2$), 4.46 (1H, s, $-^{\alpha}CH$), 7.05–7.68 (5H, m, ArH); Gly^3 = 4.22 (2H, s, $-^{\alpha}CH$); Phe^4 = 3.34, 3.74 (2H, m, $-^{\beta}CH_2$), 4.82 (1H, s, $-^{\alpha}CH$), 7.05–7.68 (5H, m, ArH); Pro^5 = 2.13–3.68 (6H, m, $-CH_2$), 4.41 (1H, m, $-^{\alpha}CH$); Heterocycle = 1.80 (4H, m, $-CH_2$), 2.81 (1H, m, −CH), 3.70, 3.83 (4H, m, $-CH_2$), 7.05–7.68 (3H, m, ArH); Elemental Analysis: Calc. C = 63.35, H = 5.77, N = 12.58, S = 3.60, Found C = 63.59, H = 5.75, N = 12.60, S = 3.57.

4.6.25. 2F-Urea derivative of GE(OcHx)GFPGVGVPGVGVPGVGVPGFG FPGFGFP-Heterocycle 1 (**40**)

IR ν_{max} (nujol): 1621 (CO), 3327 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Urea = 8.17 (1H, s, NH), 8.02 (1H, m, NH), 7.02–7.86 (4H, m, ArH); −NH = 7.98–8.01 (24H, m); Gly = 4.03, 4.84 (24H, m, $-^{\alpha}CH$); Val = 1.00, 1.03 (36H, m, $(-CH_3)_2$), 2.43, 2.60 (6H, m, $-^{\beta}CH$), 4.44 (6H, m, $-^{\alpha}CH$); Glu = 1.18–1.29 (10H, m, $-CH_2$ of cyclohexyl ring), 2.05, 2.10 (4H, m, $-^{\beta,\gamma}CH_2$), 3.76 (1H, m, −CH of cyclohexyl ring), 4.75 (1H, m, $-^{\alpha}CH$); Phe = 3.55, 3.78 (10H, m, $-^{\beta}CH_2$), 4.20, 4.63 (5H, m, $-^{\alpha}CH$), 7.02–7.86 (25H, m, ArH); Pro = 1.98, 3.64, 3.70 (36H, m, $-CH_2$), 4.68 (6H, m, $-^{\alpha}CH$); Heterocycle = 1.95, 1.97 (4H, m, $-CH_2$), 2.99 (1H, m, −CH), 3.64, 3.68 (4H, m, $-CH_2$), 7.02–7.86 (3H, m, ArH); Elemental Analysis: Calc. C = 61.59, H = 6.81, N = 14.46, Found C = 61.51, H = 6.89, N = 14.40.

4.6.26. 4Cl-Thiourea derivative of GE(OcHx)GFPGVGVPGVGVPGVG VPGFGFPGFGFP-Heterocycle 1 (**41**)

IR ν_{max} (nujol): 1616 (CO), 2124 (CS), 3297 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Thiourea = 8.87 (1H, s, NH), 8.14 (1H, m, NH), 7.14–7.92 (4H, m, ArH); −NH = 8.02–8.13 (24H, m); Gly = 4.00, 4.81 (24H, m, $-^{\alpha}CH$); Val = 0.89, 0.98 (36H, m, $(-CH_3)_2$), 2.41, 2.67 (6H, m, $-^{\beta}CH$), 4.41 (6H, m, $-^{\alpha}CH$); Glu = 1.15–1.27 (10H, m, $-CH_2$ of cyclohexyl ring), 2.03, 2.08 (4H, m, $-^{\beta,\gamma}CH_2$), 3.73 (1H, m, −CH of cyclohexyl ring), 4.77 (1H, m, $-^{\alpha}CH$); Phe = 3.50, 3.77 (10H, m, $-^{\beta}CH_2$), 4.19, 4.60 (5H, m, $-^{\alpha}CH$), 7.14–7.92 (25H, m, ArH); Pro = 1.96, 3.60, 3.75 (36H, m, $-CH_2$), 4.72 (6H, m, $-^{\alpha}CH$); Heterocycle = 1.97, 1.99 (4H, m, $-CH_2$), 2.85 (1H, m, −CH), 3.66, 3.70 (4H, m, $-CH_2$), 7.14–7.92 (3H, m, ArH); Elemental Analysis: Calc. C = 59.37, H = 6.57, N = 13.94, S = 1.00, Found C = 59.39, H = 6.50, N = 13.88, S = 0.99.

4.6.27. 4OMe-Thiourea derivative of GE(OcHx)GFPGVGVPGVGVPGV GVPGFGFPGFGFP-Heterocycle 1 (**42**)

IR ν_{max} (nujol): 1630 (CO), 2129 (CS), 3321 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Thiourea = 8.88 (1H, s, NH), 8.13 (1H, m, NH), 7.06–7.98 (4H, m, ArH), 3.64 (3H, m, OMe); −NH = 8.00–8.13 = 1 (24H, m); Gly = 3.99, 4.79 (24H, m, $-^{\alpha}CH$); Val = 0.92, 1.05 (36H, m, $(-CH_3)_2$), 2.44, 2.68 (6H, m, $-^{\beta}CH$), 4.45 (6H, m, $-^{\alpha}CH$); Glu = 1.12–1.27 (10H, m, $-CH_2$ of cyclohexyl ring), 2.04, 2.07 (4H, m, $-^{\beta,\gamma}CH_2$), 3.76 (1H, m, −CH of cyclohexyl ring), 4.79 (1H, m, $-^{\alpha}CH$); Phe = 3.52, 3.79 (10H, m, $-^{\beta}CH_2$), 4.20, 4.65 (5H, m, $-^{\alpha}CH$), 7.06–7.98 (25H, m, ArH); Pro = 1.97, 3.63, 3.77 (36H, m, $-CH_2$), 4.75 (6H, m, $-^{\alpha}CH$); Heterocycle = 1.94, 1.98 (4H, m, $-CH_2$), 2.86 (1H, m, −CH), 3.67, 3.72 (4H, m, $-CH_2$), 7.06–7.98 (3H, m, ArH); Elemental Analysis: Calc. C = 59.83, H = 6.67, N = 13.96, S = 1.10, Found C = 59.89, H = 6.72, N = 13.99, S = 1.01.

