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Original article

Isoprenyl-thiourea and urea derivatives as new farnesyl diphosphate analogues: Synthesis and *in vitro* antimicrobial and cytotoxic activities

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ABSTRACT

A series of new isoprenyl-thiourea and urea derivatives were synthesized by the reaction of alkyl or aryl isothiocyanate or isocyanate and primary amines. The structures of the compounds were established by ^{1}H NMR, ^{13}C NMR, MS, HRMS and elemental analysis. The new compounds were screened for *in vitro* antimicrobial activity against seven strains representing different types of gram-positive and gram-negative bacteria. More than a third of the synthesized compounds showed variable inhibition activities against the tested strains. Best antimicrobial activities were found for those thiourea analogues with 3-methyl-2-butenyl, isobutyl or isopentyl groups and aromatic rings possessing electron withdrawing substituents. The new compounds were also subjected to a preliminary screening for antitumoral activity. The presence of a highly lipophilic group and an electron withdrawing group in the aromatic rings enhanced anticancer activity of the synthesized compounds, showing in most cases more activity than that of the controls.

1. Introduction

Due isoprenoids represent the largest class of small molecules on earth, many of the enzymes that are involved in isoprenoid biosynthesis are drug targets [1,2].

Farnesyl diphosphate and its C20 homologue, geranylgeranyl diphosphate are important isoprenoids involved in a number of cellular processes including cholesterol biosynthesis, glycoprotein synthesis, vitamin and cofactor synthesis, and protein prenylation [3,4]. The design of novel inhibitors of compounds involved in these cellular processes has attracted considerable attention as these inhibitors are possible chemotherapeutic agents.

For example, compounds that inhibit squalene synthase are expected to be effective therapeutic agents for lowering serum cholesterol levels, an interesting alternative to prevent atherosclerosis and subsequent cardiovascular disease [5]. New antiparasitic agents that block sterol biosynthesis in protozoa can be designed focusing on farnesyl diphosphate synthase inhibition [1].

Both farnesyl diphosphate and geranylgeranyl diphosphate are also used in protein prenylation, an important post-translational modification central to many cellular processes. They are substrates of farnesyltransferase (FTase) and geranylgeranyltransferase (GGTase-I) respectively, which catalize the transfer of the prenyl group from farnesyl diphosphate or geranylgeranyl diphosphate to the intracellular protein active, so that the attached lipid acts as hydrophobic membrane anchor leading to the membrane localization. In this sense, an active area of research is the development of protein prenylation inihibitors [6–11]. The primary force for such efforts came from the finding that Ras proteins require farnesylation. Oncogenic Ras proteins that are found in a significant number of cancers contribute to malignancy and are therefore considered favored targets for direct therapy. The research is oriented to the preparation of highly potent and selective compounds that are reversible inhibitors of human FTase. Inhibitors of Ras FTase have been designed based both on the farnesyl moiety of the farnesyl diphosphate susbtrate and the diphosphate group FDP [12].

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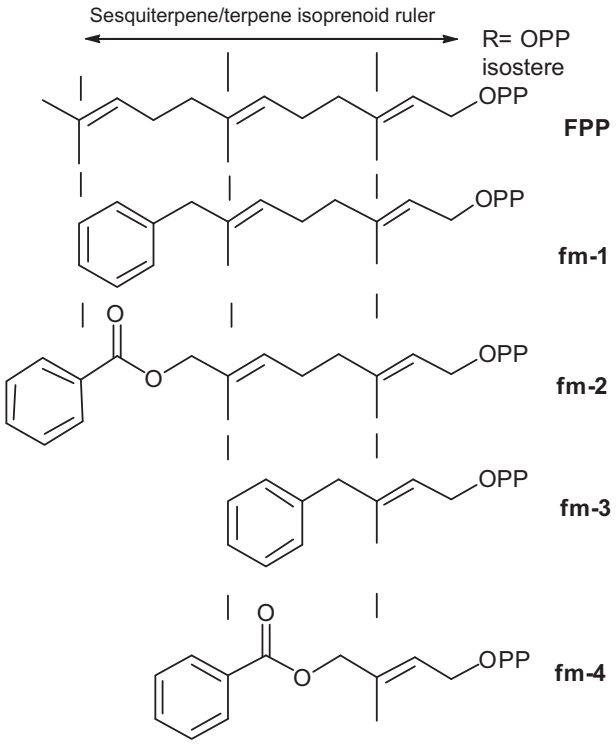


Fig. 1. Molecular hypothesis for isoprenoid specificity.

The emergence of drug resistant pathogenic bacteria continues to be a serious health problem worldwide [13]. As a result, it has become critical to identify new structural classes of antibacterial agents to combat the growing threat of bacterial resistance.

In this line, a recent approach to the design of new antibacterial compounds is the development of easily synthesizable farnesyl diphosphate mimetics. A wide range of structurally diverse farnesyl diphosphate mimetics have been described for antimicrobial evaluation considering a farnesyl mimic and diphosphate isostere essential for inhibitory activity [3,14]. According to the "molecular ruler" hypothesis for isoprenoid substrate specificity where the depth of the hydrophobic binding cavity acts as a ruler in discriminating between isoprenoids of different lengths, those

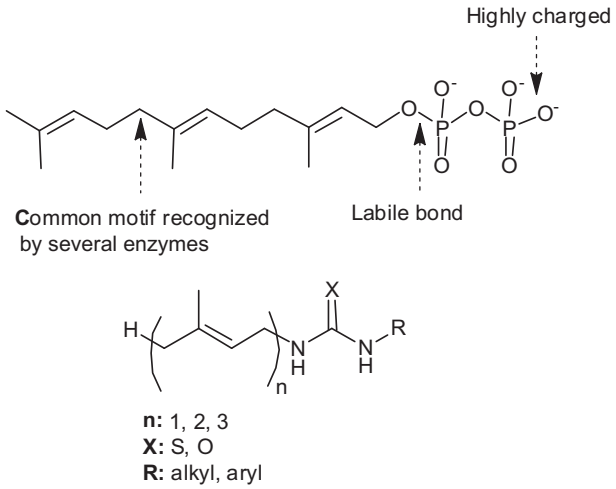
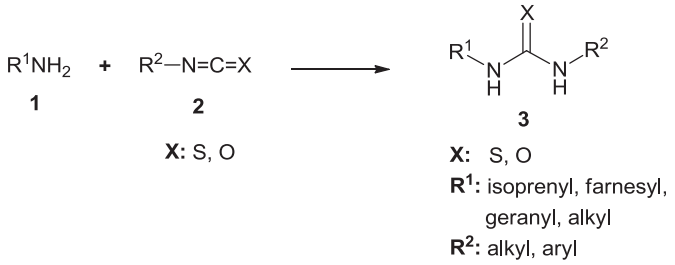


Fig. 2. General backbone for new isoprenyl-thiourea and urea derivatives.



Scheme 1. Reaction for the synthesis of the isoprenyl-thiourea/urea derivatives library **3**.

farnesyl mimics (fm) smaller than farnesyl residue might be less specific towards squalene synthase and FTase. On the other hand an ideal diphosphate isostere would be one that shares electronic and steric similarities with the diphosphate moiety. Such isosteres include biphosphonic acids, mixed phosphonic/carboxyl acids and dicarboxyl acid moieties [15]. These farnesyl diphosphate analogues exhibited promising antimicrobial activities (Fig. 2, fm-1 and fm-2) that were thought to be attributable to inhibition of squalene synthase. However, the low squalene synthase inhibition results suggest an alternative site of inhibition, possibly FTase (Fig. 1).

Additionally and closely related to results presented in this work, new chemotherapeutics agents have been described with urea or thiourea functions present in their structures. A survey of the literature reveals many N-acyl-thiourea derivatives with wide application as insecticides [16], antitumorals [17,18], antimicrobials and antifungals [19–24]. Substituted halopyridyl, indolyl and naphthyl thiourea compounds have been synthesized and evaluated as an efficient new chemical class of anti-allergic [25].

Additionally, urea derivatives have been used for the treatment of a wide range of solid tumors [26], have also been reported as protein kinasa inhibitors, and have become an important class of potential anticancer drugs [27]. For these reasons, the synthesis and biological evaluation of new functionalized urea derivatives has acquired a high interest. Indeed, during the preparation of this manuscript the synthesis of ureido and thioureido derivatives of peptide conjugated heterocycles has been reported [28]. Our effort

Table 1
Isoprenyl-thiourea derivatives **4**–**20**. R^1 = 3-methyl-2-butenyl.

Entry	Compound	R^2	Yield (%)
1	**4**	Methyl	97
2	**5**	*tert*-Butyl	92
3	**6**	Allyl	87
4	**7**	Phenyl	79
5	**8**	4-Nitrophenyl	93
6	**9**	4-Trifluoromethylphenyl	97
7	**10**	4-Fluorophenyl	78
8	**11**	4-Chlorophenyl	95
9	**12**	4-Cyanophenyl	85
10	**13**	4-Methoxyphenyl	88
11	**14**	3-Methoxyphenyl	96
12	**15**	2-Methoxyphenyl	92
13	**16**	3-Pyridyl	90
14	**17**	2-(1-Piperidino)ethyl	85
15	**18**	2-(4-Morpholino)ethyl	79
16	**19**	3-(4-Morpholino)propyl	90
17	**20**	Ethoxycarbonylmethyl	96

Table 2
Geranyl thiourea derivatives **21**–**40**. R^1 = geranyl.

Entry	Compound	R^2	Yield (%)
1	**21**	Methyl	78
2	**22**	*tert*-Butyl	97
3	**23**	Allyl	98
4	**24**	Phenyl	98
5	**25**	4-Nitrophenyl	94
6	**26**	3-Nitrophenyl	90
7	**27**	4-Trifluoromethylphenyl	97
8	**28**	4-Fluorophenyl	90
9	**29**	4-Chlorophenyl	95
10	**30**	4-Cyanophenyl	98
11	**31**	4-Methoxyphenyl	85
12	**32**	3-Methoxyphenyl	90
13	**33**	2-Methoxyphenyl	90
14	**34**	3-Pyridyl	90
15	**35**	2-(1-Piperidino)ethyl	84
16	**36**	2-(4-Morpholino)ethyl	92
17	**37**	3-(4-Morpholino)propyl	96
18	**38**	4-Piperidyl	80
19	**39**	Ethoxycarbonymethyl	96
20	**40**	Ethoxycarbonyl	83

in this field, taking into consideration the aforementioned biological significance of isoprenoids and thiourea and urea functions, was the development of new chemotherapeutic agents (as a part of our research focused in the synthesis of new compounds with potential biological activity [29]) by joining in one single structure these two important biologically active scaffolds, the thiourea or urea function and the isoprenyl residue, seeking an improved biological activity.

The major aim of this report is to present the synthesis, by a short and high yielded methodology, of small libraries of new isoprenyl urea/thiourea derivatives. Biological screening and SAR studies were done in order to identify novel lead molecules.

Table 3
Farnesyl thiourea derivatives **41**–**58**. R^1 = farnesyl.

Entry	Compound	R^2	Yield (%)
1	**41**	Methyl	94
2	**42**	*tert*-Butyl	79
3	**43**	Allyl	85
4	**44**	Phenyl	96
5	**45**	4-Nitrophenyl	97
6	**46**	3-Nitrophenyl	91
7	**47**	4-Trifluoromethylphenyl	85
8	**48**	4-Fluorophenyl	97
9	**49**	4-Chlorophenyl	78
10	**50**	4-Cyanophenyl	85
11	**51**	4-Methoxyphenyl	91
12	**52**	3-Methoxyphenyl	91
13	**53**	2-Methoxyphenyl	92
14	**54**	2-(1-Piperidino)ethyl	85
15	**55**	2-(4-Morpholino)ethyl	76
16	**56**	3-(4-Morpholino)propyl	90
17	**57**	Ethoxycarbonylmethyl	96
18	**58**	Ethoxycarbonyl	96

Table 4
Alkyl thiourea derivatives **59**–**68**.

Entry	Compound	R^1	R^2	Yield (%)
1	**59**	Isobutyl	4-Nitrophenyl	89
2	**60**	Isopentyl	4-Nitrophenyl	92
3	**61**	Benzyl	4-Nitrophenyl	96
4	**62**	Cyclohexyl	4-Nitrophenyl	90
5	**63**	1-Dodecyl	4-Nitrophenyl	99
6	**64**	1-Dodecyl	3-Nitrophenyl	82
7	**65**	1-Dodecyl	4-Methoxyphenyl	96
8	**66**	1-Dodecyl	3-Methoxyphenyl	93
9	**67**	1-Dodecyl	2-Methoxyphenyl	86
10	**68**	4-Morpholino	4-Nitrophenyl	90

2. Results and discussion

2.1. Design

Our general structure has been designed by an attempt to generate farnesyl diphosphate analogues by challenges in the FDP structure illustrated in Fig. 2. We made the following structural modifications: (1) we have replaced the farnesyl residue by different unsaturated lipidic moieties, commonly isoprenyl derived; (2) another aspect taken under consideration is the lability of the diphosphate bond, which has been replaced in our model with a more resistant bond, urea or thiourea, thus introducing a less polar, less charged group; (3) and finally our general backbone possesses another structural variability point, R substituent, so different alkyl and aryl substituents can be introduced in order to evaluate their effects on the biological activity of the compounds.

As several different enzymes in the cell utilize FDP, these analogues are expected to act as inhibitors, so a part of our current investigation involved their evaluation, both antimicrobial and citotoxic.

Table 5
Urea derivatives **69**–**89**.

Entry	Compound	R^1	R^2	Yield (%)
1	**69**	3-Methyl-2-butenyl	Ethyl	87
2	**70**	3-Methyl-2-butenyl	Allyl	87
3	**71**	3-Methyl-2-butenyl	Phenyl	63
4	**72**	3-Methyl-2-butenyl	4-Nitrophenyl	83
5	**73**	Geranyl	Ethyl	98
6	**74**	Geranyl	*tert*-Butyl	97
7	**75**	Geranyl	Allyl	98
8	**76**	Geranyl	Phenyl	98
9	**77**	Geranyl	4-Nitrophenyl	94
10	**78**	Geranyl	4-Trifluoromethylphenyl	97
11	**79**	Geranyl	4-Chlorophenyl	95
12	**80**	Geranyl	4-Cyanophenyl	95
13	**81**	Farnesyl	Ethyl	95
14	**82**	Farnesyl	*tert*-Butyl	70
15	**83**	Farnesyl	Allyl	95
16	**84**	Farnesyl	Phenyl	96
17	**85**	Farnesyl	4-Nitrophenyl	87
18	**86**	Farnesyl	4-Trifluoromethylphenyl	85
19	**87**	Farnesyl	4-Chlorophenyl	78
20	**88**	Farnesyl	4-Cyanophenyl	85
21	**89**	1-Dodecyl	4-Nitrophenyl	93

2.2. Chemistry

Our objective was to prepare a small library of new isoprenyl-thiourea and urea derivatives through a short synthetic methodology. By choosing the appropriate precursors, the primary amine and the alkyl or aryl isothiocyanate or isocyanate derivative, we can generate the chemical diversity of compounds. Apart from isoprenyl and farnesyl amines (easily prepared [30]) all cyanate derivatives and primary amines employed were commercial reagents.

Scheme 1 outlines the synthesis of the thiourea/urea derived compounds. The reaction took place at room temperature in dichloromethane, and was completed in 15–20 min in high yields.

With this method we obtained a structurally varied library consisting of 63 new isoprenyl-thiourea derivatives (Tables 1–4) and 21 isoprenylurea derivatives (Table 5).

The general backbone of these compounds (Scheme 1) shows that both amide function substituents are structural variation points. R^1 (from the amine precursor) are groups with different degrees of lipophilia, mainly unsaturated, and R^2 (from the isocyanate reactant) is the position we use to widen the range of possibilities: alkyl groups of different sizes, aromatic carbocyclic and heterocyclic groups (with different substituents, possessing electron withdrawing or electron-releasing groups). That gives us a pool of compounds that, after screening process, will provide information about the structure–activity relationship.

Tables 1–4 show the new thiourea derivatives grouped by the type of lipophilic substituent.

In a similar way, employing isocyanate compounds as reactant we synthesized the urea derivatives **69**–**89**.

All compounds were obtained in high yields (over 80% in almost all cases).

^{1}H NMR spectra of the thioureas and ureas showed the signals of the isoprenoid chains in all cases. NHCH_2 protons appear at around 3.98 ppm, the signals corresponding to the double bonds of the isoprenyl chains are observed at 5.23 ppm, other signal for geranyl derivatives corresponding to the second double bond present in the geranyl chains is observed at 5.02 ppm and farnesyl derivatives present a signal at 5.06 ppm attributed to the third double bond. These signals of the alkenyl protons permitted the characterization of the hydrogens showing similar values for those thioureas and ureas with the same substituents. For dodecyl derivatives, the $(CH_2)_{10}$ protons are observed at 1.7–1.2 ppm and the CH_3 terminal as a triplet at 0.87 in all cases.

^{13}C NMR spectra of the thioureas and ureas showed the typical absorptions for the signals for the thiocarbonylic and carbonylic carbons, in the range of δ 181–182 ppm and 155–156 ppm respectively.

Spectral (NMR, mass spectrometry) and analytical data of all the synthesized compounds were in full agreement with the proposed structures.

The next step in our research was to subject these compounds to biological assays [our group have previously described their use of few of them (**7**, **8**, **21**, **40**, **45**, **69**, **73**, **81**) for the treatment of hepatic encephalopathy [31].

2.3. In vitro antimicrobial activity

Antimicrobial activity of the synthesized compounds was evaluated against seven strains representing different types of gram-positive and gram-negative bacteria, *Bacillus subtilis* ATCC6633, *Staphylococcus aureus* ATCC2595, *Klebsiella pneumoniae* ATCC10031, *Pseudomonas aeruginosa* CECT110, *Escherichia coli* ATCC25922, *Salmonella enterica* ATCC10708, *Serratia marcescens* ATCC 14756. Antifungal activity was also evaluated against *Candida albicans.*

Our procedure started with a preliminary screening preliminary screening in order to identify those compounds that presented some antibacterial activity. Once detected, the most interesting (more active or selective) were chosen and subjected to a compared analysis of growth in liquid medium versus commercial substances.

Preliminary *in vitro* evaluation was carried out by disk diffusion method using nutrient agar medium. The tests were repeated three times and the results are reported as means of at least three determinations. After the incubation time, the radius of the clear zones showing no bacterial growth was measured around each well. The zones of inhibition (mm scale) were calculated and reflect the degree of antibacterial activity. The compounds were dissolved in dimethylsulfoxide (DMSO). Commercial antibiotics Tobramycine, Tetracycline and Ketoconazol were used as a positive control and the solvent was used as a negative control at the same concentrations.

The observed data (inhibitory zone) for our compounds are presented in Table 6.

The data generated from this study (Table 6) revealed that around 40% of the synthesized compounds showed variable inhibition activities against the tested strains. However no activity was detected against enterobacter strains in any case.

Best activities, highest inhibition zone (17–23 mm), were detected for those compounds with a small group at R^1 position (such as isoprenyl, isobutyl and isopentyl) and a 4-nitrophenyl group at R^2 (compounds **8**, **59**, **60**, entries 5, 49 and 50). These three compounds possessed broad-spectrum antibacterial activity against gram-positive pathogens (*Staphylococcus aureus* and *Bacillus subtilis*) and against gram-negative pathogens (*Klebsiella pneumonia* and *Pseudomonas aeruginosa*).

In compounds with an isoprenyl group, changes in the aromatic ring in position R^2 (4-trifluoromethylphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-cyanophenyl, 4-methoxyphenyl, 3-methoxypheny, 2-methoxyphenyl, 3-pyridyl) brought either a decrease in activity (compound **9**, entry 6) or total loss of activity (compounds **15** and **16**, entries 12 and 13). It should be noted that some of these compounds have moderate activity (inhibition zone 10–12 mm) against *P. aeruginosa*, (compounds **9**–**11**, entries 6–8) or are completely selective (compounds **14** and **17**, entries 11 and 14).

Replacing the isoprenyl group with a geranyl group decreased the activity (compound **25**, entry 21 *vs* compound **8**, entry 5). However, geranyl derivatives with groups other than 4-nitrophenyl at R^2 position have a moderate activity against gram-positive pathogens (compounds **27**–**30**, **34**, **35** and **37**, entries 22–25, 28–29 and 31).

Most compounds with a farnesyl group in R^1 position present no antibacterial activity (entries 34–43). Only those with 3-methoxyphenyl, 2-(1-piperidino)ethyl, 2-(4-morpholino)ethyl and 3-(4-morpholino)propyl grops at R^2 present a small inhibition zone against gram-positive pathogens (compounds **52**, **54**–**56**, entries 44–47).

If, in position R^1, the isobutyl or isopentyl alkyl chain is replaced by a benzyl or cyclohexyl group the resulting compounds present the same antibacterial spectrum, but a decreased activity (11–14 mm, compounds **61** and **62**, entries 51–52).

The results of this preliminary antimicrobial screening lead to the following assumptions about the structural activity relationship (SAR), Fig. 3.

- The substituent R^1 (from the primary amine employed in the reaction) plays a key role in varying the efficacy of antimicrobial activity. Thiourea analogues with 3-methyl-2-butenyl, isobutyl or isopentyl groups gave best activities.

Table 6
Antimicrobial bioassay screnning.

Entry	Compd	Antimicrobial activity[a]							
		Gram-positive		Gram-negative fungi					
		B. subtilis	*S. aureus*	*K. pneumoniae*	*P. aeruginosa*	*E. coli*	*S. enterica*	*S. marcenscens*	*C. albicans*
1	**4**	–	–	–	–	–	–	–	–
2	**5**	–	–	11	–	–	–	–	22
3	**6**	–	–	–	–	–	–	–	21
4	**7**	–	–	11	–	–	–	–	–
5	**8**	18	20	17	–	–	–	–	20
6	**9**	9	13	9	10	–	–	–	–
7	**10**	11	–	–	12	–	–	–	12
8	**11**	–	–	–	11	–	–	–	–
9	**12**	–	14	11	–	–	–	–	–
10	**13**	–	–	–	–	–	–	–	–
11	**14**	–	–	–	12	–	–	–	13
12	**15**	–	–	–	–	–	–	–	18
13	**16**	–	–	–	–	–	–	–	–
14	**17**	–	–	–	12	–	–	–	–
15	**18**	–	–	–	–	–	–	–	–
16	**19**	–	–	–	–	–	–	–	–
17	**21**	12	–	10	–	–	–	–	21
18	**22**	–	–	–	–	–	–	–	–
19	**23**	–	–	–	–	–	–	–	10
20	**24**	–	–	–	–	–	–	–	–
21	**25**	13	15	–	–	–	–	–	–
22	**27**	–	10	–	–	–	–	–	–
23	**28**	11	8	–	–	–	–	–	–
24	**29**	–	9	–	–	–	–	–	–
25	**30**	13	16	–	–	–	–	–	–
26	**31**	12	–	–	–	–	–	–	–
27	**32**	–	–	–	–	–	–	–	–
28	**34**	11	12	–	12	–	–	–	–
29	**35**	15	–	11	–	–	–	–	–
30	**36**	–	–	8	–	–	–	–	–
31	**37**	11	8	13	–	–	–	–	11
32	**39**	–	–	–	–	–	–	–	–
33	**40**	–	–	–	–	–	–	–	–
34	**41**	–	–	–	–	–	–	–	–
35	**42**	–	–	–	–	–	–	–	–
36	**43**	–	–	–	–	–	–	–	–
37	**44**	–	–	–	–	–	–	–	–
38	**45**	–	–	–	–	–	–	–	–
39	**47**	–	–	–	–	–	–	–	–
40	**48**	–	–	–	–	–	–	–	–
41	**49**	–	–	–	–	–	–	–	–
42	**50**		–	–	–	–	–	–	–
43	**51**	–	–	–	–	–	–	–	–
44	**52**	11	8	–	–	–	–	–	–
45	**54**	11	8	–	–	–	–	–	–
46	**55**	12	9	–	–	–	–	–	–
47	**56**	10	–	–	–	–	–	–	–
48	**58**	–	–	–	–	–	–	–	–
49	**59**	18	20	19	–	–	–	–	–
50	**60**	18	22	20	23	–	–	–	–
51	**61**	13	12	14	–	–	–	–	–
52	**62**	13	13	11	–	–	–	–	–
53	**63**	–	8	9	–	–	–	–	–
54	**65**	–	–	–	–	–	–	–	–
55	**66**	–	7	13	–	–	–	–	–
56	**68**	–	–	–	–	–	–	–	–
57	**69**	–	–	–	–	–	–	–	–
58	**70**	–	–	–	–	–	–	–	–
59	**71**	–	–	–	–	–	–	–	–
60	**72**	20	–	–	–	–	–	–	–
61	**73**	–	–	–	–	–	–	–	–
62	**74**	–	14	11	–	–	–	–	–
63	**75**	–	–	–	–	–	–	–	–
64	**76**	–	–	–	–	–	–	–	–
65	**77**	–	–	–	–	–	–	–	–
66	**78**	–	–	–	–	–	–	–	–
67	**79**	–	–	–	–	–	–	–	–
68	**80**	–	11	–	–	–	–	–	–
69	**81**	–	–	–	–	–	–	–	–
70	**82**	–	–	–	–	–	–	–	–

(*continued on next page*)

Table 6 (*continued*)

Entry	Compd	Antimicrobial activity[a]							
		Gram-positive		Gram-negative fungi					
		B. subtilis	*S. aureus*	*K. pneumoniae*	*P. aeruginosa*	*E. coli*	*S. enterica*	*S. marcenscens*	*C. albicans*
71	**83**	–	–	–	–	–	–	–	–
72	**84**	–	–	–	–	–	–	–	–
73	**85**	–	–	–	–	–	–	–	–
74	**86**	–	–	–	–	–	–	–	–
75	**87**	–	–	–	–	–	–	–	–
76	**88**	–	–	–	–	–	–	–	–
77	**89**	–	–	–	–	–	–	–	–
78	**Tobramycine**	41	28	21	34	23	30	23	–
79	**Tetracycline**	48	33	36	14	31	39	12	8
80	**Ketoconazol**	20	15	–	–	–	–	–	25

–, No activity.
[a] Zone of inhibition (radius, mm).

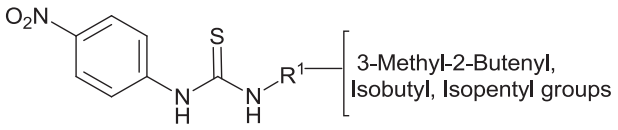


Fig. 3. Structural requirements for antimicrobial activity of thiourea derivatives.

- According to the nature of R^2 substituent most active compounds were those with 4-nitrophenyl group (the role of electron withdrawing groups in improving antimicrobial activities has been reported in the literature [32]).

Antifungal activity evaluation results revealed that most of the tested compounds were not active. Only a few isoprenyl and geranyl derivatives showed high activity (18–21 mm). From observed data, for those isoprenyl derivatives, R^2 position admitted greater structural variability, *tert*-butyl, allyl, 4-nitrophenyl, 2-methoxyphenyl groups (compounds **5**, **6**, **8** and **15,** entries 2, 3, 5 and 12). Compound **21** with R^1 geranyl and R^2 methyl showed similar activity (entry 17), Fig. 4.

Compounds with R^1 farnesyl or alkyl group did not exhibit activity.

Urea derivatives did not exhibit either antibacterian or antifungal activity. Notably, compound **72**, R^1 geranyl and R^2 4-nitrophenyl, gave high and selective activity against *Bacillus subtilis* (entry 60).

2.4. Growth inhibitory effect of selected compounds

Those compounds which presented remarkable antimicrobial activity in the assay and/or were selective against a specific reference strain using the disc diffusion method were selected to compare their activity with clinical commercial compounds. For that purpose, growth of different strains was monitored during a long period (60–300 h) in absence and presence of different concentrations of antimicrobial compounds (0, 20, 50, 100, 200 μg/ml) and compared with the growth in the presence of the minimal concentration of commercial ones that produce total inhibitory effect.

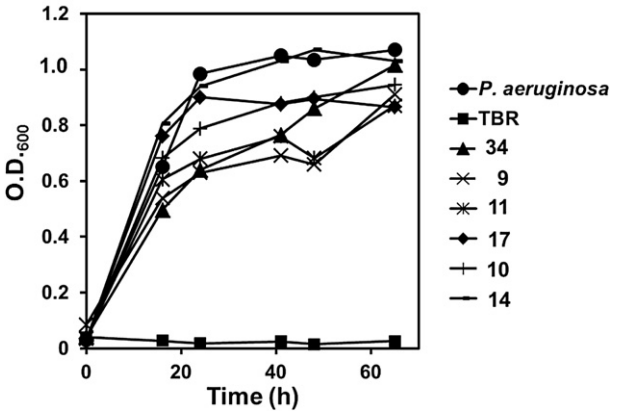


Fig. 5. Growth inhibitory effect against *P. aeruginosa* of selected compounds and Tobramycine.

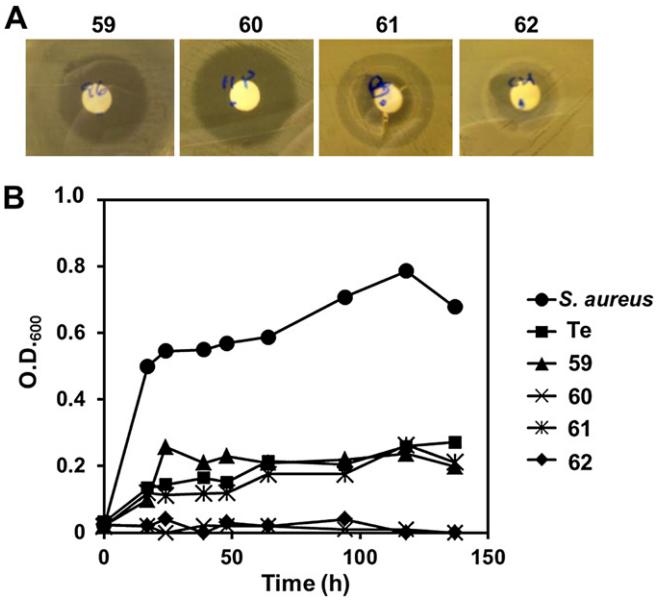


Fig. 6. Growth inhibitory effect against *S. aureus* of selected compounds and Tetracycline.

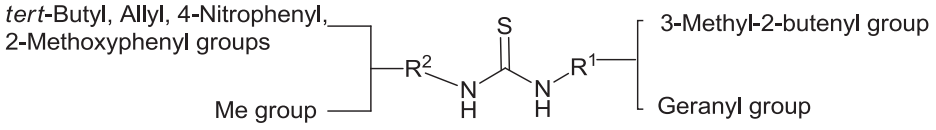


Fig. 4. Structural requirements for antifungal activity of thiourea derivatives.

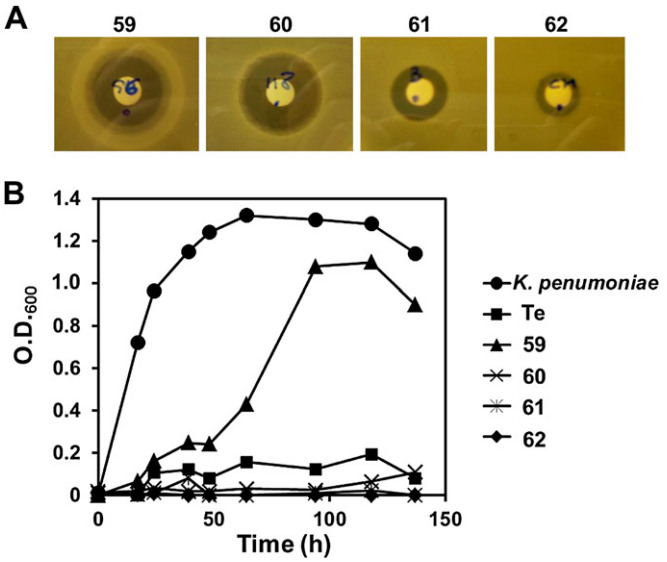


Fig. 7. Growth inhibitory effect against *K. pneumoniae* of selected compounds and Tetracycline.

The *Pseudomonas aeruginosa* growth was monitored during 70 h against compounds **9**, **10**, **11**, **14**, **17** and **34** and compared with the growth against Tobramycine in a final concentration of 20 μg/ml. Only compounds **9**, **11** and **34** showed a partial inhibitory effect as a delayed growth of *P. aeruginosa* was observed (Fig. 5). However none of the tested compounds showed higher antimicrobial activity against *P. aeruginosa* than the commercial one, Tobramycine (TBR).

Staphylococcus aureus and Klebsiella pneumoniae were grown in the presence of 20 μg/ml of compounds **59**, **60**, **61**, **62** and Tetracycline. In the case of *S. aureus* compounds **59** and **61** showed an inhibitory effect comparable with Tetracycline and, interestingly, compounds **60** and **62** were even more effective (Fig. 6). On the other hand, *K. pneumoniae* was also sensitive to the effect of compounds **60**, **61**, **62** (Fig. 7). Compound **59** presented an inhibitory effect comparable to Tetracycline during 50 h, however it disappeared after this period allowing *K. pneumoniae* to grow and

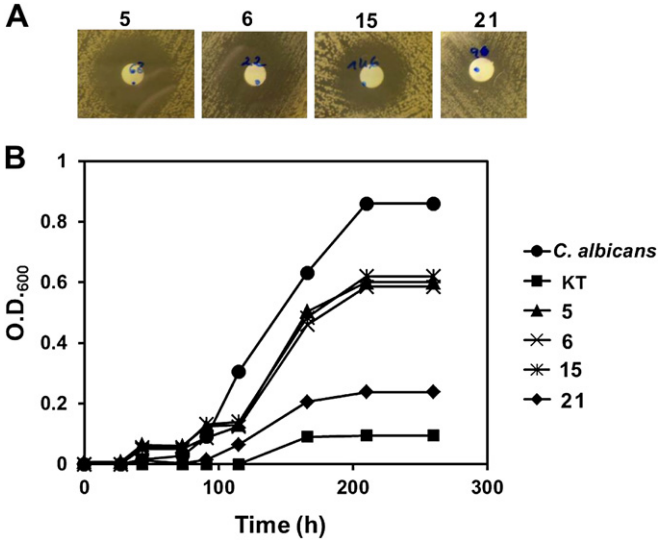


Fig. 8. Growth inhibitory effect against *C. albicans* of selected compounds and Ketoconazol.

Table 7
Citotoxic activity data.

Entry	Compound	X	R^1	R^2	IC_{50} (μM)
1	**4**	S	3-Methyl -2-butenyl	Methyl	89.48 ± 8.59
2	**6**	S	3-Methyl -2-butenyl	Allyl	75.00 ± 20.41
3	**7**	S	3-Methyl -2-butenyl	Phenyl	> 100.00
4	**8**	S	3-Methyl -2-butenyl	4-Nitrophenyl	4.79 ± 0.81
5	**21**	S	Geranyl	Methyl	30.70 ± 6.90
6	**23**	S	Geranyl	Allyl	47.07 ± 15.10
7	**24**	S	Geranyl	Phenyl	13.81 ± 5.33
8	**25**	S	Geranyl	4-Nitrophenyl	5.58 ± 1.49
9	**26**	S	Geranyl	3-Nitrophenyl	15.21 ± 13.81
10	**27**	S	Geranyl	4-Trifluoromethylphenyl	4.28 ± 0.24
11	**28**	S	Geranyl	4-Fluorophenyl	21.86 ± 3.48
12	**29**	S	Geranyl	4-Chlorophenyl	27.08 ± 3.89
13	**30**	S	Geranyl	4-Cyanophenyl	4.72 ± 0.37
14	**31**	S	Geranyl	4-Methoxyphenyl	16.96 ± 2.13
15	**32**	S	Geranyl	3-Methoxyphenyl	27.36 ± 3.58
16	**33**	S	Geranyl	2-Methoxyphenyl	28.50 ± 2.12
17	**34**	S	Geranyl	3-Pyridyl	28.50 ± 2.12
18	**39**	S	Geranyl	Ethoxycarbonylmethyl	30.31 ± 2.40
19	**40**	S	Geranyl	Ethoxycarbonyl	38.43 ± 1.68
20	**41**	S	Farnesyl	Methyl	40.17 ± 0.33
21	**43**	S	Farnesyl	Allyl	15.34 ± 0.08
22	**44**	S	Farnesyl	Phenyl	17.03 ± 4.79
23	**45**	S	Farnesyl	4-Nitrophenyl	1.48 ± 0.78
24	**46**	S	Farnesyl	3-Nitrophenyl	1.14 ± 0.36
25	**47**	S	Farnesyl	4-Trifluoromethylphenyl	1.60 ± 1.01
26	**48**	S	Farnesyl	4-Fluorophenyl	3.73 ± 0.09
27	**49**	S	Farnesyl	4-Chlorophenyl	2.65 ± 0.12
28	**50**	S	Farnesyl	4-Cyanophenyl	0.36 ± 0.03
29	**51**	S	Farnesyl	4-Methoxyphenyl	8.03 ± 1.48
30	**52**	S	Farnesyl	3-Methoxyphenyl	4.20 ± 0.40
31	**53**	S	Farnesyl	2-Methoxyphenyl	10.97 ± 2.22
32	**55**	S	Farnesyl	2-(4-Morpholino)ethyl	5.11 ± 0.26
33	**56**	S	Farnesyl	3-(4-Morpholino)propyl	3.13 ± 0.25
34	**57**	S	Farnesyl	Ethoxycarbonylmethyl	19.69 ± 7.08
35	**58**	S	Farnesyl	Ethoxycarbonyl	28.75 ± 1.52
36	**63**	S	1-Dodecyl	4-Nitrophenyl	2.50 ± 1.04
37	**64**	S	1-Dodecyl	3-Nitrophenyl	4.14 ± 0.38
38	**65**	S	1-Dodecyl	4-Methoxyphenyl	27.01 ± 15.04
39	**66**	S	1-Dodecyl	3-Methoxyphenyl	10.28 ± 1.49
40	**67**	S	1-Dodecyl	2-Methoxyphenyl	8.28 ± 2.51
41	**69**	O	3-Methyl -2-butenyl	Ethyl	>100.00
42	**70**	O	3-Methyl -2-butenyl	Allyl	>100.00
43	**71**	O	3-Methyl -2-butenyl	Phenyl	>100.00
44	**73**	O	Geranyl	Ethyl	71.83 ± 23.00
45	**75**	O	Geranyl	Allyl	41.82 ± 18.84
46	**76**	O	Geranyl	Phenyl	39.19 ± 4.41
47	**77**	O	Geranyl	4-Nitrophenyl	3.97 ± 0.42
48	**78**	O	Geranyl	4-Trifluoromethylphenyl	15.75 ± 5.87
49	**79**	O	Geranyl	4-Chlorophenyl	51.06 ± 23.71
50	**80**	O	Geranyl	4-Cyanophenyl	10.43 ± 6.94
51	**81**	O	Farnesyl	Ethyl	30.91 ± 3.16
52	**83**	O	Farnesyl	Allyl	37.37 ± 8.99
53	**84**	O	Farnesyl	Phenyl	16.89 ± 10.51
54	**85**	O	Farnesyl	4-Nitrophenyl	1.67 ± 0.60
55	**86**	O	Farnesyl	4-Trifluoromethylphenyl	2.98 ± 0.56
56	**87**	O	Farnesyl	4-Chlorophenyl	76.01 ± 12.07
57	**88**	O	Farnesyl	4-Cyanophenyl	2.63 ± 0.37
58	**89**	O	1-Dodecyl	4-Nitrophenyl	2.73 ± 1.12
59	5-Fluorouracil				4.32 ± 2.15
60	Hydroyurea				86.21 ± 13.79

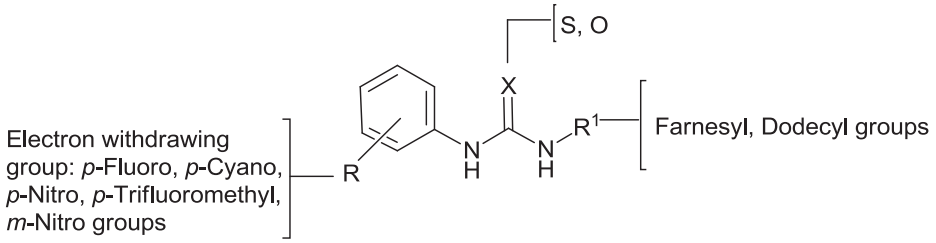


Fig. 9. Structural requirements for cytotoxic activity of thiourea and urea derivatives.

reach O.D. similar to that without any antimicrobial compound (Fig. 7) suggesting that compound **59** could be a better antimicrobial agent to be use in Gram positive than in Gram-negative bacteria.