4.6.28. 2F-Urea derivative of Trp-Heterocycle 2 (**53**)

IR ν_{max} (nujol): 1624 (CO), 3327 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Urea = 8.19 (1H, s, NH), 8.05 (1H, m, NH), 7.12–7.96 (4H, m, ArH); Trp = 3.59–3.74 (2H, d, $-^{\beta}CH_2$), 4.71 (1H, t, $-^{\alpha}CH$), 6.94 (1H, s, −CH of indole), 7.12–7.96 (4H, m, ArH), Exchanged (−NH of indole); Heterocycle = 3.70–3.93 (4H, m, $-CH_2$), 7.12–7.96 (3H, m, ArH); Elemental Analysis: Calc. C = 60.66, H = 4.73, N = 12.63, Found C = 60.62, H = 4.75, N = 12.66.

4.6.29. 2F-Urea derivative of $G^1G^2I^3P^4$-Heterocycle 2 (**54**)

IR ν_{max} (nujol): 1620 (CO), 3296 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Urea = 8.17 (1H, s, NH), 7.97 (1H, m, NH), 7.02–7.84 (4H, m, ArH); −NH = 8.07–8.17 (2H, m); Gly^1 = 3.94 (2H, s, $-^{\alpha}CH$); Gly^2 = 4.59 (2H, s, $-^{\alpha}CH$); Ile^3 = 0.88–0.91 (6H, m, $-(CH_3)_2$), 1.45 (2H, m, $-^{\gamma}CH_2$), 2.13 (1H, m, $-^{\beta}CH$), 4.63 (1H, m, $-^{\alpha}CH$); Pro^4 = 1.95–3.59 (6H, m, $-CH_2$), 4.58 (1H, m, $-^{\alpha}CH$); Heterocycle = 3.70,3.95 (8H, m, $-CH_2$), 7.02–7.84 (3H, m, ArH); Elemental Analysis: Calc. C = 56.09, H = 5.99, N = 13.88, Found C = 56.05, H = 6.01, N = 13.84.

4.6.30. 4Cl-Urea derivative of $G^1G^2F^3P^4$-Heterocycle 2 (**55**)

IR ν_{max} (nujol): 1624 (CO), 3318 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Urea = 8.18 (1H, s, NH), 7.97 (1H, m, NH), 6.79–7.63 (4H, m, ArH); −NH = 7.95–8.13 (2H, s); Gly^1 = 3.85 (2H, s, $-^{\alpha}CH$); Gly^2 = 3.93 (2H, s, $-^{\alpha}CH$); Phe^3 = 3.16, 3.55 (2H, d, $-^{\beta}CH_2$), 4.91 (1H, t, $-^{\alpha}CH$); 6.79–7.63 (5H, m, ArH); Pro^4 = 1.90–3.66 (6H, m, $-CH_2$),

4.81 (1H, m, $-^{\alpha}CH$); Heterocycle = 2.80–2.94 (4H, m, $-CH_2$), 6.79–7.63 (3H, m, ArH); Elemental Analysis: Calc. C = 56.57, H = 5.15, N = 13.19, Found C = 56.60, H = 5.13, N = 13.16.

*4.6.31. 4OMe-Urea derivative of $G^1G^2F^3P^4$-Heterocycle 2 (**56**)*

IR ν_{max} (nujol): 1629 (CO), 3307 (NH); ^1H NMR data ($CDCl_3$, δ ppm): Urea = 8.13 (1H, s, NH), 7.95 (1H, m, NH), 7.02–7.86 (4H, m, ArH), 3.61 (3H, s, OMe); −NH = 7.91–8.07 (2H, s); Gly^1 = 3.93 (2H, s, $-^{\alpha}CH$); Gly^2 = 4.10 (2H, s, $-^{\alpha}CH$); Phe^3 = 3.18, 3.58 (2H, d, $-^{\beta}CH_2$), 4.89 (1H, t, $-^{\alpha}CH$); 7.02–7.86 (5H, m, ArH); Pro^4 = 1.94–3.70 (6H, m, $-CH_2$), 4.90 (1H, m, $-^{\alpha}CH$); Heterocycle = 2.80–2.97 (4H, m, $-CH_2$), 7.02–7.86 (3H, m, ArH); Elemental Analysis: Calc. C = 58.54, H = 5.59, N = 13.27, Found C = 58.51, H = 5.61, N = 13.26.

*4.6.32. 2F-Urea derivative of $G^1V^2G^3V^4P^5$-Heterocycle 2 (**57**)*

IR ν_{max} (nujol): 1617 (CO), 3300 (NH); ^1H NMR data ($CDCl_3$, δ ppm): Urea = 8.10 (1H, s, NH), 7.84 (1H, m, NH), 7.01–7.94 (4H, m, ArH); −NH = 8.04–8.09 (3H, s); Gly^1 = 3.85 (2H, s, $-^{\alpha}CH$); Val^2 = 1.02 (6H, m, $(-CH_3)_2$), 2.54 (1H, m, $-^{\beta}CH$), 4.58 (1H, m, $-^{\alpha}CH$); Gly^3 = 4.17 (2H, s, $-^{\alpha}CH$); Val^4 = 0.99 (6H, m, $(-CH_3)_2$), 2.64 (1H, m, $-^{\beta}CH$), 4.53 (1H, m, $-^{\alpha}CH$); Pro^5 = 2.09–3.67 (6H, m, $-CH_2$), 4.54 (1H, m, $-^{\alpha}CH$); Heterocycle = 2.25–2.97 (8H, m, $-CH_2$), 7.01–7.94 (3H, m, ArH); Elemental Analysis: Calc. C = 55.60, H = 6.09, N = 14.41, Found C = 55.57, H = 6.12, N = 14.44.