Finally to test the inhibitory effect of selective antifungal compounds, *Candida albicans* growth was monitored in the presence of 20 μg/ml of compounds **5**, **6**, **15** and **21**. In this case Ketoconazol was used as commercial control. As shown in Fig. 8 compounds **5**, **6** and **15** presented partial inhibitory effect on *C. albicans* growth but only compound **21** presented the best antifungal activity comparable with that of Ketoconazol.

2.5. In vitro citotoxic activity

For each group of analogues, representative compounds were chosen and they were subjected to a preliminary screening for antitumoral activity.

In vitro evaluation of the citotoxic activity of these compounds was carried against HT-29 human colon adenocarcinoma cell line by sulforhodamine B (SRB) assay. Cell viability was expressed as percentage in relation to controls. Data were averaged from at least three independent experiments and are expressed as means ± standard error of the means (SEM). 5-Fluorouracil, a drug widely used in the treatment of colon cancers, and hydroxyurea were used as positive controls.

Data (IC_{50}) observed for compounds submitted to antitumoral assay are presented in Table 7.

From data shown in Table 7, we can see that the most active compounds ($IC_{50} < 2$ μM) were those having a highly lipophilic group, farnesyl, at R^1, and an aromatic substituent with electron withdrawing groups (NO_2, CF_3, CN) at R^2 position (entries 23–25, 28, and 54, compounds **45**–**47**, **50** and **85**). The presence of other electron withdrawing groups (F, Cl) produced a slight increase in IC_{50} (<4) being still very active (entries 26–27, compounds **48** and **49**).

High activity ($IC_{50} < 4$) was also found in 1-dodecyl derivatives with aromatic substituent with electron withdrawing groups (entries 36–37, compounds **63**–**64**).

3-Methyl-2-butenyl and geranyl derivatives possessing an aromatic substituent with electron withdrawing groups gave antitumoral activity (IC_{50} 4–5) (entries 4, 8, 10 and 13, compounds **8**, **25**, **27** and **30**).

In general, urea derivatives provided higher values of IC_{50} (but still active) than thiourea analogues.

Based on these data we can suggest that the presence of a highly lipophilic group (farnesyl or dodecyl) in R^1 and an electron withdrawing group (more variability than that for antimicrobial activity) in the aromatic ring located at R^2 position enhanced anticancer activity against HT-29 cancer cell line of the synthesized compounds, showing in most cases more activity than that of the controls (Fig. 9).

An addition to these preliminary cell cytotoxicity tests is the study of the possible mechanism by which the new compounds inhibit the growth of tumor cells. Evidence suggests that the anticancer activity of several anticancer drugs commonly used in clinic (e.g. cisplatin, doxorubicin, arsenic trioxide, bortezomib, procarbazine, etoposide, etc) is mediated, at least in part, by reactive oxygen species (ROS) such as hydrogen peroxide (H_2O_2) [33]. For instance, although it has been known for many years that the anticancer effect of paclitaxel (taxol) is mediated by its activity on the microtubule protein tubulin, recent experiments have shown that H_2O_2 plays an important role in paclitaxel-induced cancer cell death [34]. The induction of oxidative stress by pro-oxidant agents is emerging as an attractive anticancer strategy [33,35,36]. In addition, our most cytotoxic compounds have a farnesyl radical in their structure, and recent data indicate that the generation of ROS is a primary mechanism by which farnesol kills cells [37]. Data also suggest that nitrobenzene, a radical that is present in several of our most potent compounds, may also generate ROS [38]. This made us consider the possible involvement of ROS in the cytotoxic activity of our compounds. HT-29 cells were treated with the five most active compounds in the presence or absence of the antioxidants N-acetylcysteine (NAC) or Mn(III) Tetrakis(1-methyl-4-pyridyl) porphyrin pentachloride (MnTMPyP); NAC and MnTMPyP have been shown to reduce the cytotoxic activity of drugs that generate ROS [39]. The five compounds and 5-FU were tested at three different concentrations (1, 10 and 100 μM). The antioxidants were added to the cells at a final concentration of 5 mM (NAC) and 5 μM (MnTMPyP) 30 min before the compounds. After a 48 h drug exposure, cell viability was estimated using the SRB assay. Neither antioxidant significantly modified the cytotoxic activity of any compound at any of the tested concentrations (results not shown). The cytotoxicity of pyrogallol (100 μM) and curcumin (10 μM) were significantly reduced by MnTMPyP and NAC, respectively (results not shown); these two drugs can be taken as positive controls for the assay. Our results suggested that the cytotoxic activity of these compounds is not mediated by the formation ROS.

3. Conclusions

Based on the design of new farnesyl diphosphate analogues we have prepared a series of new isoprenyl-thiourea and urea derivatives through an easy, high yielded reaction. We have evaluated their inhibitory activity on the growth of pathogenic bacteria and fungi, and we have detected antimicrobial activity in some of them (40% of the newly synthesized compounds). Higher antibacterial activity was observed in those thiourea derivatives having small chains (3-methyl-2-butenyl, isobutyl or isopentyl) and *p*-nitrophenyl group as substituents. Some of our compounds presented inhibitory activity comparable to that of commercial compounds against pathogenic strains *Staphylococcus aureus* and *Klebsiella pneumonia*.

Most of these compounds did not exhibit antifungal activity. Only a few isoprenyl and geranyl thiourea derivatives possessing certain structurally varied groups (*tert*-butyl, allyl, 4-nitrophenyl, 2-methoxyphenyl, methyl) showed high activity.

For both purposes (antibacterial and antifungal) urea derivatives were not active.

We have also subjected representative compounds to a preliminary screening for antitumoral activity. In this case our most active compounds possessed phenyl rings with electron withdrawing group and, unlike those with high antibacterial activity, a highly lipophilic group (specially farnesyl, but also 1-dodecyl substituents). In general thiourea derivatives were most active than urea ones. Our most active farnesyl derivatives presented greater activity than the standard used in the assay.

We have described a simple general backbone that allows (operating to its structural variation points) to improve/modulate antimicrobial or antitumoral activities, by choosing the appropriate reactants (amine and isothiocyanate/isocyanate). For the two biological activities studied (antimicrobial and cytotoxic) an aromatic ring with electron withdrawing groups at one position is required to be active. The presence of a small chain at the other position improves antibacterial activity, while if a highly lipophilic group is present, these compounds are fundamentally cytotoxic.

The results presented in this work encourage us to continue in this line of research.

4. Experimental section

4.1. Chemistry

4.1.1. General

All reagents, solvents, and starting materials were obtained from commercial suppliers and used without further purification. Evaporations were conducted under reduced pressure. Reactions were monitored by thin layer chromatography (TLC) using Kieselgel 60 F_{254} (E. Merck) plates and UV detector for visualization. Flash column chromatography was performed on Silica Gel 60 (E. Merck). Yields are of purified products. Melting points were obtained on a Stuart Melting Point Apparatus SMP 10 and are uncorrected. Optical rotations were obtained on a Perkin Elmer Polarimeter Model 341 at 25 °C. Mass spectra were recorded on a Micromass AUTOSPECQ mass spectrometer: EI at 70 eV and CI at 150 eV, HR mass measurements with resolutions of 10,000. NMR spectra were recorded at 25 °C on a Bruker AMX500 spectrometer and on a Bruker AV500 spectrometer at 500 MHz for ^{1}H and 125 MHz for ^{13}C. The chemical shifts are reported in ppm on the δ scale relative to TMS. COSY, DEPT, HSQC, and NOESY experiments were performed to assign the signals in the NMR spectra.

4.1.2. General procedure for synthesis of thiourea/urea derivatives (**4**–**89**)

To a solution of the isothiocyanate or isocyanate (1.0 mmol) in dichloromethane (10 ml), the amine (1.0 mmol) was added. The reaction was kept at room temperature for 15–20 min (TLC showed that all the starting material had reacted). The reaction mixture was evaporated to dryness to obtain the corresponding thiourea/urea derivative. Column chromatography gave the pure compounds in high yields.

*4.1.2.1. N-methyl-N′-(3-methyl-2-butenyl) thiourea (**4**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (15:10) as eluent (153 mg, 97% yield). MS (CI): *m/z* 159 (100%) $[M + H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 6.08, 5.84 (2m, 2H, 2NH), 5.23 [m, 1H, $(CH_3)_2C = CHCH_2N$], 3.98 [m, 2H, $(CH_3)_2C = CHCH_2N$], 2.98 [d, 3H, *J* 3.9 Hz, NCH_3], 1.72, 1.67 [d, 3H, ^4J = 1.0 Hz, s, 3H, $(CH_3)_2C = CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 182.2 (C═S), 137.7 [$(CH_3)_2C = CHCH_2N$], 119.0 [$(CH_3)_2C = CHCH_2N$], 42.5 [$(CH_3)_2C = CHCH_2N$], 30.8 (NCH_3), 25.6, 18.0 [$(CH_3)_2C = CHCH_2N$]; HRMS (CI): calcd for $C_7H_{15}N_2S$ 159.095595; found, 159.095439 $[M + H]^+$.

*4.1.2.2. N-tert-butyl-N′-(3-methyl-2-butenyl) thiourea (**5**).* The solid was purified by column chromatography, using hexane–ethyl acetate (4:1) as eluent (184 mg, 92% yield). M.p. 68–69 °C; MS (EI): *m/z* 200 (40%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 5.92, 5.48 (2s, 2H, 2NH), 5.28 [m, 1H, $(CH_3)_2C = CHCH_2N$], 4.08 [m, 2H, $(CH_3)_2C = CHCH_2N$], 1.76, 1.71 [2s, 6H, $(CH_3)_2C = CHCH_2N$], 1.42 [9 H, $NC(CH_3)_3$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.9 (C═S), 137.9 [$(CH_3)_2C = CHCH_2N$], 119.3 [$(CH_3)_2C = CHCH_2N$], 52.8 [$NC(CH_3)_3$], 43.7 [$(CH_3)_2C = CHCH_2N$], 29.6 [$NC(CH_3)_3$], 25.6, 18.1 [$(CH_3)_2C = CHCH_2N$]; HRMS (EI): calcd. for $C_{10}H_{20}N_2S$ 200.134721; found, 200.134344 $[M]^{+\cdot}$. Anal. Calcd for $C_{10}H_{20}N_2S$: C, 59.95; H, 10.06; N, 13.98; S, 16.00. Found: C, 60.11; H, 10.25; N, 13.87; S, 15.83.

*4.1.2.3. N-allyl-N′-(3-methyl-2-butenyl) thiourea (**6**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (5:1) as eluent (160 mg, 87% yield). MS (EI): *m/z* 184 (45%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 6.10–5.80 (m, 3H, 2NH, $NCH_2CH = CH_2$), 5.27–5.17 [m, 3H, $(CH_3)_2C = CHCH_2N$, $NCH_2CH = CH_2$], 4.08 (m, 2H, $NCH_2CH = CH_2$), 3.97 [m, 2H, $(CH_3)_2C = CHCH_2N$], 1.72, 1.67 [d, 3H, ^4J = 1.0 Hz, s, 3H, $(CH_3)_2C = CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 181.8 (C═S), 137.8 [$(CH_3)_2C = CHCH_2N$], 133.3 ($NCH_2CH = CH_2$), 119.0 [$(CH_3)_2C = CHCH_2N$], 117.3 ($NCH_2CH = CH_2$), 46.9 ($NCH_2CH = CH_2$), 42.5 [$(CH_3)_2C = CHCH_2N$], 25.6, 18.0 [$(CH_3)_2C = CHCH_2N$]; HRMS (EI): calcd. for $C_9H_{16}N_2S$ 184.103420; found, 184.103966 $[M]^{+\cdot}$.

*4.1.2.4. N-(3-methyl-2-butenyl)-N′-phenyl thiourea (**7**).* The solid was purified by column chromatography, using hexane–ethyl acetate (6:1) as eluent (176 mg, 79% yield). M.p. 115–117 °C; MS (CI): *m/z* 221 (70%) $[M + H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.01 (s, 1H, N*H*Ph), 7.46–7.16 (m, 5H, Ph), 5.91 (m, 1H, NH), 5.19 [m, 1H, $(CH_3)_2C = CHCH_2N$], 4.20 [m, 2H, $(CH_3)_2C = CHCH_2N$], 1.69, 1.65 [2s, 6H, $(CH_3)_2C = CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.2 (C═S), 137.5 [$(CH_3)_2C = CHCH_2N$], 136.2, 130.1, 127.1, 125.0 (Ph), 119.0 [$(CH_3)_2C = CHCH_2N$], 43.7 [$(CH_3)_2C = CHCH_2N$], 25.6, 18.0 [$(CH_3)_2C = CHCH_2N$]; HRMS (CI): calcd. for $C_{12}H_{17}N_2S$ 221.111245; found, 221.111332 $[M + H]^+$. Anal. Calcd for $C_{12}H_{16}N_2S$: C, 65.41; H, 7.32; N, 12.71; S, 14.55. Found: C, 65.43; H, 7.47; N, 12.59; S, 14.11.

*4.1.2.5. N-(3-methyl-2-butenyl)-N′-(4-nitrophenyl) thiourea (**8**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (35:10) as eluent (246 mg, 93% yield). MS (CI): *m/z* 266 (20%) $[M + H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.39 (s, 1H, N*H*Ar), 8.24, 7.43 (2m, 4H, Ar), 6.26 (m, 1H, NH), 5.27 [m, 1H, $(CH_3)_2C = CHCH_2N$], 4.21 [m, 2H, $(CH_3)_2C = CHCH_2N$], 1.75, 1.71 [2s, 6H, $(CH_3)_2C = CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.2 (C═S), 137.5 [$(CH_3)_2C = CHCH_2N$], 143.3–122.3 (Ar), 119.0 [$(CH_3)_2C = CHCH_2N$], 43.7 [$(CH_3)_2C = CHCH_2N$], 25.6, 18.0 [$(CH_3)_2C = CHCH_2N$]; HRMS (CI): calcd. for $C_{12}H_{16}N_3O_2S$ 266.096324; found, 266.095976 $[M + H]^+$.

*4.1.2.6. N-(4-Trifluoromethyl)phenyl-N′-(3-methyl-2-butenyl) thiourea (**9**).* The solid was purified by column chromatography, using hexane–ethyl acetate (4:1) as eluent (279 mg, 97% yield). M.p. 128–129 °C; MS (EI): *m/z* 288 (30%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.06 (s, 1H, N*H*Ar), 7.67, 7.34 (2m, 4H, Ar), 6.03 (m, 1H, NH), 5.24 [m, 1H, $(CH_3)_2C = CHCH_2N$], 4.22 [m, 2H, $(CH_3)_2C = CHCH_2N$], 1.73, 1.69 [2s, 6H, $(CH_3)_2C = CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.2 (C═S), 139.9, 127.3, 123.9 (Ar), 138.3 [$(CH_3)_2C = CHCH_2N$], 118.5 [$(CH_3)_2C = CHCH_2N$], 43.9 [$(CH_3)_2C = CHCH_2N$], 25.6, 18.1 [$(CH_3)_2C = CHCH_2N$]; HRMS (EI): calcd. for $C_{13}H_{15}F_3N_2S$ 288.090805; found, 288.090886 $[M]^{+\cdot}$. Anal.

Calcd for $C_{13}H_{15}F_3N_2S$: C, 54.15; H, 5.24; N, 9.72; S, 11.12. Found: C, 54.26; H, 5.06; N, 9.66; S, 11.40.

*4.1.2.7. N-(4-Fluorophenyl)-N′-(3-methyl-2-butenyl) thiourea (**10**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (35:10) as eluent (185 mg, 78% yield). MS (CI): *m/z* 239 (100%) $[M + H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 7.69 (s, 1H, N*H*Ar), 7.24–7.09 (m, 4H, Ar), 5.69 (m, 1H, NH), 5.18 [m, 1H, J = 7.0 Hz, $(CH_3)_2C = CHCH_2N$], 4.19 [m, 2H, $(CH_3)_2C = CHCH_2N$], 1.70, 1.66 [2s, 6H, $(CH_3)_2C = CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.7 (C=S), 162.4, 160.5, 127.8, 117.0 (Ar), 137.7 [$(CH_3)_2C = CHCH_2N$], 118.9 [$(CH_3)_2C = CHCH_2N$], 43.8 [$(CH_3)_2C = CHCH_2N$], 25.6, 18.1 [$(CH_3)_2C = CHCH_2N$]; HRMS (CI): calcd. for $C_{12}H_{16}FN_2S$ 239.101824; found, 239.102189 $[M + H]^+$.

*4.1.2.8. N-(4-Chlorophenyl)-N′-(3-methyl-2-butenyl) thiourea (**11**).* The solid was purified by column chromatography, using hexane–ethyl acetate (3:1) as eluent (241 mg, 95% yield). M.p. 119–120 °C; MS (EI): *m/z* 254 (30%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm). 8.18 (s, 1H, N*H*Ar), 7.37, 7.16 (2m, 4H, Ar), 5.85 (m, 1H, NH), 5.19 [m, 1H, $(CH_3)_2C = CHCH_2N$], 4.18 [m, 2H, $(CH_3)_2C = CHCH_2N$], 1.70, 1.66 [2s, 6H, $(CH_3)_2C = CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.3 (C=S), 137.8 [$(CH_3)_2C = CHCH_2N$], 134.9, 132.6, 130.2, 126.3 (Ar), 118.8 [$(CH_3)_2C = CHCH_2N$], 43.7 [$(CH_3)_2C = CHCH_2N$], 25.6, 18.1 [$(CH_3)_2C = CHCH_2N$]; HRMS (EI): calcd. for $C_{12}H_{15}ClN_2S$ 254.064448; found, 254.064256 $[M]^{+\cdot}$. Anal. Calcd for $C_{12}H_{15}ClN_2S$: C, 56.57; H, 5.93; N, 11.00; S, 12.60. Found: C, 56.76; H, 6.10; N, 11.02; S, 12.72.

*4.1.2.9. N-(4-Cyanophenyl)-N′-(3-methyl-2-butenyl) thiourea (**12**).* The solid was purified by column chromatography, using hexane–ethyl acetate (3:1) as eluent (208 mg, 85% yield). M.p. 148–149 °C; MS (CI): *m/z* 246 (100%) $[M + H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.41 (s, 1H, N*H*Ar), 7.66, 7.39 (2m, 4H, Ar), 6.21 (m, 1H, NH), 5.25 [m, 1H, $(CH_3)_2C = CHCH_2N$], 4.19 [m, 2H, $(CH_3)_2C = CHCH_2N$], 1.74, 1.70 [2s, 6H, $(CH_3)_2C = CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 179.8 (C=S), 141.3, 133.8, 123.1 (Ar), 138.5 [$(CH_3)_2C = CHCH_2N$], 118.3 [$(CH_3)_2C = CHCH_2N$], 108.5 (Ar*C*N), 43.7 [$(CH_3)_2C = CHCH_2N$], 25.6, 18.1 [$(CH_3)_2C = CHCH_2N$]; HRMS (CI): calcd. for $C_{13}H_{16}N_3S$ 246.106494; found, 246.107236 $[M + H]^+$. Anal. Calcd for $C_{13}H_{15}N_3S$: C, 63.64; H, 6.16; N, 17.13; S, 13.07. Found: C, 63.93; H, 6.39; N, 16.83; S, 12.81.