*4.6.33. 2F-Urea derivative of $G^1F^2G^3F^4P^5$-Heterocycle 2 (**58**)*

IR ν_{max} (nujol): 1610 (CO), 3294 (NH); ^1H NMR data ($CDCl_3$, δ ppm): Urea = 8.06 (1H, s, NH), 7.81 (1H, m, NH), 6.99–7.92 (4H, m, ArH); −NH = 8.02–8.11 (3H, s); Gly^1 = 3.86 (2H, s, $-^{\alpha}CH$); Phe^2 = 3.58, 3.68 (2H, m, $-^{\beta}CH_2$), 4.62 (1H, m, $-^{\alpha}CH$), 6.99–7.92 (5H, m, ArH); Gly^3 = 4.14 (2H, s, $-^{\alpha}CH$); Phe^4 = 3.45, 3.67 (2H, m, $-^{\beta}CH_2$), 4.68 (1H, m, $-^{\alpha}CH$), 6.99–7.92 (5H, m, ArH); Pro^5 = 2.12–3.64 (6H, m, $-CH_2$), 4.50 (1H, m, $-^{\alpha}CH$); Heterocycle = 3.42–3.74 (8H, m, $-CH_2$), 6.99–7.92 (3H, m, ArH); Elemental Analysis: Calc. C = 60.48, H = 5.42, N = 12.82, Found C = 60.45, H = 5.39, N = 12.81.

*4.6.34. 2F-Thiourea derivative of Trp-Heterocycle 2 (**59**)*

IR ν_{max} (nujol): 1622 (CO), 2124 (CS), 3276 (NH); ^1H NMR data ($CDCl_3$, δ ppm): Thiourea = 8.79 (1H, s, NH), 8.11 (1H, m, NH), 7.04–7.92 (4H, m, ArH); Trp = 3.60–3.71 (2H, d, $-^{\beta}CH_2$), 4.74 (1H, t, $-^{\alpha}CH$), 6.98 (1H, s, −CH of indole), 7.04–7.92 (4H, m, ArH), Exchanged (−NH of indole); Heterocycle = 3.72–3.94 (4H, m, $-CH_2$), 7.04–7.92 (3H, m, ArH); Elemental Analysis: Calc. C = 58.95, H = 4.59, N = 12.28, S = 5.62, Found C = 58.99, H = 4.60, N = 12.31, S = 5.64.

*4.6.35. 4Cl-Thiourea derivative of $G^1G^2I^3P^4$-Heterocycle 2 (**60**)*

IR ν_{max} (nujol): 1618 (CO), 2118 (CS), 3308 (NH); ^1H NMR data ($CDCl_3$, δ ppm): Thiourea = 8.89 (1H, s, NH), 8.09 (1H, m, NH), 7.00–7.82 (4H, m, ArH); −NH = 8.01–8.08 (2H, m); Gly^1 = 3.93 (2H, s, $-^{\alpha}CH$); Gly^2 = 4.61 (2H, s, $-^{\alpha}CH$); Ile^3 = 0.86–0.90 (6H, m, $-(CH_3)_2$), 1.43 (2H, m, $-^{\gamma}CH_2$), 2.11 (1H, m, $-^{\beta}CH$), 4.61 (1H, m, $-^{\alpha}CH$); Pro^4 = 1.97–3.61 (6H, m, $-CH_2$), 4.56 (1H, m, $-^{\alpha}CH$); Heterocycle = 3.73, 3.97 (4H, m, $-CH_2$), 7.00–7.82 (3H, m, ArH); Elemental Analysis: Calc. C = 53.62, H = 5.73, N = 13.26, S = 4.34, Found C = 53.60, H = 5.72, N = 13.22, S = 4.38.

*4.6.36. 4OMe-Thiourea derivative of $G^1G^2I^3P^4$-Heterocycle 2 (**61**)*

IR ν_{max} (nujol): 1624 (CO), 2124 (CS), 3314 (NH); ^1H NMR data ($CDCl_3$, δ ppm): Thiourea = 8.91 (1H, s, NH), 8.12 (1H, m, NH), 7.05–7.89 (4H, m, ArH), 3.64 (3H, s, OMe); −NH = 8.03–8.11 (2H, m); Gly^1 = 3.97 (2H, s, $-^{\alpha}CH$); Gly^2 = 4.65 (2H, s, $-^{\alpha}CH$); Ile^3 = 0.82–0.94 (6H, m, $-(CH_3)_2$), 1.47 (2H, m, $-^{\gamma}CH_2$), 2.14 (1H, m, $-^{\beta}CH$), 4.64 (1H, m, $-^{\alpha}CH$); Pro^4 = 1.98–3.64 (6H, m, $-CH_2$), 4.58 (1H, m, $-^{\alpha}CH$); Heterocycle = 3.74, 3.99 (4H, m, $-CH_2$), 7.05–7.89 (3H, m, ArH); Elemental Analysis: Calc. C = 55.58, H = 6.17, N = 13.34, S = 4.36, Found C = 55.61, H = 6.21, N = 13.37, S = 4.33.

*4.6.37. 4Cl-Thiourea derivative of $G^1G^2F^3P^4$-Heterocycle 2 (**62**)*

IR ν_{max} (nujol): 1611 (CO), 2020 (CS), 3298 (NH); ^1H NMR data ($CDCl_3$, δ ppm): Thiourea = 8.78 (1H, s, NH), 8.08 (1H, m, NH), 6.74–7.69 (4H, m, ArH); −NH = 7.93–8.12 (2H, s); Gly^1 = 3.88 (2H, s, $-^{\alpha}CH$); Gly^2 = 3.97 (2H, s, $-^{\alpha}CH$); Phe^3 = 3.14, 3.58 (2H, d, $-^{\beta}CH_2$), 4.94 (1H, t, $-^{\alpha}CH$); 6.74–7.69 (5H, m, ArH); Pro^4 = 1.93–3.67 (6H, m, $-CH_2$), 4.85 (1H, m, $-^{\alpha}CH$); Heterocycle = 2.84–2.99 (4H, m, $-CH_2$), 6.74–7.69 (3H, m, ArH); Elemental Analysis: Calc. C = 55.37, H = 5.05, N = 12.92, S = 4.22, Found C = 55.38, H = 5.02, N = 12.95, S = 4.25.

*4.6.38. 4OMe-Thiourea derivative of $G^1G^2F^3P^4$-Heterocycle 2 (**63**)*

IR ν_{max} (nujol): 1604 (CO), 2014 (CS), 3325 (NH); ^1H NMR data ($CDCl_3$, δ ppm): Thiourea = 8.83 (1H, s, NH), 8.07 (1H, m, NH), 6.79–7.75 (4H, m, ArH), 3.59 (3H, s, Ome); −NH = 7.94–8.09 (2H, s); Gly^1 = 3.91 (2H, s, $-^{\alpha}CH$); Gly^2 = 4.05 (2H, s, $-^{\alpha}CH$); Phe^3 = 3.20, 3.60 (2H, d, $-^{\beta}CH_2$), 4.99 (1H, t, $-^{\alpha}CH$); 6.79–7.75 (5H, m, ArH); Pro^4 = 1.97–3.69 (6H, m, $-CH_2$), 4.88 (1H, m, $-^{\alpha}CH$); Heterocycle = 2.80–2.97 (4H, m, $-CH_2$), 6.79–7.75 (3H, m, ArH); Elemental Analysis: Calc. C = 57.29, H = 5.48, N = 12.99, S = 4.25, Found C = 57.32, H = 5.51, N = 12.96, S = 4.22.

*4.6.39. 4Cl-Thiourea derivative of $G^1V^2G^3V^4P^5$-Heterocycle 2 (**64**)*

IR ν_{max} (nujol): 1625 (CO), 2041 (CS), 3320 (NH); ^1H NMR data ($CDCl_3$, δ ppm): Thiourea = 8.83 (1H, s, NH), 8.14 (1H, m, NH), 7.04–7.88 (4H, m, ArH); −NH = 8.01–8.09 (3H, s); Gly^1 = 3.84 (2H, s, $-^{\alpha}CH$); Val^2 = 1.00 (6H, m, $(-CH_3)_2$), 2.56 (1H, m, $-^{\beta}CH$), 4.57 (1H, m, $-^{\alpha}CH$); Gly^3 = 4.15 (2H, s, $-^{\alpha}CH$); Val^4 = 0.97 (6H, m, $(-CH_3)_2$), 2.62 (1H, m, $-^{\beta}CH$), 4.54 (1H, m, $-^{\alpha}CH$); Pro^5 = 2.11–3.68 (6H, m, $-CH_2$), 4.57 (1H, m, $-^{\alpha}CH$); Heterocycle = 2.20–2.91 (8H, m, $-CH_2$), 7.04–7.88 (3H, m, ArH); Elemental Analysis: Calc. C = 53.37, H = 5.85, N = 13.83, S = 3.96, Found C = 53.40, H = 5.88, N = 13.88, S = 3.94.

*4.6.40. 4OMe-Thiourea derivative of $G^1V^2G^3V^4P^5$-Heterocycle 2 (**65**)*

IR ν_{max} (nujol): 1620 (CO), 2012 (CS), 3285 (NH); ^1H NMR data ($CDCl_3$, δ ppm): Thiourea = 8.89 (1H, s, NH), 8.17 (1H, m, NH), 7.07–7.96 (4H, m, ArH), 3.64 (3H, s, Ome); −NH = 8.08–8.22 (3H, s); Gly^1 = 3.88 (2H, s, $-^{\alpha}CH$); Val^2 = 1.07 (6H, m, $(-CH_3)_2$), 2.54 (1H, m, $-^{\beta}CH$), 4.53 (1H, m, $-^{\alpha}CH$); Gly^3 = 4.10 (2H, s, $-^{\alpha}CH$); Val^4 = 1.05 (6H, m, $(-CH_3)_2$), 2.68 (1H, m, $-^{\beta}CH$), 4.56 (1H, m, $-^{\alpha}CH$); Pro^5 = 2.10–3.67 (6H, m, $-CH_2$), 4.56 (1H, m, $-^{\alpha}CH$); Heterocycle = 2.16–2.94 (8H, m, $-CH_2$), 7.07–7.96 (3H, m, ArH); Elemental Analysis: Calc. C = 55.15, H = 6.25, N = 13.91, S = 3.98, Found C = 55.18, H = 6.28, N = 13.94, S = 3.97.

*4.6.41. 4Cl-Thiourea derivative of $G^1F^2G^3F^4P^5$-Heterocycle 2 (**66**)*

IR ν_{max} (nujol): 1632 (CO), 2029 (CS), 3310 (NH); ^1H NMR data ($CDCl_3$, δ ppm): Thiourea = 8.76 (1H, s, NH), 8.11 (1H, m, NH), 7.02–7.84 (4H, m, ArH); −NH = 8.01–8.39 (3H, s); Gly^1 = 3.83 (2H, s, $-^{\alpha}CH$); Phe^2 = 3.50, 3.63 (2H, m, $-^{\beta}CH_2$), 4.65 (1H, m, $-^{\alpha}CH$), 7.02–7.84 (5H, m, ArH); Gly^3 = 4.18 (2H, s, $-^{\alpha}CH$); Phe^4 = 3.47, 3.69 (2H, m, $-^{\beta}CH_2$), 4.70 (1H, m, $-^{\alpha}CH$), 7.02–7.84 (5H, m, ArH); Pro^5 = 2.10–3.66 (6H, m, $-CH_2$), 4.54 (1H, m, $-^{\alpha}CH$); Heterocycle = 3.40–3.79 (8H, m, $-CH_2$), 7.02–7.84 (3H, m, ArH); Elemental Analysis: Calc. C = 58.31, H = 5.23, N = 12.36, S = 3.54, Found C = 58.27, H = 5.26, N = 12.28, S = 3.51.