*4.1.2.10. N-(4-Methoxyphenyl)-N′-(3-methyl-2-butenyl) thiourea (**13**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (3:1) as eluent (220 g, 88% yield). MS (CI): *m/z* 251 (30%) $[M + H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 7.52 (s, 1H, N*H*Ar), 7.14–6.93 (m, 4H, Ar), 5.65 (m, 1H, NH), 5.16 [m, 1H, $(CH_3)_2C = CHCH_2N$], 4.19 [m, 2H, $(CH_3)_2C = CHCH_2N$], 3.82 (OCH_3), 1.69, 1.65 [2s, 6H, $(CH_3)_2C = CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.9 (C=S), 162.4, 158.9, 127.7, 115.3 (Ar), 137.4 [$(CH_3)_2C = CHCH_2N$], 119.1 [$(CH_3)_2C = CHCH_2N$], 55.5 (OCH_3), 43.7 [$(CH_3)_2C = CHCH_2N$], 25.6, 18.1 [$(CH_3)_2C = CHCH_2N$]; HRMS (CI): calcd. for $C_{13}H_{19}N_2OS$ 251.1218; found, 251.1235 $[M + H]^+$.

*4.1.2.11. N-(3-Methoxyphenyl)-N′-(3-methyl-2-butenyl) thiourea (**14**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (4:1) as eluent (240 mg, 96% yield). MS (CI): *m/z* 251 (55%) $[M + H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 7.80 (s, 1H, N*H*Ar), 7.31, 6.82, 6.77, 6.73 (4m, 4H, Ar), 6.00 (m, 1H, NH), 5.20 [m, 1H, $(CH_3)_2C = CHCH_2N$], 4.21 [m, 2H, $(CH_3)_2C = CHCH_2N$], 3.80 (OCH_3), 1.70, 1.66 [2s, 6H, $(CH_3)_2C = CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.2 (C=S), 161.0, 137.6, 130.9, 116.9, 112.7, 110.6 (Ar), 137.3 [$(CH_3)_2C = CHCH_2N$], 119.0 [$(CH_3)_2C = CHCH_2N$], 55.4 (OCH_3), 43.8 [$(CH_3)_2C = CHCH_2N$], 25.6, 18.1 [$(CH_3)_2C = CHCH_2N$]; HRMS (CI): calcd. for $C_{13}H_{19}N_2OS$ 251.1218; found, 251.1215 $[M + H]^+$.

*4.1.2.12. N-(2-Methoxyphenyl)-N′-(3-methyl-2-butenyl) thiourea (**15**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (4:1) as eluent (230 mg, 92% yield). MS (EI): *m/z* 250 (30%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 7.53 (s, 1H, N*H*Ar), 7.21, 6.97 (2m, 4H, Ar), 6.02 (m, 1H, NH), 5.22 [m, 1H, $(CH_3)_2C = CHCH_2N$], 4.21 [m, 2H, $(CH_3)_2C = CHCH_2N$], 3.84 (OCH_3), 1.71, 1.67 [2s, 6H, $(CH_3)_2C = CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.2 (C=S), 152.3, 127.3, 125.5, 124.5, 121.0, 111.9 (Ar), 137.5 [$(CH_3)_2C = CHCH_2N$], 119.1 [$(CH_3)_2C = CHCH_2N$], 55.6 (OCH_3), 43.7 [$(CH_3)_2C = CHCH_2N$], 25.6, 18.1 [$(CH_3)_2C = CHCH_2N$]; HRMS (EI): calcd. for $C_{13}H_{18}N_2OS$ 250.1140; found, 250.1141 $[M]^{+\cdot}$.

*4.1.2.13. N-(3-methyl-2-butenyl)-N′-(3-pyridyl) thiourea (**16**).* The solid was purified by column chromatography, using hexane–ethyl acetate (1:1) as eluent (199 mg, 90% yield). M.p. 123–124 °C; MS (EI): *m/z* 221 (30%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.52, 7.65, 7.37 (3m, 4H, Py), 7.72 (s, 1H, N*H*Py), 5.85 (m, 1H, NH), 5.22 [m, 1H, $(CH_3)_2C = CHCH_2N$], 4.20 [m, 2H, $(CH_3)_2C = CHCH_2N$], 1.72, 1.69 [2s, 6H, $(CH_3)_2C = CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.9 (C=S), 148.0, 146.4, 135.3, 132.5, 124.3 (Py), 138.3 [$(CH_3)_2C = CHCH_2N$], 118.6 [$(CH_3)_2C = CHCH_2N$], 43.8 [$(CH_3)_2C = CHCH_2N$], 25.6, 18.1 [$(CH_3)_2C = CHCH_2N$]; HRMS (EI): calcd. for $C_{11}H_{15}N_3S$ 221.098669; found, 221.098908 $[M]^{+\cdot}$. Anal. Calcd for $C_{16}H_{23}N_3S$: C, 59.69; H, 6.83; N, 18.99; S, 14.49. Found: C, 59.86; H, 6.97; N, 18.78; S, 14.29.

*4.1.2.14. N-(3-methyl-2-butenyl)-N′-(2-piperidinoethyl) thiourea (**17**).* The solid was purified by column chromatography, using hexane–ethyl acetate (1:6) as eluent (216 mg, 85% yield). M.p. 148–149 °C; MS (CI): *m/z* 256 (60%) $[M + H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 6.71 (m, 2H, NH), 5.26 [t, 1H, J = 6.7 Hz, $(CH_3)_2C = CHCH_2N$], 4.06 [m, 2H, $(CH_3)_2C = CHCH_2N$], 3.44 (m, 2H, NCH_2CH_2N), 2.52 [m, 6H, $CH_2N(CH_2)_2$], 1.71, 1.68 [2s, 6H, $(CH_3)_2C = CHCH_2N$], 1.60 (m, 4H, $2CH_2$), 1.45 (m, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 182.4 (C=S), 136.2 [$(CH_3)_2C = CHCH_2N$], 120.1 [$(CH_3)_2C = CHCH_2N$], 58.8, 54.5 (NCH_2CH_2N), 43.4 [$(CH_3)_2C = CHCH_2N$], 42.0, 25.6, 25.5 (piperidine), 23.7, 18.0 [$(CH_3)_2C = CHCH_2N$]; HRMS (CI): calcd. for $C_{13}H_{26}N_3S$ 256.184745; found, 256.183576 $[M + H]^+$. Anal. Calcd for $C_{13}H_{25}N_3S$: C, 61.13; H, 9.87; N, 16.45; S, 12.55. Found: C, 62.96; H, 9.67; N, 16.61; S, 12.43.

*4.1.2.15. N-(3-methyl-2-butenyl)-N′-[2-(4-morpholino)ethyl] thiourea (**18**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (1:4) as eluent (203 mg, 79% yield). MS (EI): *m/z* 257 (20%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 6.61 (m, 2H, NH), 5.20 [t, 1H, J = 6.8 Hz, $(CH_3)_2C = CHCH_2N$], 3.97 [m, 2H, $(CH_3)_2C = CHCH_2N$], 3.63 (t, 4H, J = 4.4 Hz, CH_2OCH_2), 3.42 (m, 2H, NCH_2CH_2N), 2.58–2.40 [m, 6H, $CH_2N(CH_2)_2$], 1.68, 1.64 [2s, 6H, $(CH_3)_2C = CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 181. (C=S), 136.6 [$(CH_3)_2C = CHCH_2N$], 119.6 [$(CH_3)_2C = CHCH_2N$], 66.4 (CH_2OCH_2), 57.7, 53.4 [$NCH_2CH_2N(CH_2)_2$], 42.7 [$(CH_3)_2C = CHCH_2N$], 25.5, 17.9 [$(CH_3)_2C = CHCH_2N$]; HRMS (EI): calcd. for $C_{12}H_{23}N_3OS$ 257.156184; found, 257.155985 $[M]^{+\cdot}$.

*4.1.2.16. N-(3-methyl-2-butenyl)-N′-[3-(4-morpholino)propyl] thiourea (**19**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (1:3) as eluent (245 mg, 90% yield). MS (CI): *m/z* 272 (5%) $[M + H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 7.40 (m, 2H, NH), 5.23 [m, 1H, $(CH_3)_2C = CHCH_2N$], 4.00 [m, 2H, $(CH_3)_2C = CHCH_2N$], 3.69 (m, 4H, CH_2OCH_2), 3.49 (m, 2H, $NCH_2CH_2CH_2N$), 2.56–2.44 [m, 6H, $CH_2N(CH_2)_2$], 1.83–1.65 (m, 8H, $NCH_2CH_2CH_2N$, $(CH_3)_2C = CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 181.7 (C=S), 136.6 [$(CH_3)_2C = CHCH_2N$], 119.6 [$(CH_3)_2C = CHCH_2N$], 66.5 (CH_2OCH_2), 58.9, 53.8, 23.4 [$NCH_2CH_2CH_2N(CH_2)_2$], 47.4 (CH_2NCH_2), 40.7 [$(CH_3)_2C = CHCH_2N$],

25.6, 18.1 [(CH_3)$_2$C = CHCH$_2$N]; HRMS (CI): calcd. for $C_{13}H_{26}N_3OS$ 272.179660; found, 272.179292 $[M + H]^+$.

*4.1.2.17. N-ethoxycarbonyl-N′-(3-methyl-2-butenyl) thiourea (**20**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (3:1) as eluent (286 mg, 96% yield). MS (EI): *m/z* 230 (25%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 6.44 (m, 2H, 2NH), 5.22 [m, 1H, (CH_3)$_2$C = C*H*CH$_2$N], 4.40 [m, 2H, (CH_3)C=CHC*H*$_2$N], 4.30 [d, 2H, *J* 4.8 Hz, (NC*H*$_2$CONCH$_2$CH$_3$)], 4.20 (q, 2H, *J* 7.2 Hz, NCH$_2$CO$_2$C*H*$_2$CH$_3$), 1.69, 1.66, [2s, 6H, (C*H*$_3$)$_2$C = CHCH$_2$N], 1.25 (t, 3H, *J* 7.2 Hz, NCH$_2$CO$_2$CH$_2$C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 185.0 (C=S), 171.2 (C=O), 137.6 [(CH_3)$_2$*C* = CHCH$_2$N], 117.2 [(CH_3)$_2$C = *C*HCH$_2$N], 61.0 (NCH$_2$CO$_2$*C*H$_2$CH$_3$), 46.7 (NCH$_2$COCH$_2$CH$_3$), 39.4 [(CH_3)$_2$C = CH*C*H$_2$N], 25.6, 18.24 [(*C*H$_3$)$_2$C = CHCH$_2$N], 14.0 (NCH$_2$CO$_2$CH$_2$*C*H$_3$); HRMS (EI): calcd. for $C_{10}H_{18}N_2O_2S$ 230.10890; found, 230.10901 $[M]^{+\cdot}$.

*4.1.2.18. N-geranyl-N′-methyl thiourea (**21**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (35:10) as eluent (180 mg, 78% yield). MS (CI): *m/z* 227 (100%) $[M + H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 6.20, 5.96 (2m, 2H, 2NH), 5.21 [m, 1H, (CH_3)$_2$C = CHCH$_2$CH$_2$C(CH$_3$) = C*H*CH$_2$N], 5.02 [m, 1H, (CH_3)$_2$C = C*H*CH$_2$CH$_2$C(CH$_3$) = CHCH$_2$N], 3.97 [m, 2H, (CH_3)$_2$C = CHCH$_2$CH$_2$C(CH$_3$) = CHC*H*$_2$N], 2.97 (d, 3H, *J* = 4.2 Hz, NCH$_3$), 2.10–1.95 [m, 4H, (CH_3)$_2$C = CHC*H*$_2$C*H*$_2$C(CH$_3$) = CHCH$_2$N], 1.65, 1.64, 1.57 [3s, 9H, (C*H*$_3$)$_2$C = CHCH$_2$CH$_2$C(C*H*$_3$) = CHCH$_2$N]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 182.1 (C=S), 141.0, 137.8 [(CH_3)$_2$*C* = CHCH$_2$CH$_2$*C*(CH$_3$) = CHCH$_2$N], 123.5 [(CH_3)$_2$C = *C*HCH$_2$CH$_2$C(CH$_3$) = CHCH$_2$N], 118.8 [(CH_3)$_2$C = CHCH$_2$CH$_2$C(CH$_3$) = *C*HCH$_2$N], 42.4 [(CH_3)$_2$C = CHCH$_2$ CH$_2$C(CH$_3$) = CH*C*H$_2$N], 39.3, 26.2 [(CH_3)$_2$C = CH*C*H$_2$C*H*$_2$C(CH$_3$) = CHCH$_2$N], 30.8 (NCH$_3$), 25.5, 17.6, 16.3 [(*C*H$_3$)$_2$C = CHCH$_2$CH$_2$C(*C*H$_3$) = CHCH$_2$N]; HRMS (CI): calcd. for $C_{12}H_{23}N_2S$ 227.158196; found, 227.158051 $[M + H]^+$.

*4.1.2.19. N-tert-butyl-N′-geranyl thiourea (**22**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (4:1) as eluent (259 mg, 97% yield). MS (EI): *m/z* 268 (20%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 5.91, 5.49 (2s, 2H, 2NH), 5.29 [t, 1H, *J* = 7.0 Hz, (CH_3)$_2$C = CHCH$_2$CH$_2$C(CH$_3$) = C*H*CH$_2$N], 5.06 [m, 1H, (CH_3)$_2$C = C*H*CH$_2$CH$_2$C(CH$_3$) = CHCH$_2$N], 4.09 [m, 2H, (CH_3)$_2$C = CHCH$_2$CH$_2$C(CH$_3$) = CHC*H*$_2$N], 2.13–2.02 [m, 4H, (CH_3)$_2$C = CHC*H*$_2$C*H*$_2$C(CH$_3$) = CHCH$_2$N], 1.70, 1.67, 1.60 [3s, 9H, (C*H*$_3$)$_2$C = CHCH$_2$CH$_2$C(C*H*$_3$) = CHCH$_2$N], 1.42 [NC(CH$_3$)$_3$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.9 (C=S), 141.5, 131.9 [(CH_3)$_2$*C* = CHCH$_2$CH$_2$*C*(CH$_3$) = CHCH$_2$N], 123.6 [(CH_3)$_2$C = *C*HCH$_2$CH$_2$C(CH$_3$) = CHCH$_2$N], 119.1 [(CH_3)$_2$C = CHCH$_2$CH$_2$ C(CH$_3$) = *C*HCH$_2$N], 52.8 [NC(CH$_3$)$_3$], 43.6 [(CH_3)$_2$C = CHCH$_2$CH$_2$C(CH$_3$) = CHCH$_2$N], 39.4, 26.3 [(CH_3)$_2$C = C HCH$_2$CH$_2$C(CH$_3$) = CHCH$_2$N], 29.5 [NC(*C*H$_3$)$_3$], 25.7, 17.7, 16.4 [(CH_3)$_2$C = CHCH$_2$CH$_2$C(*C*H$_3$) = CHCH$_2$N]; HRMS (EI): calcd. for $C_{15}H_{28}N_2S$ 268.197321; found, 268.197912 $[M]^{+\cdot}$.

*4.1.2.20. N-allyl-N′-geranyl thiourea (**23**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (5:1) as eluent (245 mg, 98% yield). MS (CI): *m/z* 253 (95%) $[M + H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 6.10–5.80 (m, 3H, 2NH, NCH$_2$C*H* = CH$_2$), 5.28–5.18 [m, 3H, (CH_3)$_2$C = CHCH$_2$CH$_2$ C(CH$_3$) = C*H*CH$_2$N, NCH$_2$CH = C*H*$_2$], 5.04 [m, 1H, (CH_3)$_2$C = C*H* CH$_2$CH$_2$C(CH$_3$) = CHCH$_2$N], 4.09 (m, 2H, NC*H*$_2$CH = CH$_2$), 3.98 [m, 2H, (CH_3)$_2$C = CHCH$_2$CH$_2$C(CH$_3$) = CHC*H*$_2$N], 2.11–1.98 [m, 4H, (CH_3)$_2$C = CHC*H*$_2$C*H*$_2$C(CH$_3$) = CHCH$_2$N], 1.67, 1.57 [2s, 9H, (C*H*$_3$)$_2$C = CHCH$_2$CH$_2$C(C*H*$_3$) = CHCH$_2$N]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 182.0 (C=S), 141.4, 131.9 [(CH_3)$_2$*C* = CHCH$_2$CH$_2$ *C*(CH$_3$) = CHCH$_2$N], 133.3 (NCH$_2$*C*H = CH$_2$), 123.5 [(CH_3)$_2$C = *C*HCH$_2$CH$_2$C(CH$_3$) = CHCH$_2$N], 118.7 [(CH_3)$_2$C = CHCH$_2$ CH$_2$C(CH$_3$) = *C*HCH$_2$N], 117.4 (NCH$_2$CH = *C*H$_2$), 47.0 (N*C*H$_2$CH = CH$_2$), 42.4 [(CH_3)$_2$C = CHCH$_2$CH$_2$C(CH$_3$) = CH*C*H$_2$N], 39.4, 26.3 [(CH_3)$_2$C = CH*C*H$_2$C*H*$_2$C(CH$_3$) = CHCH$_2$N], 25.6, 17.6, 16.4 [(*C*H$_3$)$_2$C = CHCH$_2$CH$_2$C(*C*H$_3$) = CHCH$_2$N]; HRMS (CI): calcd. for $C_{14}H_{25}N_2S$ 253.173846; found, 253.174184 $[M + H]^+$.

*4.1.2.21. N-geranyl-N′-phenyl thiourea (**24**).* The solid was purified by column chromatography, using hexane–ethyl acetate (6:1) as eluent (282 mg, 98% yield). M.p. 108–109 °C; MS (CI): *m/z* 289 (100%) $[M + H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 7.93 (s, 1H, N*H*Ph), 7.44–7.18 (m, 5H, Ph), 5.91 (m, 1H, NH), 5.20 [m, 1H, (CH_3)$_2$C = CHCH$_2$CH$_2$C(CH$_3$) = C*H*CH$_2$N], 5.02 [m, 1H, (CH_3)$_2$C = C*H* CH$_2$CH$_2$C(CH$_3$) = CHCH$_2$N], 4.22 [m, 2H, (CH_3)$_2$C = CHCH$_2$ CH$_2$C(CH$_3$) = CHC*H*$_2$N], 2.08–1.96 [m, 4H, (CH_3)$_2$C = CHC*H*$_2$C*H*$_2$ C(CH$_3$) = CHCH$_2$N], 1.65, 1.64, 1.56 [3s, 9H, (C*H*$_3$)$_2$C = CHCH$_2$ CH$_2$C(C*H*$_3$) = CHCH$_2$N]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.3 (C=S), 141.0, 136.3 [(CH_3)$_2$*C* = CHCH$_2$CH$_2$*C*(CH$_3$) = CHCH$_2$N], 131.8, 130.1, 127.1, 125.0 (Ph), 123.6 [(CH_3)$_2$C = *C*HCH$_2$CH$_2$C(CH$_3$) = CH CH$_2$N], 118.8 [(CH_3)$_2$C = CHCH$_2$CH$_2$C(CH$_3$) = *C*HCH$_2$N], 43.7 [(CH_3)$_2$C = CHCH$_2$CH$_2$C(CH$_3$) = CHC*H*$_2$N], 39.4, 26.2 [(CH_3)$_2$C = CHC*H*$_2$C*H*$_2$C(CH$_3$) = CHCH$_2$N], 25.6, 17.6, 16.5 [(*C*H$_3$)$_2$C = CHCH$_2$ CH$_2$C(*C*H$_3$) = CHCH$_2$N]; HRMS (CI): calcd. for $C_{17}H_{25}N_2S$ 289.173846; found, 289.173140 $[M + H]^+$. Anal. Calcd for $C_{17}H_{24}N_2S$: C, 70.79; H, 8.39; N, 9.71; S, 11.12. Found: C, 70.92; H, 8.37; N, 9.77; S, 11.01.