*4.6.42. 4OMe-Thiourea derivative of $G^1F^2G^3F^4P^5$-Heterocycle 2 (**67**)*

IR ν_{max} (nujol): 1611 (CO), 2033 (CS), 3296 (NH); ^1H NMR data ($CDCl_3$, δ ppm): Thiourea = 8.79 (1H, s, NH), 8.17 (1H, m, NH),

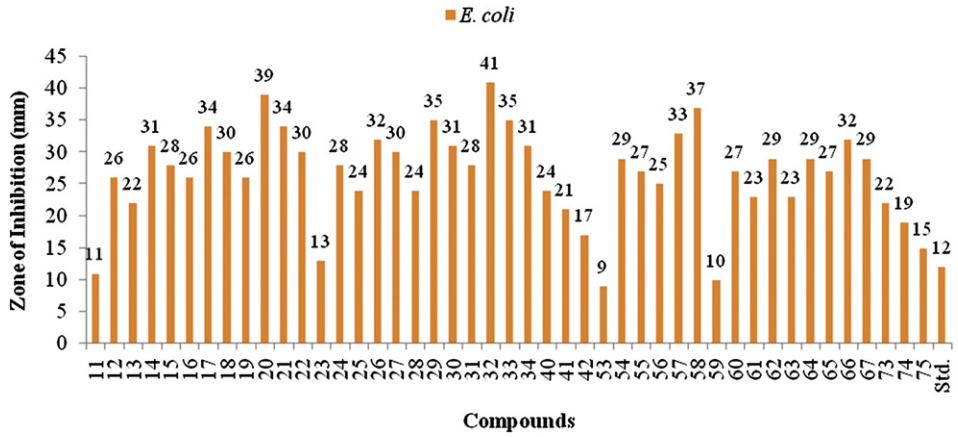


Fig. 1. Diagramatic representation of antibacterial activity of the compounds against *E. coli.*

7.11–7.90 (4H, m, ArH), 3.68 (3H, s, Ome); −NH = 8.04–8.40 (3H, s); Gly[1] = 3.87 (2H, s, $-^{\alpha}CH$); Phe[2] = 3.49, 3.67 (2H, m, $-^{\beta}CH_2$), 4.61 (1H, m, $-^{\alpha}CH$), 7.11–7.90 (5H, m, ArH); Gly[3] = 4.15 (2H, s, $-^{\alpha}CH$); Phe[4] = 3.44, 3.61 (2H, m, $-^{\beta}CH_2$), 4.75 (1H, m, $-^{\alpha}CH$), 7.11–7.90 (5H, m, ArH); Pro[5] = 2.08–3.61 (6H, m, $-CH_2$), 4.55 (1H, m, $-^{\alpha}CH$); Heterocycle = 3.44–3.80 (8H, m, $-CH_2$), 7.11–7.90 (3H, m, ArH); Elemental Analysis: Calc. C = 59.93, H = 5.59, N = 12.42, S = 3.56, Found C = 59.90, H = 5.55, N = 12.38, S = 3.53.

*4.6.43. 2F-Urea derivative of GE(OcHx)GFPGVGVPGVGFPGFGFPGVG VPGVGFP-Heterocycle 2 (**73**)*

IR ν_{max} (nujol): 1604 (CO), 3311 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Urea = 8.18 (1H, s, NH), 8.07 (1H, m, NH), 7.16–7.75 (4H, m, ArH); −NH = 8.04–8.17 (23H, m); Gly = 4.05, 4.94 (24H, m, $-^{\alpha}CH$); Val = 0.99, 1.02 (36H, m, $(-CH_3)_2$), 2.43, 2.64 (6H, m, $-^{\beta}CH$), 4.44 (6H, m, $-^{\alpha}CH$); Glu = 1.12–1.27 (10H, m, $-CH_2$ of cyclohexyl ring), 2.08, 2.20 (4H, m, $-^{\beta,\gamma}CH_2$), 3.74 (1H, m, −CH of cyclohexyl ring), 4.78 (1H, m, $-^{\alpha}CH$); Phe = 3.54, 3.76 (10H, m, $-^{\beta}CH_2$), 4.24, 4.66 (5H, m, $-^{\alpha}CH$), 7.16–7.75 (25H, m, ArH); Pro = 2.00, 3.54, 3.72 (36H, m, $-CH_2$), 4.72 (6H, m, $-^{\alpha}CH$); Heterocycle = 3.43, 3.60 (8H, m, $-CH_2$), 7.16–7.75 (3H, m, ArH); Elemental Analysis: Calc. C = 58.75, H = 6.58, N = 14.41, Found C = 58.79, H = 6.65, N = 14.50.