*4.1.2.22. N-geranyl-N′-(4-nitrophenyl) thiourea (**25**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (35:10) as eluent (313 mg, 94% yield). MS (CI): *m/z* 334 (15%) $[M + H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.46 (s, 1H, N*H*Ar), 8.22, 7.44 (2m, 4H, Ar), 6.31 (m, 1H, NH), 5.28 [m, 1H, (CH_3)$_2$C = CHCH$_2$CH$_2$C(CH$_3$) = C*H*CH$_2$N], 5.04 [m, 1H, (CH_3)$_2$C = C*H*CH$_2$CH$_2$ C(CH$_3$) = CHCH$_2$N], 4.22 [m, 2H, (CH_3)$_2$C = CHCH$_2$CH$_2$C(CH$_3$) = CHC*H*$_2$N], 2.12–2.01 [m, 4H, (CH_3)$_2$C = CHC*H*$_2$C*H*$_2$C(CH$_3$) = CHCH$_2$N], 1.71, 1.65, 1.58 [3s, 9H, (C*H*$_3$)$_2$C = CHCH$_2$CH$_2$ C(C*H*$_3$) = CHCH$_2$N]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 179.9 (C=S), 144.4, 132.0 [(CH_3)$_2$*C* = CHCH$_2$CH$_2$*C*(CH$_3$) = CHCH$_2$N], 143.3, 142.2, 125.5, 122.3 (Ar), 123.4 [(CH_3)$_2$C = *C*HCH$_2$CH$_2$C(CH$_3$) = CHCH$_2$N], 118.0 [(CH_3)$_2$C = CHCH$_2$CH$_2$C(CH$_3$) = *C*HCH$_2$N], 43.6 [(CH_3)$_2$C = CHCH$_2$CH$_2$C(CH$_3$) = CHC*H*$_2$N], 39.4, 26.3 [(CH_3)$_2$C = CHC*H*$_2$C*H*$_2$ C(CH$_3$) = CHCH$_2$N], 25.6, 17.7, 16.6 [(*C*H$_3$)$_2$C = CHCH$_2$CH$_2$C(*C*H$_3$) = CHCH$_2$N]; HRMS (CI): calcd. for $C_{17}H_{24}N_3O_2S$ 334.158924; found, 334.160376 $[M + H]^+$.

*4.1.2.23. N-geranyl-N′-(3-nitrophenyl) thiourea (**26**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (4:1) as eluent (300 mg, 90% yield). MS (CI): *m/z* 334 (10%) $[M + H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.14 (s, 1H, N*H*Ar), 8.07, 7.65, 7.58 (3m, 4H, Ar), 6.04 (m, 1H, NH), 5.27 [m, 1H, (CH_3)$_2$C = CHCH$_2$CH$_2$C(CH$_3$) = C*H*CH$_2$N], 5.04 [m, 1H, (CH_3)$_2$C = C*H*CH$_2$CH$_2$C(CH$_3$) = CHCH$_2$N], 4.21 [m, 2H, (CH_3)$_2$C = CHCH$_2$CH$_2$ C(CH$_3$) = CHC*H*$_2$N], 2.12–2.00 [m, 4H, (CH_3)$_2$C = CHC*H*$_2$C*H*$_2$ C(CH$_3$) = CHCH$_2$N], 1.71, 1.64, 1.58 [3s, 9H, (C*H*$_3$)$_2$C = CHCH$_2$CH$_2$ C(C*H*$_3$) = CHCH$_2$N]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.5 (C=S), 149.0, 130.1, 120.9, 118.9 (Ar), 142.4, 132.0 [(CH_3)$_2$*C* = CHCH$_2$CH$_2$*C*(CH$_3$) = CHCH$_2$N], 123.5 [(CH_3)$_2$C = *C*HCH$_2$CH$_2$ C(CH$_3$) = CHCH$_2$N], 118.1 [(CH_3)$_2$C = CHCH$_2$CH$_2$C(CH$_3$) = *C*HCH$_2$N], 43.5 [(CH_3)$_2$C = CHCH$_2$CH$_2$C(CH$_3$) = CHC*H*$_2$N], 39.4, 26.2 [(CH_3)$_2$C = CHC*H*$_2$C*H*$_2$C(CH$_3$) = CHCH$_2$N], 25.6, 17.7, 16.6 [(*C*H$_3$)$_2$C = CHCH$_2$CH$_2$C(*C*H$_3$) = CHCH$_2$N]; HRMS (CI): calcd. for $C_{17}H_{24}N_3O_2S$ 334.1589; found, 334.1608 $[M + H]^+$.

*4.1.2.24. N-(4-Trifluoromethyl)phenyl-N′-geranyl thiourea (**27**).* The solid was purified by column chromatography, using hexane–ethyl acetate (4:1) as eluent (345 mg, 97% yield). M.p. 83–84 °C; MS

(EI): *m/z* 356 (10%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.47 (s, 1H, N*H*Ar), 7.66, 7.35 (2m, 4H, Ar), 6.05 (m, 1H, NH), 5.24 [t, 1H, *J* = 6.8 Hz, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 5.03 [m, 1H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 4.23 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 2.12–1.98 [m, 4H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.68, 1.64, 1.57 [3s, 9H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 179.9 (C=S), 147.8, 141.7, [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 139.9, 128.3, 128.1, 123.8 (Ar), 123.5 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 118.3 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 43.7 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 39.4, 26.2 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 25.6, 17.6, 16.5 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; HRMS (EI): calcd. for $C_{18}H_{23}F_3N_2S$ 356.153405; found, 356.153753 $[M]^{+\cdot}$. Anal. Calcd for $C_{18}H_{23}F_3N_2S$: C, 60.65; H, 6.50; N, 7.86; S, 9.00. Found: C, 60.90; H, 6.43; N, 7.83; S, 9.31.

*4.1.2.25. N-(4-fluorophenyl)-N′-geranyl thiourea (**28**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (4:1) as eluent (275 mg, 90% yield). MS (EI): *m/z* 306 (15%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 7.71 (s, 1H, N*H*Ar), 7.24–7.08 (m, 4H, Ar), 5.70 (m, 1H, NH), 5.19 [t, 1H, *J* = 6.8 Hz, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 5.02 [m, 1H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 4.21 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 2.09–1.96 [m, 4H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.65, 1.64, 1.57 [3s, 9H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.8 (C=S), 162.4, 160.5, 127.7, 117.0 (Ar), 141.2, 131.9 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 123.6 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 118.7 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 43.7 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 39.4, 26.3 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 25.6, 17.7, 16.5 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; HRMS (EI): calcd. for $C_{17}H_{23}FN_2S$ 306.156599; found, 306.156477 $[M]^{+\cdot}$.

*4.1.2.26. N-(4-Chlorophenyl)-N′-geranyl thiourea (**29**).* The solid was purified by column chromatography, using hexane–ethyl acetate (4:1) as eluent (306 mg, 95% yield). M.p. 101–102 °C, MS (EI): *m/z* 322 (10%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 7.75 (s, 1H, N*H*Ar), 7.39, 7.16 (2m, 4H, Ar), 5.80 (m, 1H, NH), 5.20 [t, 1H, *J* = 7.0 Hz, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 5.02 [m, 1H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 4.21 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 2.10–1.97 [m, 4H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.67, 1.65, 1.57 [3s, 9H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.4 (C=S), 141.4, 131.9 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 134.7, 132.8, 130.3, 126.3 (Ar), 123.6 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 118.5 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 43.8 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 39.4, 26.2 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 25.6, 17.7, 16.5 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; HRMS (EI): calcd. for $C_{17}H_{23}ClN_2S$ 322.127048; found, 322.126797 $[M]^{+\cdot}$. Anal. calcd for $C_{17}H_{23}ClN_2S$: C, 63.23; H, 7.18; N, 8.68; S, 9.93. Found: C, 63.50; H, 7.44; N, 8.76; S, 9.81.

*4.1.2.27. N-(4-cyanophenyl)-N′-geranyl thiourea (**30**).* The solid was purified by column chromatography, using hexane–ethyl acetate (5:1) as eluent (306 mg, 98% yield). M.p. 59–60 °C, MS (EI): *m/z* 313 (10%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.58 (s, 1H, N*H*Ar), 7.66, 7.39 (2m, 4H, Ar), 6.20 (m, 1H, NH), 5.25 [t, 1H, *J* = 7.1 Hz, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 5.03 [m, 1H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 4.21 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 2.12–1.98 [m, 4H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.69, 1.65, 1.58 [3s, 9H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 179.7 (C=S), 141.3, 132.0 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 142.0, 133.8, 123.4, 118.2 (Ar), 123.0 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 118.0 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 108.7 (ArCN), 43.6 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 39.4, 26.2 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 25.6, 17.7, 16.5 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; HRMS (EI): calcd. for $C_{18}H_{23}N_3S$ 313.161270; found, 313.161017 $[M]^{+\cdot}$. Anal. Calcd for $C_{18}H_{23}N_3S$: C, 68.97; H, 7.40; N, 13.41; S, 10.23. Found: C, 69.22; H, 7.32; N, 13.44; S, 10.12.

*4.1.2.28. N-geranyl-N′-(4-methoxyphenyl) thiourea (**31**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (3:1) as eluent (270 mg, 85% yield). MS (CI): *m/z* 319 (20%) $[M + H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 7.47 (s, 1H, N*H*Ar), 7.17–6.90 (m, 4H, Ar), 5.65 (m, 1H, NH), 5.17 [m, 1H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 5.02 [m, 1H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 4.22 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 3.82 (OCH_3), 2.10–1.94 [m, 4H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.64, 1.58, 1.56 [3s, 9H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.1 (C=S), 159.0, 128.3, 127.7, 115.3 (Ar), 140.8, 131.8 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 123.6 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 118.9 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 55.5 (OCH_3), 43.7 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 39.9, 26.2 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 25.6, 17.7, 17.2 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; HRMS (CI): calcd. for $C_{18}H_{27}N_2OS$ 319.1844; found, 319.1825 $[M + H]^+$.

*4.1.2.29. N-geranyl-N′-(3-methoxyphenyl) thiourea (**32**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (4:1) as eluent (285 mg, 90% yield). MS (CI): *m/z* 319 (50%) $[M + H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 7.68 (s, 1H, N*H*Ar), 7.32, 6.82, 6.77, 6.72 (4m, 4H, Ar), 6.00 (m, 1H, NH), 5.21 [m, 1H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 5.03 [m, 1H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 4.23 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 3.80 (OCH_3), 2.09–1.96 [m, 4H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.66, 1.64, 1.60, 1.57 [4s, 9H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.1 (C=S), 160.9, 137.2, 130.9, 116.8, (Ar), 140.8, 131.8 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 123.6 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 118.7 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 55.4 (OCH_3), 43.8 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 39.4, 26.3 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 25.6, 17.7, 16.5 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; HRMS (CI): calcd. for $C_{18}H_{27}N_2OS$ 319.1844; found, 319.1840 $[M + H]^+$.

*4.1.2.30. N-geranyl-N′-(2-methoxyphenyl) thiourea (**33**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (4:1) as eluent (285 mg, 90% yield). MS (EI): *m/z* 318 (15%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 7.52 (s, 1H, N*H*Ar), 7.21, 6.97 (2m, 4H, Ar), 6.02 (m, 1H, NH), 5.23 [m, 1H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 5.03 [m, 1H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 4.23 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 3.84 (OCH_3), 2.10–1.97 [m, 4H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.67, 1.65, 1.57 [3s, 9H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$; δ ppm): 180.2 (C=S), 152.3, 127.3, 125.5, 111.9 (Ar), 141.0, 131.8 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 123.6 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 118.9 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 55.6 (OCH_3), 43.7 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 39.4, 26.3 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 25.6, 17.7, 16.5 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; HRMS (EI): calcd. for $C_{18}H_{26}N_2OS$ 318.1766; found, 318.1767 $[M]^{+\cdot}$.

*4.1.2.31. N-geranyl-N′-(3-pyridyl) thiourea (**34**).* The solid was purified by column chromatography, using hexane–ethyl acetate (1:1) as eluent (260 mg, 90% yield). M.p. 110–111 °C; MS (CI): *m/z* 290 (80%) $[M + H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.50, 7.70, 7.30 (3m, 4H, Py), 8.04 (s, 1H, N*H*Py), 5.92 (m, 1H, NH), 5.22 [t, 1H, *J* = 6.6 Hz, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = *CH*CH_2N], 5.03 [m, 1H, $(CH_3)_2C$ = *CH*$CH_2CH_2C(CH_3)$ = $CHCH_2$N], 4.21 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 2.10–1.97 [m, 4H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 1.67, 1.65, 1.57 [3s, 9H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.7 (C=S), 147.8, 146.3, 135.2, 124.3 (Py), 141.8, 131.9 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 123.5 [$(CH_3)_2C$ = *C*$HCH_2CH_2C(CH_3)$ = $CHCH_2$N], 118.0 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = *C*HCH_2N], 43.6 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 39.4, 26.2 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 25.6, 17.7, 16.5 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N]; HRMS (CI): calcd. for $C_{16}H_{24}N_3S$ 290.169095; found, 290.168810 $[M + H]^+$. Anal. calcd for $C_{16}H_{23}N_3S$: C, 66.39; H, 8.01; N, 14.52; S, 11.08. Found: C, 66.54; H, 8.23; N, 14.31; S, 11.08.

*4.1.2.32. N-geranyl-N′-[1-(2-piperidino)ethyl] thiourea (**35**).* The solid was purified by column chromatography, using ethyl acetate-methanol (1:1) as eluent (271 mg, 84% yield). M.p. 94–95 °C; MS (EI): *m/z* 323 (10%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 6.62 (m, 2H, 2NH), 5.25 [t, 1H, *J* = 6.2 Hz, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = *CH*CH_2N], 5.04 [m, 1H, $(CH_3)_2C$ = *CH*$CH_2CH_2C(CH_3)$ = $CHCH_2$N], 4.08 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 3.32 (m, 2H, N*C*H_2CH_2N), 2.40 [m, 6H, $CH_2N(CH_2)_2$], 2.10–1.92 [m, 4H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 1.67, 1.64, 1.57 [3s, 9H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 1.52 (m, 4H, $2CH_2$), 1.41 (m, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 182.4 (C=S), 139.5, 131.7 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 123.7 [$(CH_3)_2C$ = *C*$HCH_2CH_2C(CH_3)$ = $CHCH_2$N], 119.8 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = *C*HCH_2N], 59.4, 54.5 (NCH_2CH_2N), 43.3 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 42.2, 25.6, 25.5 (piperidine), 39.4, 26.3 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 23.9, 17.6, 16.4 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N]; HRMS (EI): calcd. for $C_{18}H_{33}N_3S$ 323.239520; found, 323.239517 $[M]^{+\cdot}$. Anal. calcd for $C_{18}H_{33}N_3S$: C, 66.82; H, 10.28; N, 12.99; S, 9.91. Found: C, 66.62; H, 10.42; N, 12.97; S, 9.72.

*4.1.2.33. N-geranyl-N′-[2-(4-morpholino)ethyl] thiourea (**36**).* The solid was purified by column chromatography, using hexane–ethyl acetate (1:4) as eluent (300 mg, 92% yield). M.p. 77–78 °C; MS (EI): *m/z* 325 (5%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 6.38 (m, 2H, 2NH), 5.26 [m, 1H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = *CH*CH_2N], 5.06 [m, 1H, $(CH_3)_2C$ = *CH*$CH_2CH_2C(CH_3)$ = $CHCH_2$N], 4.02 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 3.68 (t, 4H, *J* = 4.5 Hz, CH_2OCH_2), 3.47 (m, 2H, N*C*H_2CH_2N), 2.58–2.45 [m, 6H, $CH_2N(CH_2)_2$], 2.11–1.99 [m, 4H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 1.70, 1.67, 1.59 [2s, 9H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 182.2 (C=S), 140.7, 131.9 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 123.6 [$(CH_3)_2C$ = *C*$HCH_2CH_2C(CH_3)$ = $CHCH_2$N], 119.4 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = *C*HCH_2N], 66.7 (CH_2OCH_2), 57.7, 53.4, 32.4 [$NCH_2CH_2N(CH_2)_2$], 41.4 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 39.5, 26.3 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 25.7, 17.7, 16.5 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N]; HRMS (EI): calcd. for $C_{17}H_{31}N_3OS$ 325.218785; found, 325.219632 $[M]^{+\cdot}$. Anal. Calcd for $C_{17}H_{31}N_3OS$: C, 62.73; H, 9.60; N, 12.91; S, 9.85. Found: C, 62.63; H, 9.84; N, 12.66; S, 9.64.

*4.1.2.34. N-geranyl-N′-[3-(4-morpholino)propyl] thiourea (**37**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (1:5) as eluent (325 mg, 96% yield). MS (EI): *m/z* 339 (25%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 7.05 (m, 2H, 2NH), 5.25 [m, 1H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = *CH*CH_2N], 5.05 [m, 1H, $(CH_3)_2C$ = *CH*$CH_2CH_2C(CH_3)$ = $CHCH_2$N], 4.02 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 3.69 (t, 4H, *J* = 4.6 Hz, CH_2OCH_2), 3.48 (m, 2H, N*C*$H_2CH_2CH_2$N), 2.45 [m, 6H, $CH_2N(CH_2)_2$], 2.11–1.99 [m, 4H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 1.74 (m, 2H, $NCH_2CH_2CH_2$N), 1.67, 1.59 [2s, 9H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 181.8 (C=S), 141.0, 131.9 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 123.6 [$(CH_3)_2C$ = *C*$HCH_2CH_2C(CH_3)$ = $CHCH_2$N], 118.5 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = *C*HCH_2N], 66.7 (CH_2OCH_2), 57.0, 53.5, 24.6 [$NCH_2CH_2CH_2N(CH_2)_2$], 42.8 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 39.4, 26.3 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 25.6, 17.7, 16.5 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N]; HRMS (EI): calcd. for $C_{18}H_{33}N_3OS$ 339.234435; found, 339.234560 $[M]^{+\cdot}$.

*4.1.2.35. N-geranyl-N′-(4-piperidyl) thiourea (**38**).* The solid was purified by column chromatography, using methanol-ethyl acetate (1:2) as eluent (240 mg, 80% yield). M.p. 94–95 °C; MS (EI): *m/z* 295 (15%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 5.35 (m, 1H, NH), 5.27 [m, 1H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = *CH*CH_2N], 5.05 [m, 1H, $(CH_3)_2C$ = *CH*$CH_2CH_2C(CH_3)$ = $CHCH_2$N], 4.45, 311, 2.95, 1.86, 1.35 (5m, 9H, piperidine), 4.20 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 2.10–1.98 [m, 4H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 1.67, 1.65, 1.58 [3s, 9H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 181.3 (C=S), 140.7, 131.7 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 123.7 [$(CH_3)_2C$ = *C*$HCH_2CH_2C(CH_3)$ = $CHCH_2$N], 119.6 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = *C*HCH_2N], 48.2, 46.3, 34.9 (piperidine), 44.5 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 39.4, 26.3 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 25.6, 17.6, 16.4 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N]; HRMS (EI): calcd. for $C_{16}H_{29}N_3S$ 295.2082; found, 295.2080 $[M]^{+\cdot}$.

*4.1.2.36. N-ethoxycarbonylmethyl-N′-geranyl thiourea (**39**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (3:1) as eluent (286 mg, 96% yield). MS (EI): *m/z* 298 (15%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 6.44 (m, 2H, 2NH), 5.22 [m, 1H, *J* = 6.9 Hz, ^4J = 1.4 Hz, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = *CH*CH_2N], 5.04 [m, 1H, *J* = 6.9 Hz, ^4J = 1.4 Hz, $(CH_3)_2C$ = *CH*$CH_2CH_2C(CH_3)$ = $CHCH_2$N], 4.37 (d, 2H, *J* = 4.8 Hz, N*C*$H_2CO_2CH_2CH_3$), 4.21 (q, 2H, *J* = 7.2 Hz, $NCH_2CO_2CH_2CH_3$), 3.95 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 2.10–1.98 [m, 4H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 1.69, 1.66, 1.58 [3s, 9H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 1.27 (t, 3H, *J* = 7.2 Hz, $NCH_2CO_2CH_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 182.0 (C=S), 170.3 (C=O), 141.3, 131.8 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 123.6 [$(CH_3)_2C$ = *C*$HCH_2CH_2C(CH_3)$ = $CHCH_2$N], 118.5 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = *C*HCH_2N], 61.6 ($NCH_2CO_2CH_2CH_3$), 46.6 ($NCH_2CO_2CH_2CH_3$), 42.1 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 39.4, 26.3 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 25.6, 17.6, 16.4 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$N], 14.0 ($NCH_2CO_2CH_2CH_3$); HRMS (EI): calcd. for $C_{15}H_{26}N_2O_2S$ 298.171500; found, 298.171739 $[M]^{+\cdot}$.

*4.1.2.37. N-ethoxycarbonyl-N′-geranyl thiourea (**40**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (10:1) as eluent (235 mg, 83% yield). MS (EI): *m/z* 284 (20%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 9.51 (m, 1H NH), 8.16 (s, 1H, NHCO), 5.29 [m, 1H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = *CH*CH_2N], 5.06 [m, 1H, *J* = 6.8 Hz, ^4J = 1.4 Hz, $(CH_3)_2C$ = *CH*$CH_2CH_2C(CH_3)$ = $CHCH_2$N], 4.25–4.17 [m, 4H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$, $NCO_2CH_2CH_3$], 2.13–2.00 [m, 4H, $(CH_3)_2C$ = $CHCH_2CH_2$ $C(CH_3)$ = $CHCH_2$N], 1.69, 1.67, 1.59 [3s, 9H, $(CH_3)_2C$ = $CHCH_2$

$CH_2C(CH_3)=CHCH_2N$], 1.29 (t, 3H, J = 7.1 Hz, $NCO_2CH_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 178.6 (C=S), 152.7 (C=O), 141.6, 131.8 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 123.6 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 117.9 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 62.6 ($NCO_2CH_2CH_3$), 43.7 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 39.4, 26.2 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 25.6, 17.6, 16.5 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 14.1 ($NCO_2CH_2CH_3$); HRMS (EI): calcd. for $C_{14}H_{24}N_2O_2S$ 284.155850; found, 284.155992 $[M]^{+\cdot}$.

*4.1.2.38. N-farnesyl-N′-methyl thiourea (**41**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (35:10) as eluent (276 mg, 94% yield). MS (CI): *m/z* 295 (100%) $[M+H]^+$; ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 6.05, 5.84 (2m, 2H, 2NH), 5.24 [t, 1H, J = 6.7 Hz, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 5.06 [m, 2H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 3.99 [m, 2H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 2.99 (d, 3H, J = 3.1 Hz, NCH_3), 2.12–1.93 [m, 8H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 1.68, 1.65, 1.58 [3s, 12H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 182.3 (C=S), 141.3, 135.5, 131.3 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 124.2, 123.4, 118.8 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 42.5 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 39.6, 39.4, 26.7, 26.2 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 30.9 ($NCH_3$), 25.6, 17.6, 16.4, 16.0 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$]; HRMS (CI): calcd. for $C_{17}H_{31}N_2S$ 295.220796; found, 295.220282 $[M+H]^+$.

*4.1.2.39. N-tert-butyl-N′-farnesyl thiourea (**42**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (6:1) as eluent (265 mg, 79% yield). MS (EI): *m/z* 336 (10%) $[M]^{+\cdot}$; ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 5.89, 5.49 (2s, 2H, 2NH), 5.29 [m, 1H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 5.08 [m, 2H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 4.09 [m, 2H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 2.14–1.93 [m, 8H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 1.71, 1.67, 1.59 [3s, 12H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 1.42 [$NC(CH_3)_3$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.9 (C=S), 141.5, 135.6, 131.4 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 124.2, 123.5, 119.1 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 52.8 [$NC(CH_3)_3$], 43.5 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 39.7, 39.4, 26.7, 26.3 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 29.5 [$NC(CH_3)_3$], 25.7, 17.7, 16.5, 16.0 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$]; HRMS (EI): calcd. for $C_{20}H_{36}N_2S$ 336.259921; found, 336.259808 $[M]^{+\cdot}$.

*4.1.2.40. N-allyl-N′-farnesyl thiourea (**43**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (6:1) as eluent (272 mg, 85% yield). MS (CI): *m/z* 321 (100%) $[M+H]^+$; ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 6.00–5.80 (m, 3H, 2NH, $NCH_2CH=CH_2$), 5.24 [t, 1H, J = 6.7 Hz, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$, $NCH_2CH=CH_2$], 5.07 [m, 2H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 4.08 (m, 2H, $NCH_2CH=CH_2$), 3.98 [m, 2H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 2.12–1.93 [m, 8H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 1.68, 1.66, 1.59 [3s, 12H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 181.9 (C=S), 141.5, 135.6, 131.3 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 133.3 ($NCH_2CH=CH_2$), 124.2, 123.4, 118.8 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 117.4 ($NCH_2CH=CH_2$), 47.0 ($NCH_2CH=CH_2$), 42.4 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 39.6, 39.4, 26.7, 26.2 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 25.6, 17.6, 16.5, 16.0 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$]; HRMS (CI): calcd. for $C_{19}H_{33}N_2S$ 321.236446; found, 321.235194 $[M+H]^+$.

*4.1.2.41. N-farnesyl-N′-phenyl thiourea (**44**).* The solid was purified by column chromatography, using hexane–ethyl acetate (7:1) as eluent (341 mg, 96% yield). M.p. 54–55 °C; MS (CI): *m/z* 357 (40%) $[M+H]^+$; ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 7.89 (s, 1H, NHPh), 7.45–7.17 (m, 5H, Ph), 5.90 (m, 1H, NH), 5.20 [t, 1H, J = 7.0 Hz, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 5.05 [m, 2H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 4.22 [m, 2H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 2.10–1.90 [m, 8H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 1.67, 1.66, 1.59, 1.56 [4s, 12H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.3 (C=S), 141.1, 135.4, 131.3 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 136.2, 130.2, 127.1, 125.0 (Ph), 124.2, 123.5, 118.8 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 43.7 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 39.6, 39.4, 26.7, 26.2 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 25.6, 17.6, 16.5, 16.0 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$]; HRMS (CI): calcd. for $C_{22}H_{33}N_2S$ 357.236446; found, 357.236188 $[M+H]^+$. Anal. calcd for $C_{22}H_{32}N_2S$: C, 74.11; H, 9.05; N, 7.86; S, 8.99. Found: C, 74.27; H, 9.18; N, 7.72; S, 8.74.

*4.1.2.42. N-farnesyl-N′-(4-nitrophenyl) thiourea (**45**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (5:1) as eluent (390 mg, 97% yield). MS (CI): *m/z* 402 (5%) $[M+H]^+$; ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 8.34 (s, 1H, NHAr), 8.24, 7.43 (2m, 4H, Ar), 6.25 (m, 1H, NH), 5.28 [t, 1H, J = 7.0 Hz, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 5.06 [m, 2H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 4.23 [m, 2H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 2.15–1.90 [m, 8H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 1.72, 1.67, 1.58 [3s, 12H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 179.9 (C=S), 144.4, 135.7, 131.3 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 143.1, 142.4, 125.6, 122.3 (Ar), 124.2, 123.3, 117.9 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 43.7 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 39.7, 39.4, 26.7, 26.2 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 25.7, 17.7, 16.6, 16.0 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$]; HRMS (CI): calcd. for $C_{22}H_{32}N_3O_2S$ 402.221524; found, 402.219803 $[M+H]^+$.

*4.1.2.43. N-farnesyl-N′-(3-nitrophenyl) thiourea (**46**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (4:1) as eluent (365 mg, 91% yield). MS (CI): *m/z* 402 (5%) $[M+H]^+$; ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 8.14 (s, 1H, NHAr), 8.08, 7.65, 7.57 (3m, 4H, Ar), 6.05 (m, 1H, NH), 5.27 [m, 1H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 5.06 [m, 2H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 4.21 [m, 2H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 2.15–1.85 [m, 8H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$], 1.71, 1.67, 1.59, 1.57 [4s, 12H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(CH_3)=CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.3 (C=S), 148.9, 130.0, 120.9,

118.8 (Ar), 142.3, 135.6, 131.4 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = CH $CH_2CH_2C(CH_3)$ = $CHCH_2N$], 124.2, 123.4, 118.0 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 43.6 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 39.6, 39.4, 26.7, 26.2 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 25.7, 17.7, 16.6, 16.0 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = CHCH $_2CH_2C(CH_3)$ = $CHCH_2N$]; HRMS (CI): calcd. for $C_{22}H_{32}N_3O_2S$ 402.2215; found, 402.2205 $[M + H]^+$.

*4.1.2.44. N-farnesyl-N′-(4-trifluoromethyl)phenyl thiourea (**47**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (6:1) as eluent (360 mg, 85% yield). MS (EI): *m/z* 424 (10%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.19 (s, 1H, N*H*Ar), 7.66, 7.34 (2m, 4H, Ar), 6.03 (m, 1H, NH), 5.25 [t, 1H, *J* = 6.8 Hz, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 5.06 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 4.23 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2$ $C(CH_3)$ = $CHCH_2N$], 2.13–1.88 [m, 8H, $(CH_3)_2C$ = $CHCH_2CH_2$ $C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.69, 1.67, 1.59, 1.57 [4s, 12H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.1 (C=S), 141.8, 135.6, 131.4 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 139.9, 127.3, 124.8, 122.6 (Ar), 124.2, 123.4, 118.3 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 43.8 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 39.7, 39.4, 26.7, 26.2 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 25.7, 17.7, 16.6, 16.0 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; HRMS (EI): calcd. for $C_{23}H_{31}F_3N_2S$ 424.216006; found, 424.215286 $[M]^{+\cdot}$.

*4.1.2.45. N-farnesyl-N′-(4-fluorophenyl) thiourea (**48**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (5:1) as eluent (362 mg, 97% yield). MS (CI): *m/z* 375 (100%) $[M + H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 7.66 (s, 1H, N*H*Ar), 7.24–7.08 (m, 4H, Ar), 5.69 (m, 1H, NH), 5.19 [t, 1H, *J* = 6.7 Hz, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 5.05 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$ $CH_2C(CH_3)$ = $CHCH_2N$], 4.21 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2$ $C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 2.10–1.87 [m, 8H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.67, 1.66, 1.59, 1.57 [4s, 12H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.8 (C=S), 162.4, 160.5, 127.8, 117.1 (Ar), 141.3, 135.5, 131.4 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 124.2, 123.5, 118.6 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2$ $C(CH_3)$ = $CHCH_2N$], 43.7 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$ $CH_2C(CH_3)$ = $CHCH_2N$], 39.7, 39.4, 26.7, 26.2 [$(CH_3)_2C$ = CH $CH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 25.7, 17.7, 16.5, 16.0 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; HRMS (CI): calcd. for $C_{22}H_{32}FN_2S$ 375.227024; found, 375.229071 $[M + H]^+$.

*4.1.2.46. N-(4-Chlorophenyl)-N′-farnesyl thiourea (**49**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (6:1) as eluent (300 mg, 78% yield). MS (EI): *m/z* 390 (5%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 7.62 (s, 1H, N*H*Ar), 7.39, 7.16 (2m, 4H, Ar), 5.79 (m, 1H, NH), 5.21 [t, 1H, *J* = 6.8 Hz, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 5.06 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 4.22 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = CH $CH_2CH_2C(CH_3)$ = $CHCH_2N$], 2.11–1.92 [m, 8H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.67, 1.60, 1.57 [3s, 12H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.1 (C=S), 141.8, 135.6, 131.4 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2$ $C(CH_3)$ = $CHCH_2N$], 134.7–126.3 (Ar), 124.2, 123.4, 118.3 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 43.8 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 39.7, 39.4, 26.7, 26.2 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 25.7, 17.7, 16.6, 16.0 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; HRMS (EI): calcd. for $C_{22}H_{31}ClN_2S$ 390.189649; found, 390.189853 $[M]^{+\cdot}$.

*4.1.2.47. N-(4-Cyanophenyl)-N′-farnesyl thiourea (**50**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (4:1) as eluent (323 mg, 85% yield). MS (EI): *m/z* 381 (5%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.16 (s, 1H, N*H*Ar), 7.66, 7.39 (2m, 4H, Ar), 6.15 (m, 1H, NH), 5.27 [m, 1H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 5.07 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 4.22 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = CH $CH_2CH_2C(CH_3)$ = $CHCH_2N$], 2.13–1.93 [m, 8H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.71, 1.67, 1.59, 1.58 [4s, 12H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$ $CH_2C(CH_3)$ = $CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 179.9 (C=S), 141.3, 135.7, 131.4 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 142.2, 133.9, 123.4, 122.4 (Ar), 124.2, 123.7, 118.1 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = CH $CH_2CH_2C(CH_3)$ = $CHCH_2N$], 108.9 (Ar*C*N), 43.7 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 39.7, 39.4, 26.7, 26.2 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 25.7, 17.7, 16.6, 16.0 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; HRMS (EI): calcd. for $C_{23}H_{31}N_3S$ 381.223870; found, 381.225555 $[M]^{+\cdot}$.

*4.1.2.48. N-farnesyl-N′-(4-methoxyphenyl) thiourea (**51**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (3:1) as eluent (350 mg, 91% yield). MS (CI): *m/z* 387 (30%) $[M + H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 7.61 (s, 1H, N*H*Ar), 7.16–6.90 (m, 4H, Ar), 5.66 (m, 1H, NH), 5.17 [m, 1H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 5.05 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 4.21 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 3.81 (OCH_3), 2.10–1.85 [m, 8H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.66, 1.64, 1.59, 1.56 [4s, 12H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$ δ ppm): 180.8 (C=S), 158.9, 128.4, 127.7, 115.3 (Ar), 140.9, 135.4, 131.3 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 124.2, 123.5, 118.9 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 55.5 (OCH_3), 43.7 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 39.6, 39.4, 26.7, 26.2 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2$ $CH_2C(CH_3)$ = $CHCH_2N$], 25.7, 17.7, 16.5, 16.0 [$(CH_3)_2$ C = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; HRMS (CI): calcd. for $C_{23}H_{35}N_2OS$ 387.2470; found, 387.2478 $[M + H]^+$.

*4.1.2.49. N-farnesyl-N′-(3-methoxyphenyl) thiourea (**52**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (4:1) as eluent (350 mg, 91% yield). MS (CI): *m/z* 387 (80%) $[M + H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 7.62 (s, 1H, N*H*Ar), 7.31, 6.82, 6.77, 6.72 (4m, 4H, Ar), 5.99 (m, 1H, NH), 5.22 [m, 1H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 5.06 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 4.24 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = CH $CH_2CH_2C(CH_3)$ = $CHCH_2N$], 3.80 (OCH_3), 2.10–1.91 [m, 8H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.67, 1.59, 1.57 [3s, 12H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.3 (C=S), 161.0, 137.3, 130.9, 116.8, 112.8, 110.6 (Ar), 141.2, 135.5,

131.3 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 124.3, 123.6, 118.8 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 55.4 (OCH_3), 43.8 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 39.7, 39.5, 26.7, 26.3 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 25.7, 17.7, 16.6, 16.0 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; HRMS (CI): calcd. for $C_{23}H_{35}N_2OS$ 387.2470; found, 387.2481 $[M + H]^+$.

*4.1.2.50. N-farnesyl-N′-(2-methoxyphenyl) thiourea (**53**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (4:1) as eluent (355 mg, 92% yield). MS (EI): *m/z* 386 (5%) $[M]^{+\cdot}$; ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 7.51 (s, 1H, N*H*Ar), 7.21, 6.97 (2m, 4H, Ar), 6.00 (m, 1H, NH), 5.24 [m, 1H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 5.07 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 4.23 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 3.85 (OCH_3), 2.11–1.89 [m, 8H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.68, 1.60, 1.57 [3s, 12H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.3 (C=S), 161.2, 124.4, 121.0, 112.0 (Ar), 141.1, 135.5, 131.3 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 124.3, 123.6, 118.9 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 55.7 (OCH_3), 43.7 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 39.7, 39.5, 26.7, 26.3 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 25.7, 17.7, 16.5, 16.0 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; HRMS (EI): calcd. for $C_{23}H_{34}N_2OS$ 386.2392; found, 386.2366 $[M]^{+\cdot}$.

*4.1.2.51. N-farnesyl-N′-[2-(1-piperidino)ethyl] thiourea (**54**).* The solid was purified by column chromatography, using hexane–ethyl acetate (3:1) as eluent (332 mg, 85% yield). M.p. 67–69 °C; MS (EI): *m/z* 391 (5%) $[M]^{+\cdot}$; ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 6.58 (m, 2H, 2NH), 5.27 [m, 1H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 5.07 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 4.09 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 3.35 (m, 2H, NCH_2CH_2N), 2.44 [m, 6H, $CH_2N(CH_2)_2$], 2.12–1.92 [m, 8H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.68, 1.66, 1.58 [3s, 12H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.53 (m, 4H, $2CH_2$), 1.42 (m, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 182.8 (C=S), 141.5, 135.4, 131.3 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 124.2, 123.6, 119.8 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 59.8, 54.5 (NCH_2CH_2N), 42.2 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 42.0, 25.6 (piperidine), 39.6, 39.5, 26.6, 26.3 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 23.9, 17.7, 16.4, 15.9 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; HRMS (EI): calcd. for $C_{23}H_{41}N_3S$ 391.302120; found, 391.303697 $[M]^{+\cdot}$. Anal. calcd for $C_{23}H_{41}N_3S$: C, 70.53; H, 10.55; N, 10.73; S, 8.19. Found: C, 70.56; H, 10.72; N, 10.59; S, 8.11.

*4.1.2.52. N-farnesyl-N′-[2-(4-morpholino)ethyl] thiourea (**55**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (1:3) as eluent (300 mg, 76% yield). MS (EI): *m/z* 393 (5%) $[M]^{+\cdot}$; ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 5.59 (m, 2H, 2NH), 5.24 [t, 1H, *J* = 6.6 Hz, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 5.05 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 4.01 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 3.65 (t, 4H, *J* = 4.4 Hz, CH_2OCH_2), 3.44 (m, 2H, NCH_2CH_2N), 2.55–2.43 [m, 6H, $CH_2N(CH_2)_2$], 2.10–1.90 [m, 8H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.68, 1.64, 1.56 [3s, 12H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 181.7 (C=S), 140.4, 135.4, 131.2 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 124.1, 123.4, 119.2 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 66.6 (CH_2OCH_2), 57.8, 53.3, 41.3 [$NCH_2CH_2N(CH_2)_2$], 42.7 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 39.6, 39.5, 26.6, 26.2 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 25.7, 17.6, 16.5, 15.9 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; HRMS (EI): calcd. for $C_{22}H_{39}N_3OS$ 393.281385; found, 393.281302 $[M]^{+\cdot}$.