*4.6.44. 4Cl-Thiourea derivative of GE(OcHx)GFPGVGVPGVGFPGFGFP GVGVPGVGFP-Heterocycle 2 (**74**)*

IR ν_{max} (nujol): 1610 (CO), 2111 (CS), 3305 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Thiourea = 8.88 (1H, s, NH), 8.17 (1H, m, NH), 7.12–7.69 (4H, m, ArH); −NH = 8.02–8.16 (23H, m); Gly = 4.10, 4.93 (24H, m, $-^{\alpha}CH$); Val = 1.00, 1.05 (36H, m, $(-CH_3)_2$), 2.44, 2.68 (6H, m, $-^{\beta}CH$), 4.40 (6H, m, $-^{\alpha}CH$); Glu = 1.10–1.24 (10H, m, $-CH_2$ of cyclohexyl ring), 2.06, 2.22 (4H, m, $-^{\beta,\gamma}CH_2$), 3.72 (1H, m, −CH of cyclohexyl ring), 4.70 (1H, m, $-^{\alpha}CH$); Phe = 3.51, 3.74 (10H, m, $-^{\beta}CH_2$), 4.22, 4.64 (5H, m, $-^{\alpha}CH$), 7.12–7.69 (25H, m, ArH); Pro = 2.04, 3.57, 3.76 (36H, m, $-CH_2$), 4.75 (6H, m, $-^{\alpha}CH$); Heterocycle = 3.47, 3.65 (8H, m, $-CH_2$), 7.12–7.69 (3H, m, ArH); Elemental Analysis: Calc. C = 57.87, H = 6.48, N = 14.19, S = 1.00, Found C = 57.92, H = 6.55, N = 14.25, S = 0.97.

*4.6.45. 4OMe-Thiourea derivative of GE(OcHx)GFPGVGVPGVGFPGF GFPGVGVPGVGFP-Heterocycle 2 (**75**)*

IR ν_{max} (nujol): 1621 (CO), 2104 (CS), 3290 (NH); ^{1}H NMR data ($CDCl_3$, δ ppm): Thiourea = 8.85 (1H, s, NH), 8.12 (1H, m, NH), 7.09–7.80 (4H, m, ArH), 3.62 (3H, m, Ome); −NH = 8.00–8.10 (23H, m); Gly = 4.08, 4.95 (24H, m, $-^{\alpha}CH$); Val = 0.98, 1.01 (36H, m, $(-CH_3)_2$), 2.45, 2.68 (6H, m, $-^{\beta}CH$), 4.41 (6H, m, $-^{\alpha}CH$); Glu = 1.09–1.22 (10H, m, $-CH_2$ of cyclohexyl ring), 2.05, 2.20 (4H, m, $-^{\beta,\gamma}CH_2$), 3.71 (1H, m, −CH of cyclohexyl ring), 4.73 (1H, m, $-^{\alpha}CH$); Phe = 3.54, 3.73 (10H, m, $-^{\beta}CH_2$), 4.21, 4.65 (5H, m, $-^{\alpha}CH$), 7.09–7.80 (25H, m, ArH); Pro = 2.00, 3.60, 3.80 (36H, m, $-CH_2$), 4.78 (6H, m, $-^{\alpha}CH$); Heterocycle = 3.41, 3.68 (8H, m, $-CH_2$), 7.09–7.80 (3H, m, ArH); Elemental Analysis: Calc. C = 58.32, H = 6.58, N = 14.21, S = 1.00, Found C = 58.39, H = 6.65, N = 14.15, S = 1.04.

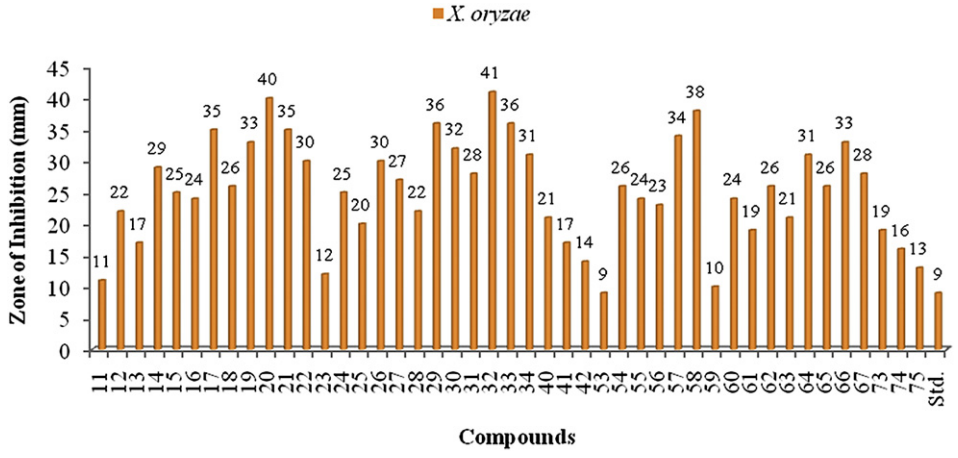


Fig. 2. Diagramatic representation of antibacterial activity of the compounds against *X. oryzae.*

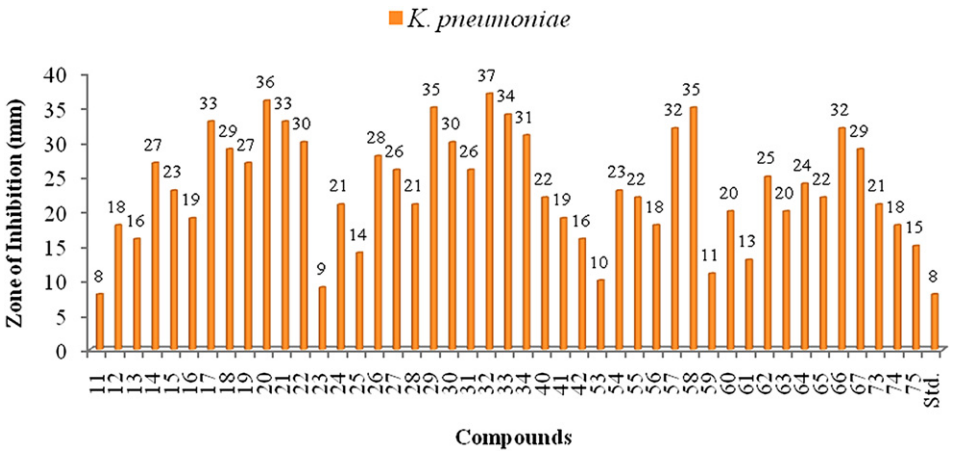


Fig. 3. Diagramatic representation of antibacterial activity of the compounds against *K. pneumoniae.*

4.7. Biology

4.7.1. Antibacterial activity

In vitro antibacterial activity was evaluated against human pathogens of both gram positive organisms namely *C. positive staphylococcus* and *K. pneumoniae* and gram negative organisms namely *X. oryzae* and *E. coli* by agar well diffusion method (Figs. 1–4) as well as microdilution method.