*4.1.2.53. N-farnesyl-N′-[3-(4-morpholino)propyl] thiourea (**56**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (1:5) as eluent (365 mg, 90% yield). MS (EI): *m/z* 407 (10%) $[M]^{+\cdot}$; ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 7.20 (m, 2H, 2NH), 5.26 [m, 1H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 5.08 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 4.03 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 3.70 (t, 4H, *J* = 4.6 Hz, CH_2OCH_2), 3.50 (m, 2H, $NCH_2CH_2CH_2N$), 2.13–1.93 [m, 8H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.75 [m, 6H, $CH_2N(CH_2)_2$], 1.68, 1.67, 1.60 [3s, 12H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 181.8 (C=S), 142.0, 135.6, 131.4 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 124.2, 123.6, 119.5 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 66.7 (CH_2OCH_2), 55.6, 53.6, 53.5, 24.8 [$NCH_2CH_2CH_2N(CH_2)_2$], 43.0 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 39.7, 39.5, 26.7, 26.3 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 25.7, 17.7, 16.6, 16.0 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; HRMS (EI): calcd for $C_{23}H_{41}N_3OS$ 407.297035; found, 407.297296 $[M]^{+\cdot}$.

*4.1.2.54. N-Ethoxycarbonylmethyl-N′-farnesyl thiourea (**57**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (5:1) as eluent (351 mg, 96% yield). MS (CI): *m/z* 366 (25%) $[M + H]^+$; ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 6.39 (m, 2H, 2NH), 5.23 [m, 1H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 5.07 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 4.37 (d, 2H, *J* = 4.7 Hz, $NCH_2CO_2CH_2CH_3$), 4.21 (q, 2H, *J* = 7.1 Hz, $NCH_2CO_2CH_2CH_3$), 3.95 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 2.12–1.93 [m, 8H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.70, 1.66, 1.58 [3s, 12H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.28 (t, 3H, *J* = 7.1 Hz, $NCH_2CO_2CH_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 182.0 (C=S), 170.3 (C=O), 141.5, 135.5, 131.3 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 124.2, 123.6, 118.4 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 61.6 ($NCH_2CO_2CH_2CH_3$), 46.7 ($NCH_2CO_2CH_2CH_3$), 42.1 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 39.6, 39.4, 26.7, 26.3 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 25.6, 17.6, 16.4, 15.9 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 14.1 ($NCH_2CO_2CH_2CH_3$); HRMS (CI): calcd. for $C_{20}H_{35}N_2O_2S$ 367.241925; found, 367.239998 $[M + H]^+$.

*4.1.2.55. N-ethoxycarbonyl-N′-farnesyl thiourea (**58**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (20:1) as eluent (338 mg, 96% yield). MS (CI): *m/z* 353 (100%) $[M + H]^+$; ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 9.51 (m, 1H NH), 8.06

(s, 1H, NHCO), 5.30 [m, 1H, $(CH_3)_2C = CHCH_2CH_2C(CH_3) = CHCH_2CH_2C(CH_3) = CHCH_2N$], 5.09 [m, 2H, $(CH_3)_2C = CHCH_2 CH_2C(CH_3) = CHCH_2CH_2C(CH_3) = CHCH_2N$], 4.25–4.17 [m, 4H, $(CH_3)_2C = CHCH_2CH_2C(CH_3) = CHCH_2CH_2C(CH_3) = CHCH_2N$, $NCO_2CH_2CH_3$], 2.14–1.94 [m, 8H, $(CH_3)_2C = CHCH_2CH_2 C(CH_3) = CHCH_2CH_2C(CH_3) = CHCH_2N$], 1.70, 1.67, 1.59 [3s, 12H, $(CH_3)_2C = CHCH_2CH_2C(CH_3) = CHCH_2CH_2C(CH_3) = CHCH_2N$], 1.30 (t, 3H, $J = 7.1$ Hz, $NCO_2CH_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 178.6 (C=S), 152.6 (C=O), 141.7, 135.5, 131.2 [$(CH_3)_2C = CHCH_2CH_2C(CH_3) = CHCH_2CH_2C(CH_3) = CHCH_2N$], 124.3, 123.5, 117.9 [$(CH_3)_2C = CHCH_2CH_2C(CH_3) = CHCH_2CH_2C(CH_3) = CHCH_2N$], 62.6 ($NCO_2CH_2CH_3$), 43.8 [$(CH_3)_2C = CHCH_2CH_2C(CH_3) = CHCH_2CH_2C(CH_3) = CHCH_2N$], 39.6, 39.4, 26.7, 26.2 [$(CH_3)_2C = CHCH_2CH_2C(CH_3) = CHCH_2CH_2C(CH_3) = CHCH_2N$], 25.6, 17.6, 16.5, 16.0 [$(CH_3)_2C = CHCH_2CH_2C(CH_3) = CHCH_2 CH_2C(CH_3) = CHCH_2N$], 14.1 ($NCO_2CH_2CH_3$); HRMS (CI): calcd. for $C_{19}H_{33}N_2O_2S$ 353.226275; found, 353.225595 $[M + H]^+$.

*4.1.2.56. N-isobutyl-N′-(4-nitrophenyl) thiourea (**59**).* The solid was purified by column chromatography, using hexane–ethyl acetate (25:10) as eluent (225 mg, 89% yield). M.p. 97–98 °C; MS (CI): *m/z* 254 (100%) $[M + H]^+$; ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 8.41 (s, 1H, NHAr), 8.27, 7.42 (2m, 4H, Ar), 6.40 (m, 1H, NH), 3.49 [m, 2H, $(CH_3)_2CHCH_2N$], 1.98 [m, 1H, $(CH_3)_2CHCH_2N$], 0.98 [d, 6H, $J = 6.8$ Hz, $(CH_3)_2CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.2 (C=S), 137.5 [$(CH_3)_2C = CHCH_2N$], 144.5, 142.9, 125.7, 122.4 (Ar), 53.1 [$(CH_3)_2CHCH_2N$], 27.9 [$(CH_3)_2CHCH_2N$], 20.3 [$(CH_3)_2CHCH_2N$]; HRMS (CI): calcd. for $C_{11}H_{16}N_3O_2S$ 254.096324; found, 254.097405 $[M + H]^+$; Anal. Calcd for $C_{11}H_{15}N_3O_2S$: C, 52.15; H, 5.97; N, 16.59; S, 12.66. Found: C, 52.34; H, 5.66; N, 16.32; S, 12.41.

*4.1.2.57. N-isopentyl-N′-(4-nitrophenyl) thiourea (**60**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (2:1) as eluent (245 mg, 92% yield). MS (EI): *m/z* 267 (70%) $[M]^{+\cdot}$; ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 8.41 (s, 1H), 8.26, 7.40 (2m, 5H, NHAr), 6.28 (m, 1H, NH), 3.67 [m, 2H, $(CH_3)_2CHCH_2CH_2N$], 1.64 [m, 1H, $(CH_3)_2CHCH_2CH_2N$], 1.53 [m, 2H, $(CH_3)_2CHCH_2CH_2N$], 0.95 [d, 6H, $J = 6.8$ Hz, $(CH_3)_2CHCH_2CH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.0 (C=S), 144.5, 125.7, 122.5 (Ar), 44.2 [$(CH_3)_2CHCH_2CH_2N$], 37.5 [$(CH_3)_2CHCH_2CH_2N$], 20.0 [$(CH_3)_2CHCH_2CH_2N$], 22.4 [$(CH_3)_2CHCH_2CH_2N$]; HRMS (EI): calcd. for $C_{12}H_{17}N_3O_2S$ 267.104149; found, 267.104037$[M]^{+\cdot}$.

*4.1.2.58. N-benzyl-N′-(4-nitrophenyl) thiourea (**61**).* The syrup [40] was purified by column chromatography, using hexane–ethyl acetate (3:1) as eluent (275 mg, 96% yield). MS (EI): *m/z* 287 (30%) $[M]^{+\cdot}$; ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 8.24, 7.37 (2m, 9H, Ar), 7.89 (s, 1H, NHAr), 6.49 (m, 1H, NH), 4.87 [m, 2H, $PhCH_2N$].

*4.1.2.59. N-cyclohexyl-N′-(4-nitrophenyl) thiourea (**62**).* The syrup was purified by column chromatography [41], using hexane–ethyl acetate (2.5:1) as eluent (250 mg, 90% yield). MS (CI): *m/z* 280 (100%) $[M + H]^+$.

*4.1.2.60. N-(1-dodecyl)-N′-(4-nitrophenyl) thiourea (**63**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (2:1) as eluent (360 mg, 99% yield). MS (EI): *m/z* 365 (5%) $[M]^{+\cdot}$; ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 8.40 (s, 1H), 8.25, 7.41 (2m, 4H, NHAr), 6.35 (m, 1H, NH), 3.64 (m, 2H, CH_2N), 1.7–1.2 [m, 20H, $(CH_2)_{10}$], 0.87 (t, 3H, $J = 7.0$ Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.0 (C=S), 144.5, 143.0, 125.7, 122.4 (Ar), 45.7 (CH_2N), 31.9–22.7 [$(CH_2)_{10}$], 14.1 (CH_3); HRMS (EI): calcd. for $C_{19}H_{31}N_3O_2S$ 365.213699; found 365.215957 $[M]^{+\cdot}$.

*4.1.2.61. N-(1-dodecyl)-N′-(3-nitrophenyl) thiourea (**64**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (3:1) as eluent (300 mg, 82% yield). MS (EI): *m/z* 365 (15%) $[M]^{+\cdot}$; ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 8.13 (s, 1H), 8.10, 7.60 (2m, 4H, NHAr), 6.15 (m, 1H, NH), 3.62 (m, 2H, CH_2N), 1.7–1.2 [m, 20H, $(CH_2)_{10}$], 0.88 (t, 3H, $J = 7.0$ Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.6 (C=S), 149.0, 138.2, 130.7, 130.2, 121.1, 119.0 (Ar), 45.7 (CH_2N), 31.9–22.7 [$(CH_2)_{10}$], 14.1 (CH_3); HRMS (EI): cald. for $C_{19}H_{31}N_3O_2S$ 365.2137; found, 365.2121 $[M]^{+\cdot}$.

*4.1.2.62. N-(1-dodecyl)-N′-(4-methoxyphenyl) thiourea (**65**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (3:1) as eluent (335 mg, 96% yield). MS (EI): *m/z* 350 (30%) $[M]^{+\cdot}$; ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 7.96 (s, 1H), 7.12, 6.91 (2m, 4H, NHAr), 5.79 (m, 1H, NH), 3.79 (s, 3H, OCH_3), 3.55 (m, 2H, CH_2N), 1.6–1.2 [m, 20H, $(CH_2)_{10}$], 0.85 (t, 3H, $J = 6.9$ Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 180.9 (C=S), 158.8, 128.5, 127.6, 115.2 (Ar), 55.4 (OCH_3), 45.4 (CH_2N), 31.8–22.6 [$(CH_2)_{10}$], 14.0 (CH_3); HRMS (EI): calcd. for $C_{20}H_{34}N_2OS$ 350.2392; found, 350.2406 $[M]^{+\cdot}$.

*4.1.2.63. N-(1-Dodecyl)-N′-(3-methoxyphenyl) thiourea (**66**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (3:1) as eluent (325 mg, 93% yield). MS (EI): *m/z* 350 (60%) $[M]^{+\cdot}$; ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 7.64 (s, 1H), 7.33, 6.83, 6.77, 6.72 (4m, 4H, NHAr), 6.10 (m, 1H, NH), 3.80 (s, 3H, OCH_3), 3.62 (m, 2H, CH_2N), 1.6–1.2 [m, 20H, $(CH_2)_{10}$], 0.87 (t, 3H, $J = 7.0$ Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.4 (C=S), 161.0, 137.1, 131.0, 117.0, 112.9, 110.7 (Ar), 55.4 (OCH_3), 45.7 (CH_2N), 31.9–22.7 [$(CH_2)_{10}$], 14.1 (CH_3); HRMS (EI): calcd. for $C_{20}H_{34}N_2OS$ 350.2392, found 350.2390 $[M]^{+\cdot}$.

*4.1.2.64. N-(1-dodecyl)-N′-(2-methoxyphenyl) thiourea (**67**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (3:1) as eluent (300 mg, 86% yield). MS (EI): *m/z* 350 (25%) $[M]^{+\cdot}$; ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 7.54 (s, 1H), 7.21, 6.96 (2m, 4H, NHAr), 6.14 (m, 1H, NH), 3.82 (s, 3H, OCH_3), 3.59 (m, 2H, CH_2N), 1.6–1.2 [m, 20H, $(CH_2)_{10}$], 0.86 (t, 3H, $J = 6.9$ Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 180.4 (C=S), 152.4, 127.4, 125.3, 124.7, 120.9, 112.0 (Ar), 55.6 (OCH_3), 45.5 (CH_2N), 31.8–22.6 [$(CH_2)_{10}$], 14.0 (CH_3); HRMS (EI): calcd. for $C_{20}H_{34}N_2OS$ 350.2392; found, 350.2393 $[M]^{+\cdot}$.

*4.1.2.65. N-(4-Morpholino)-N′-(4-nitrophenyl) thiourea (**68**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (1:1) as eluent (255 mg, 90% yield). MS (EI): *m/z* 282 (20%) $[M]^{+\cdot}$; ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 9.46 (s, 1H, NHAr), 8.24, 7.98 (2m, 4H, Ar), 7.12 (m, 1H, NH), 3.98, 3.92 (2m, 4H, CH_2OCH_2), 3.07, 2.80 (m, 4H, CH_2NCH_2); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 177.8 (C=S), 144.3, 143.6, 125.0, 124.5 (Ar), 66.4 (CH_2OCH_2), 55.8 (CH_2NCH_2); HRMS (EI): calcd. for $C_{11}H_{14}N_4O_3S$ 282.078662; found, 282.078770 $[M]^{+\cdot}$.

*4.1.2.66. N-(4-Ethyl)-N′-(3-methyl-2-butenyl) urea (**69**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (5:1) as eluent (136 mg, 87% yield). MS (EI): *m/z* 156 (45%) $[M]^{+\cdot}$; ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 5.27–5.17 [m, 2H, $(CH_3)_2C = CHCH_2N$, $NHCH_2CH_3$], 3.70 [t, 2H, $J = 6.7$ Hz, $(CH_3)_2C = CHCH_2N$], 3.17 (q, 2H, $J = 5.4$ Hz, $NHCH_2CH_3$), 1.72, 1.67 (2s, 6H, $(CH_3)_2C = CHCH_2N$], 0.97 (t, 3H, $J = 5.4$ Hz, $NHCH_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 158.8 (C=O), 134.9 [$(CH_3)_2C = CHCH_2N$], 121.5 [$(CH_3)_2C = CHCH_2N$], 38.2 [$(CH_3)_2C = CHCH_2N$], 35.0 ($NHCH_2CH_3$), 25.5, 17.6 [$(CH_3)_2C = CHCH_2N$], 15.4 ($NHCH_2CH_3$); HRMS (EI): calcd. for $C_8H_{16}N_2O$ 156.126263; found, 156.125861 $[M]^{+\cdot}$.

*4.1.2.67. N-allyl-N′-(3-methyl-2-butenyl) urea (**70**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (5:1) as eluent (146 mg, 87% yield). MS (EI): *m/z* 168 (45%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 5.84 (m, 1H, $NCH_2CH=CH_2$), 5.17 [m, 2H, $(CH_3)_2C=CHCH_2N$, $NCH_2CH=CH_AH_B$], 5.06 [m, 2H, $NHCH_2CH=CH_AH_B$, $NCH_2CH=CH_AH_B$], 4.92 [bs, 1H, $(CH_3)_2C=CHCH_2NH$], 3.76 [m, 2H, $NCH_2CH=CH_2$], 3.72 [m, 2H, $(CH_3)_2C=CHCH_2N$], 1.68, 1.64 [dd, 6H, ^4J 0 1.0 Hz, $(CH_3)_2C=CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 158.5 (C=O), 137.8 [$(CH_3)_2C=CHCH_2N$], 133.3 ($NCH_2CH=CH_2$), 119.0 [$(CH_3)_2C=CHCH_2N$], 117.3 ($NCH_2CH=CH_2$), 46.9 ($NCH_2CH=CH_2$), 42.5 [$(CH_3)_2C=CHCH_2N$], 25.6, 18.0 [$(CH_3)_2C=CHCH_2N$]; HRMS (EI): calcd. for $C_9H_{16}N_2O$ 168.126263; found, 168.125700 $[M]^{+\cdot}$.

*4.1.2.68. N-phenyl-N′-(3-methyl-2-butenyl) urea (**71**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (6:1) as eluent (140 mg, 63% yield). MS (EI): *m/z* 204 (20%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.01 (s, 1H, NHPh), 7.46–7.16 (m, 5H, Ph), 5.91 (m, 1H, NH), 5.19 [m, 1H, $(CH_3)_2C=CHCH_2N$], 4.20 [m, 2H, $(CH_3)_2C=CHCH_2N$], 1.69, 1.65 [2s, 6H, $(CH_3)_2C=CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 155.0 (C=O), 137.5 [$(CH_3)_2C=CHCH_2N$], 136.2, 130.1, 127.1, 125.0 (Ph), 119.0 [$(CH_3)_2C=CHCH_2N$], 43.7 [$(CH_3)_2C=CHCH_2N$], 25.6, 18.0 [$(CH_3)_2C=CHCH_2N$]; HRMS (EI): calcd. for $C_{12}H_{16}N_2O$ 204.126199; found, 204.126263 $[M]^{+\cdot}$.

*4.1.2.69. N-(3-methyl-2-butenyl)-N′-(4-nitrophenyl) urea (**72**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (25:10) as eluent (206 mg, 83% yield). MS (EI): *m/z* 249 (30%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.39 (s, 1H, NHAr), 8.24, 7.43 (2m, 4H, Ar), 6.26 (m, 1H, NH), 5.27 [m, 1H, $(CH_3)_2C=CHCH_2N$], 4.21 [m, 2H, $(CH_3)_2C=CHCH_2N$], 1.75, 1.71 [2s, 6H, $(CH_3)_2C=CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): δ 157.6 (C=O), 137.5 [$(CH_3)_2C=CHCH_2N$], 143.3–122.3 (Ar), 119.0 [$(CH_3)_2C=CHCH_2N$], 43.7 [$(CH_3)_2C=CHCH_2N$], 25.6, 18.0 [$(CH_3)_2C=CHCH_2N$]; HRMS (EI): calcd. for $C_{12}H_{15}N_3O_3$ 249.1113; found, 249.1125 $[M]^{+\cdot}$.

*4.1.2.70. N-(4-ethyl)-N′-geranyl urea (**73**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (3:1) as eluent (223 mg, 98% yield). MS (EI): *m/z* 224 (20%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 5.28–5.18 [m, 2H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$,], 3.78 [m, 2H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 3.2 [q, 2H, J = 7.2 Hz, NCH_2CH_3], 1.98–2.00 [m, 4H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 1.67, 1.57 [3s, 9H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 1.10 [t, 3H, J = 7.2 Hz, NCH_2CH_3]; ^{13}C RMN (125 MHz, $CDCl_3$, δ ppm): 158.5 (C=O), 138.8, 131.9 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 123.5 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 121.1 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 42.4 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 35.2 ($NCH_2CH_3$) 39.4, 26.3 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 25.6, 17.6, 16.4 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 15.4 ($NCH_2CH_3$); HRMS (EI): calcd. for $C_{13}H_{24}N_2O$ 224.188864; found, 224.188413 $[M]^{+\cdot}$.

*4.1.2.71. N-tert-butyl-N′-geranyl urea (**74**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (4:1) as eluent (244 mg, 97% yield). MS (EI): *m/z* 252 (20%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 5.91, 5.49 (2s, 2H, 2NH), 5.29 [t, 1H, J = 7.0 Hz, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 5.06 [m, 1H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 4.09 [m, 2H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 2.13–2.02 [m, 4H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 1.70, 1.67, 1.60 [3s, 9H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 1.42 [$NC(CH_3)_3$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 157.7 (C=O), 138.8, 131.6 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 123.6 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 119.1 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 52.8 [$NC(CH_3)_3$], 43.6 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 39.4, 26.3 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 29.5 [$NC(CH_3)_3$], 25.7, 17.7, 16.4 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$]; HRMS (EI): calcd. for $C_{15}H_{28}N_2O$ 252.220164; found, 252.220115 $[M]^{+\cdot}$.