4.7.1.1. Agar well diffusion method. The microorganisms were inoculated in to the sterilized nutrient broth and maintained at 37 °C for 24 h. On the day of testing, bacteria were subcultured separately into 25 mL of sterilized nutrient broth. Inoculated sub-cultured broths were kept at room temperature for the growth of inoculums. Each final compound and standard drug (amoxicillin) of 10 mg was dissolved in 10 mL of DMSO to get a concentration of 1 mg/mL and further diluted to get a final concentration of 30 μg/mL. About 15–20 mL of molten nutrient agar was poured into each of the sterile plates. With the help of cork borer of 6 mm diameter, the cups were punched and scooped out of the set agar and the plates were inoculated with the suspension of particular organism by spread plate technique. The cups of inoculated plates were then filled with 0.1 mL of the test solution, amoxicillin solution and DMSO (negative control). The plates were allowed to stay for 24 h at 37 °C and zone of inhibition (mm) was then measured.

4.7.1.2. Microdilution method. All the microorganisms were grown in Muller–Hinton broth. After cultivation for 16–18 h at 37 °C, the bacteria were harvested and their density was determined by measuring O.D at A_{600}. MIC of the compounds was determined by agar dilution method. Suspension of each microorganism was prepared to contain approximately (1×10^4–2×10^4 CFU/mL) and applied to the plates with serially diluted compounds (dissolved in DMSO) to be tested and also reference drug and incubated at 37 °C overnight. The minimum inhibitory concentration was considered to be the lowest concentration that completely inhibited the growth of microorganisms on the plates. Zone of inhibition (mm) was measured after 24 h and MIC values were determined.

4.7.2. Antifungal activity

In vitro antifungal activity was evaluated against three fungal species namely *A. niger*, *A. flavus* and *F. oxysporum* by agar well diffusion method (Figs. 5–7) as well as microdilution method (Fig. 8).

4.7.2.1. Agar well diffusion method. The fungal strains were sub-cultured separately into 25 mL of sterilized nutrient broth and incubated for one day to obtain the inoculums. Each final compound and standard drug (bavistin) of 10 mg was dissolved in 10 mL of DMSO to get a concentration of 1 mg/mL and further diluted to get a final concentration of 30 μg/mL. Molten media of

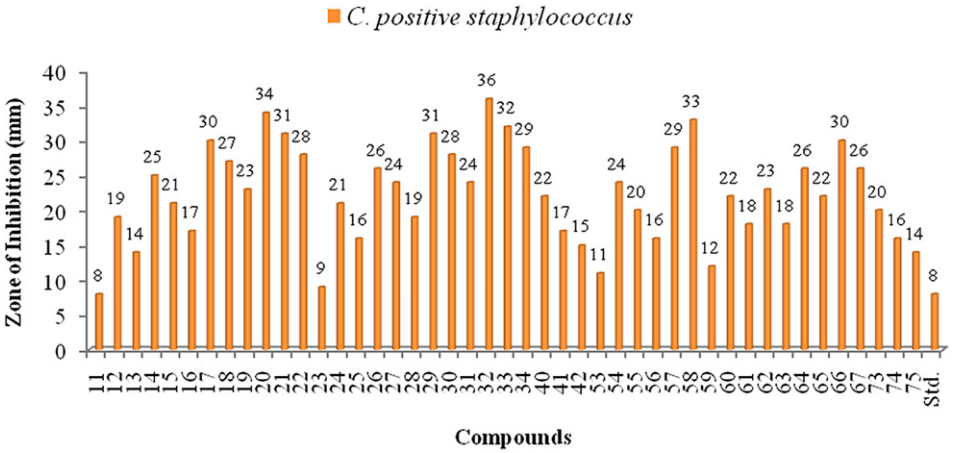


Fig. 4. Diagramatic representation of antibacterial activity of the compounds against *C. positive staphylococcus.*

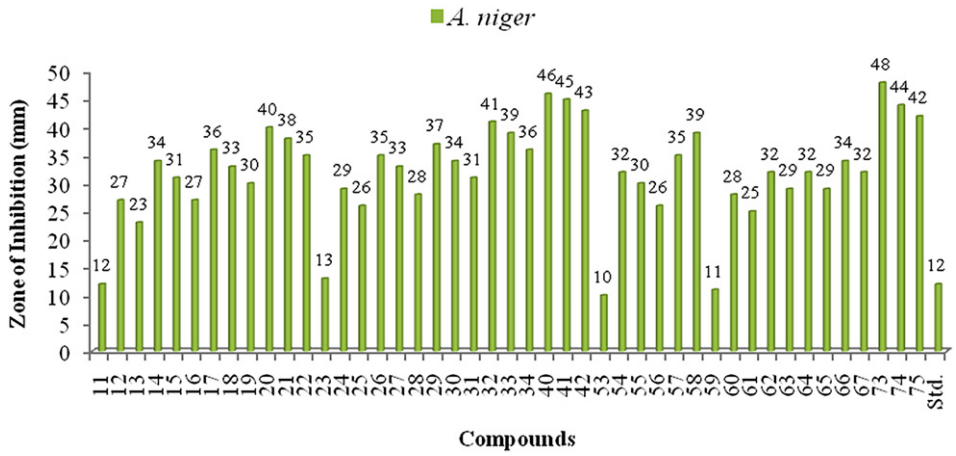


Fig. 5. Diagramatic representation of antifungal activity of the compounds against *A. niger*.