*4.1.2.72. N-allyl-N′-geranyl urea (**75**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (5:1) as eluent (245 mg, 98% yield). MS (EI): *m/z* 236 (25%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 6.10–5.80 (m, 3H, 2NH, $NCH_2CH=CH_2$), 5.28–5.18 [m, 3H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$, $NCH_2CH=CH_2$], 5.04 [m, 1H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 4.09 (m, 2H, $NCH_2CH=CH_2$), 3.98 [m, 2H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 2.11–1.98 [m, 4H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 1.67, 1.57 [2s, 9H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 182.0 (C=O), 158.2, 131.9 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 133.3 ($NCH_2CH=CH_2$), 123.5 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 118.7 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 117.4 ($NCH_2CH=CH_2$), 47.0 ($NCH_2CH=CH_2$), 42.4 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 39.4, 26.3 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 25.6, 17.6, 16.4 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$]; HRMS (EI): calcd. for $C_{14}H_{24}N_2O$ 236.188864; found, 236.187843 $[M]^{+\cdot}$.

*4.1.2.73. N-geranyl-N′-phenyl urea (**76**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (6:1) as eluent (270 mg, 98% yield). MS (EI): *m/z* 272 (25%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 7.93 (s, 1H, NHPh), 7.44–7.18 (m, 5H, Ph), 5.91 (m, 1H, NH), 5.20 [m, 1H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 5.02 [m, 1H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 4.22 [m, 2H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 2.08–1.96 [m, 4H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 1.65, 1.64, 1.56 [3s, 9H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 156.3 (C=O), 139.1, 138.8 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 131.8–125.0 (Ph), 123.6 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 120.8 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 43.7 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 39.4, 26.2 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 25.6, 17.6, 16.5 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$]; HRMS (EI): calcd. for $C_{17}H_{24}N_2O$ 272.188864; found, 272.187893$[M]^{+\cdot}$.

*4.1.2.74. N-geranyl-N′-(4-nitrophenyl) urea (**77**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (35:10) as eluent (317 mg, 94% yield). MS (EI): *m/z* 317 (35%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.46 (s, 1H, NHAr), 8.3–7.4 (m, 4H, Ar), 7.90 (m, 1H, NH), 5.28 [m, 1H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 5.04 [m, 1H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 3.82 [m, 2H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 2.12–2.01 [m, 4H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 1.71, 1.65, 1.58 [3s, 9H, $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 154.8 (C=O), 123.5, 119.8 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 145.7–123.5 (Ar), 123.4 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 118.0 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 43.6 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 39.4, 26.3 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$], 25.6, 17.7, 16.6 [$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2N$]; HRMS (EI): calcd. for $C_{17}H_{23}N_3O_3$ 317.1739; found, 317.1746 $[M]^{+\cdot}$.

*4.1.2.75. N-(4-Trifluoromethyl)phenyl-N′-geranyl urea (**78**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (4:1) as eluent (345 mg, 97% yield). MS (CI): *m/z* 341

(90%) $[M + H]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.47 (s, 1H, NHAr), 7.7–7.3 (m, 4H, Ar), 6.50 (s, 1H, NH), 5.24 [t, 1H, J = 6.8 Hz, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 5.03 [m, 1H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 3.90 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 2.12–1.98 [m, 4H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.68, 1.64, 1.57 [3s, 9H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 154.7 (C=O), 147.8, 141.7, 131.9 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 139.9–123.8 (Ar), 123.5 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 118.3 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 43.7 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 39.4, 26.2 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 25.6, 17.6, 16.5 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; HRMS (CI): calcd. for $C_{18}H_{23}F_3N_2O$ 341.184073; found, 341.183521 $[M + H]^+$.

*4.1.2.76. N-(4-chlorophenyl)-N′-geranyl urea (**79**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (4:1) as eluent (306 mg, 95% yield). MS (EI): *m/z* 306 (25%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 7.75 (s, 1H, NHAr), 7.4–7.1 (m, 4H, Ar), 5.30 (m, 1H, NH), 5.19 [t, 1H, J = 7.0 Hz, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 5.02 [m, 1H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 3.80 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 2.10–1.97 [m, 4H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.67, 1.65, 1.57 [3s, 9H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 155.9 (C=O), 139.7, 137.4 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 134.7–126.3 (Ar), 123.6 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 120.4 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 43.8 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 39.4, 26.2 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 25.6, 17.7, 16.5 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; HRMS (EI): calcd. for $C_{17}H_{23}ClN_2O$ 306.149891; found, 306.150764 $[M]^{+\cdot}$.

*4.1.2.77. N-(4-cyanophenyl)-N′-geranyl urea (**80**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (5:1) as eluent (282 mg, 95% yield). MS (EI): *m/z* 297 (25%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.58 (s, 1H, NHAr), 7.7–7.3 (m, 4H, Ar), 7.00 (m, 1H, NH), 5.25 [t, 1H, J = 7.1 Hz, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 5.03 [m, 1H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 3.82 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 2.12–1.98 [m, 4H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.69, 1.65, 1.58 [3s, 9H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 154.5(C=O), 143.5 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 140.3–119.9 (Ar), 123.0 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 118.0 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 108.7 (ArCN), 43.6 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 39.4, 26.2 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 25.6, 17.7, 16.5 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; HRMS (EI): calcd. for $C_{18}H_{23}N_3O$ 297.184113; found, 297.184327 $[M]^{+\cdot}$.

*4.1.2.78. N-ethyl-N′-farnesyl urea (**81**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (3:1) as eluent (288 mg, 95% yield). MS (EI): *m/z* 292 (10%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 5.24 [t, 1H, J = 6.7 Hz, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 5.07 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 3.78 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 3.20 (q, 2H, J = 5.4 Hz, $NHCH_2CH_3$), 2.12–1.93 [m, 8H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.68, 1.66, 1.59 [3s, 12H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 0.97 (t, 3H, J = 5.4 Hz, $NHCH_2CH_3$). ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 158.2 (C=O), 149.2, 135.6, 131.3 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 124.2, 123.4, 118.8 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 42.4 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 39.6, 39.4, 26.7, 26.2 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 35.3 ($NHCH_2CH_3$), 25.6, 17.6, 16.5, 16.0 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 15.5 ($NHCH_2CH_3$); HRMS (EI): calcd. for $C_{18}H_{32}N_2O$ 292.251464; found 292.251676 $[M]^{+\cdot}$.

*4.1.2.79. N-tert-butyl-N′-farnesyl urea (**82**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (6:1) as eluent (224 mg, 70% yield). MS (EI): *m/z* 320 (25%) $[M]^{+\cdot}$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 5.89, 5.49 (2s, 2H, 2NH), 5.29 [m, 1H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 5.08 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 4.09 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 2.14–1.93 [m, 8H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.71, 1.67, 1.59 [3s, 12H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.42 [$NC(CH_3)_3$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 157.7 (C=O), 138,2 135.6, 131.4 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 124.2, 123.5, 119.1 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 52.8 [$NC(CH_3)_3$], 43.5 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 39.7, 39.4, 26.7, 26.3 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 29.5 [$NC(CH_3)_3$], 25.7, 17.7, 16.5, 16.0 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; HRMS (EI): calcd. for $C_{20}H_{36}N_2O$ 320.282764; found, 320.282892 $[M]^{+\cdot}$.

*4.1.2.80. N-allyl-N′-farnesyl urea (**83**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (6:1) as eluent (288 mg, 95% yield). MS (CI): *m/z* 305 (100%) $[M + H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 6.00–5.80 (m, 3H, 2NH, NCH_2CH = CH_2), 5.24 [t, 1H, J = 6.7 Hz, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$, NCH_2CH = CH_2], 5.07 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 4.08 (m, 2H, NCH_2CH = CH_2), 3.98 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 2.12–1.93 [m, 8H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.68, 1.66, 1.59 [3s, 12H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 158.1 (C=O), 141.5, 135.6, 131.3 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 133.3 (NCH_2CH = CH_2), 124.2, 123.4, 118.8 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 117.4 (NCH_2CH = CH_2), 47.0 (NCH_2CH = CH_2), 42.4 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 39.6, 39.4, 26.7, 26.2 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 25.6, 17.6, 16.5, 16.0 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; HRMS (CI): calcd. for $C_{19}H_{33}N_2O$ 305.259289; found, 305.259288 $[M + H]^+$.

*4.1.2.81. N-farnesyl-N′-phenyl urea (**84**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (7:1) as eluent (326 mg, 96% yield). MS (CI): *m/z* 341 (100%) $[M + H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 7.89 (s, 1H, NHPh), 7.5–7.1 (m, 5H, Ph), 5.90 (m, 1H, NH), 5.20 [t, 1H, J = 7.0 Hz, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 5.05 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 4.22 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 2.10–1.90 [m, 8H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.67, 1.66, 1.59, 1.56 [4s, 12H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 155.8 (C=O), 141.1, 135.4, 131.3 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 136.2–125.0 (Ph), 124.2, 123.5, 118.8 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 43.7 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 39.6, 39.4, 26.7, 26.2

[$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 25.6, 17.6, 16.5, 16.0 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; HRMS (CI): calcd. for $C_{22}H_{33}N_2O$ 341.259289; found, 341.2592656 $[M + H]^+$.

*4.1.2.82. N-farnesyl-N′-(4-nitrophenyl) urea (**85**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (5:1) as eluent (335 mg, 87% yield). MS (EI): *m/z* 385 (5%) $[M]^{+\cdot}$; ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 7.85 (s, 1H, N*H*Ar), 8.3–7.4 (m, 4H, Ar), 5.55 (m, 1H, NH), 5.28 [t, 1H, *J* = 7.0 Hz, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 5.06 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 4.83 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 2.15–1.90 [m, 8H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.72, 1.67, 1.58 [3s, 12H, $(CH_3)_2C$ = $CH_2CH_2C(CH_3)$ = $CH_2CH_2C(CH_3)$ = $CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 154.9 (C=O), 125.2, 124.2, 123.4 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 145.8–135.5 (Ar), 124.2, 123.3, 117.9 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 43.7 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 39.7, 39.4, 26.7, 26.2 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 25.7, 17.7, 16.6, 16.0 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; HRMS (EI): calcd. for $C_{22}H_{32}N_3O_3$ 385.2365; found, 385.2352 $[M]^{+\cdot}$.

*4.1.2.83. N-farnesyl-N′-(4-trifluoromethyl)phenyl urea (**86**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (6:1) as eluent (360 mg, 85% yield). MS (CI): *m/z* 409 (95%) $[M + H]^+$; ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 8.19 (s, 1H, N*H*Ar), 7.7–7.3 (m, 4H, Ar), 6.50 (m, 1H, NH), 5.25 [t, 1H, *J* = 6.8 Hz, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 5.06 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 3.82 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 2.13–1.88 [m, 8H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.69, 1.67, 1.59, 1.57 [4s, 12H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 154.7 (C=O), 141.8, 135.6, 131.4 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 139.9–122.6 (Ar), 124.2, 123.4, 118.3 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 43.8 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 39.7, 39.4, 26.7, 26.2 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 25.7, 17.7, 16.6, 16.0 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; HRMS (CI): calcd. for $C_{23}H_{31}F_3N_2O$ 409.246674; found409.25811 $[M + H]^+$.

*4.1.2.84. N-(4-chlorophenyl)-N′-farnesyl urea (**87**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (6:1) as eluent (300 mg, 78% yield). MS (EI): *m/z* 374 (15%) $[M]^{+\cdot}$; ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 7.62 (s, 1H, N*H*Ar), 7.4–7.1 (m, 4H, Ar), 5.79 (m, 1H, NH), 5.21 [t, 1H, *J* = 6.8 Hz, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 5.06 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 3.80 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 2.11–1.92 [m, 8H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.67, 1.60, 1.57 [3s, 12H, $(CH_3)_2C$ = $CH_2CH_2C(CH_3)$ = $CH_2CH_2C(CH_3)$ = $CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 155.9 (C=O), 139.6, 137.4, 135.4 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 134.7–126.3 (Ar), 124.2, 123.4, 118.3 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 43.8 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 39.7, 39.4, 26.7, 26.2 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 25.7, 17.7, 16.6, 16.0 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; HRMS (EI): calcd. for $C_{22}H_{31}ClN_2O$ 374.212492; found 374.210336 $[M]^{+\cdot}$

*4.1.2.85. N-(4-Cyanophenyl)-N′-farnesyl urea (**88**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (4:1) as eluent (323 mg, 85% yield). MS (CI): *m/z* 366 (5%) $[M + H]^+$; ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 8.16 (s, 1H, N*H*Ar), 7.7–7.3 (m, 4H, Ar), 6.15 (m, 1H, NH), 5.27 [m, 1H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 5.07 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 3.82 [m, 2H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 2.13–1.93 [m, 8H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 1.71, 1.67, 1.59, 1.58 [4s, 12H, $(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 154.6 (C=O), 143.5, 140.3, 135.5 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 142.2–122.4 (Ar), 124.2, 123.7, 118.1 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 108.9 (ArCN), 43.7 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 39.7, 39.4, 26.7, 26.2 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$], 25.7, 17.7, 16.6, 16.0 [$(CH_3)_2C$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2CH_2C(CH_3)$ = $CHCH_2N$]; HRMS (CI): calcd. for $C_{23}H_{31}N_3O$ 366.254538; found, 366.255104 $[M + H]^+$.

*4.1.2.86. N-(1-dodecyl)-N′-(4-nitrophenyl) urea (**89**).* The syrup was purified by column chromatography, using hexane–ethyl acetate (2:1) as eluent (324 mg, 93% yield). MS (EI): *m/z* 349 (5%) $[M]^{+\cdot}$; ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 8.40 (s, 1H, N*H*Ar), 8.3–7.4 (m, 4H, NHAr), 6.35 (m, 1H, NH), 3.64 (m, 2H, CH_2N), 1.7–1.2 [m, 20H, $(CH_2)_{10}$], 0.87 (t, 3H, *J* = 7.0 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm): 155.0 (C=O), 144.5–122.4 (Ar), 45.7 (CH_2N), 31.9–22.7 [$(CH_2)_{10}$], 14.1 (CH_3); HRMS (EI): calcd. for $C_{19}H_{31}N_3O_3$ 349.2365; found, 349.2371 $[M]^{+\cdot}$.

4.2. Biological assays

4.2.1. Preliminary antimicrobial activity screening

An established standard disc-plate method [42] was used to evaluate the antimicrobial activity of the synthesized compounds against different types of gram-positive (*B. subtilis* ATCC6633, *S. aureus* ATCC2595), gram-negative bacteria, (*K. pneumoniae* ATCC10031, *P. aeruginosa* CECT110, *Escherichia coli* ATCC25922, *Salmonella enterica* ATCC10708 and *Serratia marcescens* ATCC 14756) and fungi (*Candida albicans* ATCC2091).

Müller–Hinton solid medium plates were prepared according to the manufacturer's instructions (SCHARLAU). Each strain was inoculated into 5 ml of Müller–Hinton broth (SCHARLAU) and incubated at the appropriate temperatures (28 °C for *S. marcencens*, *C. albicans* and *Bacillus subtillis* and 37 °C for *S. aureus* ATCC2595, *K. pneumoniae*, *P. aeruginosa*, *E. coli* and *S. enterica*) during 24–48 h. After incubation, the cultures were diluted 100 times in sterile saline solution (NaCl 0.9% p/v) and 100 μl aliquots were carefully spread onto the agar plate using sterile cotton-tipped applicators. Stock solutions of 10 mg/ml of each compound were prepared in DMSO and 20 μl aliquots were used to impregnate a sterile 6 mm diameter disc (Whatmann). The discs were placed on inoculated plates, left at 4 °C for 30 min to allow diffusion of the compound into the agar medium and further incubated at appropriate temperatures for 24 h or 48 h in the case of *C. albicans*.

Compounds **59**–**68** were prepared in DMF [43]. To ensure the validity of the results obtained in DMF, our compounds with higher inhibition zones in DMSO were also prepared in DMF, with the same results. Negative control tests were performed using DMSO and DMF at the same concentrations.

The zone of growth inhibition was measured in millimeters to estimate the antimicrobial activity of each compound.

4.2.2. Compared analysis of growth in liquid medium

Selected synthesized compounds were used to evaluate their antimicrobial activity compared with commercial ones. The commercial control used to test antimicrobial activity against *Pseudomonas aeruginose* was Tobramycine (Tbr), for *S. aureus* and *K. pneumoniae* was Tetracycline (Te) and for *C. albicans*, Ketoconazol (Kt) was selected as antifungal control. For the assays each strain was inoculated into 5 ml of Müller-Hinton broth (SCHARLAU) and incubated at the appropriate temperatures (see previous section) until they reached early stationary phase. 50 μl aliquots were used to inoculate new 5 ml Müller-Hinton broth tubes with different concentrations of the selected compounds and commercial controls (0, 20, 50, 100, 200 μg/ml) and they were incubated at appropriate temperatures. O.D. was measured at 600 nm in a Spectronic 20D+ (Thermospectronic) at different intervals of time. The minimum concentration of commercial compounds that produced total inhibition of growth was selected to compare the growth of strains incubated with similar concentration of synthesized ones.

4.2.3. Citotoxicity assays

4.2.3.1. Materials and cell culture conditions. The HT-29 human colon adenocarcinoma cell line was cultured in McCoy's medium containing 10% fetal bovine serum, 2 mM L-glutamine, 100 U/mL penicillin and 100 μg/mL streptomycin. The human A549 lung cancer cell line was maintained in DMEM supplemented with 2 mm glutamine, 50 μg/mL penicillin, 50 μg/mL streptomycin and 10% fetal bovine serum. Both cell lines were incubated at 37 °C in a 5% CO_2 atmosphere with 95% humidity. Sulforhodamine B sodium salt, MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] salt, tricloroacetic acid, 5-Fluorouracil, cisplatin and N-acetylcysteine (NAC) were purchased from Sigma Chemical Co. Mn(III) Tetrakis(1-methyl-4-pyridyl) porphyrin pentachloride (MnTMPyP) and cell culture reagents were obtained from Biomol International.

4.2.3.2. Cell proliferation assays. The sulforhodamine B (SRB) assay is a colorimetric technique that estimates cell number indirectly by staining total cellular protein with the dye SRB. HT-29 cells were seeded in 96-well plates (5000 cells/well) and incubated for 24 h. Cells were then treated for 48 h with the drugs. Cell monolayers were then fixed for 1 h with 10% (wt/vol) trichloroacetic acid, washed with H_2O and stained for 30 min with 0.4% (wt/vol) SRB. The excess dye was removed by washing repeatedly with 1% (vol/vol) acetic acid. The protein-bound dye was dissolved in 10 mM Tris base solution for optical density determination at 492 nm using a microplate reader [44,45]. Cell viability was expressed as percentage in relation to controls. Data were averaged from at least three independent experiments and are expressed as means ± standard error of the means (SEM).

The MTT assay is a colorimetric technique that allows the quantitative determination of cell viability. It is based on the capability of viable cells to transform the MTT salt [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] into a formazan dye. Exponentially growing cells were seeded into 96-well plates and drugs were added after 24 h. Following an incubation period of 48 h, the medium was removed and MTT (125 μl, 1 mg/ml in medium) was added to each well for 5 h. Then 20% sodium dodecyl sulfate (80 μl) in 0.02 m HCl was added, plates were incubated for 10 h at 37 °C and optical densities were measured at 540 nm on a multi-well plate spectrophotometer reader. Cell viability was expressed as a percentage relative to controls. All data were averaged from at least three independent experiments and were expressed as mean ± standard error of the means (SEM).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2012.10.042.

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