Sabouraud agar of 10–15 mL was poured into the petriplates and allowed to solidify. Fungal subculture was inoculated on the solidified media. With the help of 6 mm cork borer, the cups were punched and scooped out of the set agar. The cups of inoculated plates were then filled with 0.1 mL of the test solution, bavistin solution and DMSO (negative control). The plates were allowed to stay for 3 days at room temperature and zone of inhibition (mm) was then measured.

4.7.2.2. Microdilution method. Sabouraud agar was used for the preparation of plates. Suspension of each microorganism was prepared to contain 10^5 CFU/mL. The agar plates were inoculated

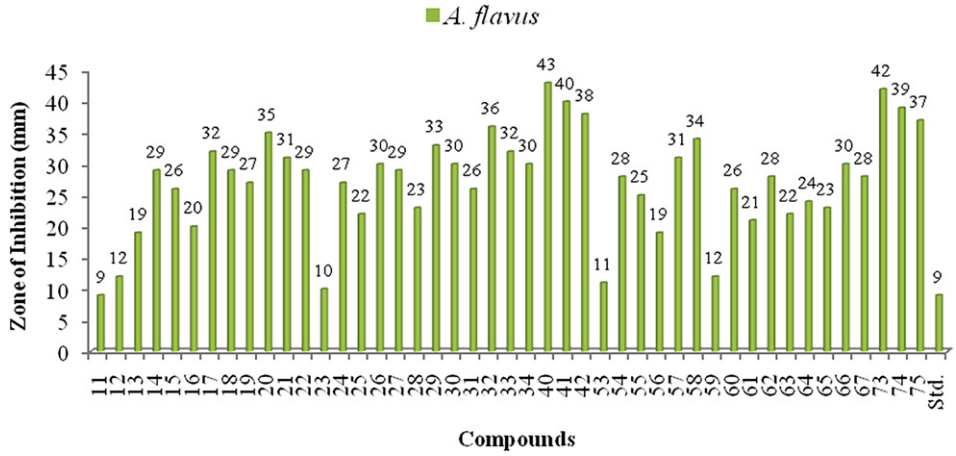


Fig. 6. Diagramatic representation of antifungal activity of the compounds against *A. flavus*.

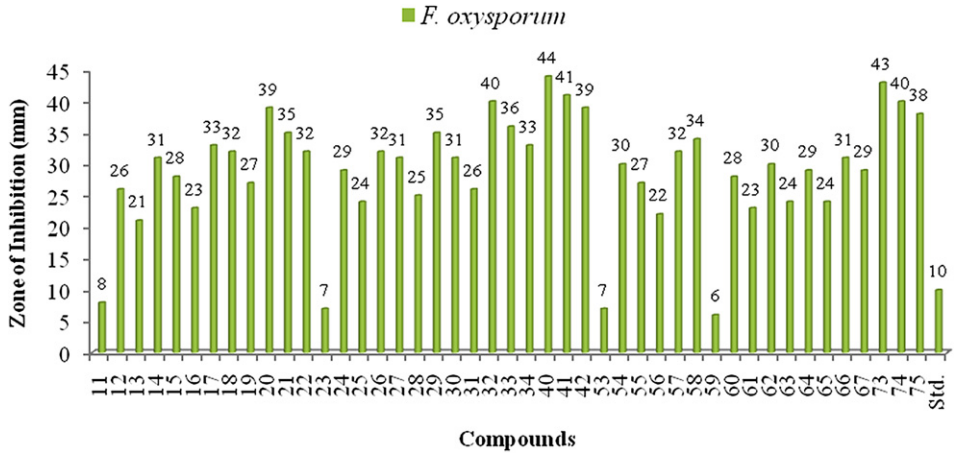


Fig. 7. Diagramatic representation of antifungal activity of the compounds against *F. oxysporum*.

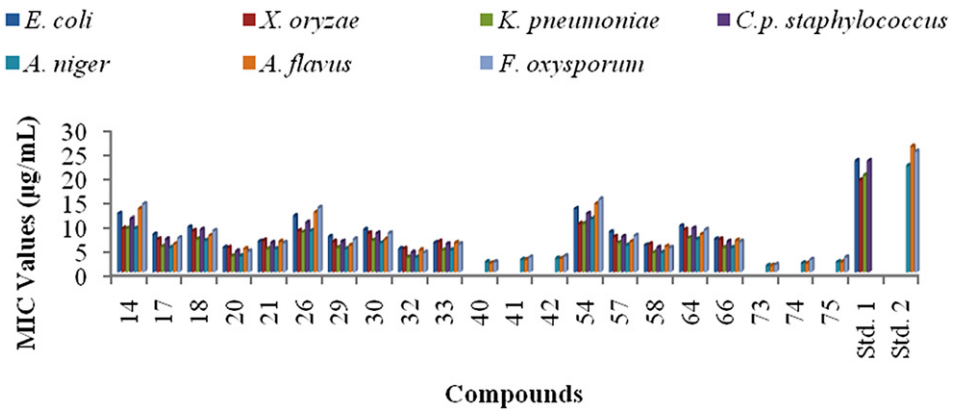


Fig. 8. Diagramatic representation of antibacterial and antifungal activities of the compounds by microdilution method.

with fungal strains and serially diluted test compounds and reference drug dissolved in DMSO. The plates were incubated at 25 °C for 48–72 h. The minimum inhibitory concentration was considered to be the lowest concentration that completely inhibited the growth of microorganisms on the plates. Zone of inhibition (mm) was measured after 72 h and MIC values were determined.

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