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Substituted Heterocyclic Thiourea Compounds as a New Class of Anti-allergic Agents Inhibiting IgE/FcεRI Receptor Mediated Mast Cell Leukotriene Release

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Abstract—Mast cell derived leukotrienes (LT's) play a vital role in pathophysiology of allergy and asthma. We synthesized various analogues of indolyl, naphthyl and phenylethyl substituted halopyridyl, thiazolyl and benzothiazolyl thioureas and examined their in vitro effects on the high affinity IgE receptor/FcεRI-mediated mast cell leukotriene release. Of the **22** naphthylethyl thiourea compounds tested, there were 7 active compounds and *N*-[1-(1-naphthyl)ethyl]-*N*′-[2-(ethyl-4-acetylthiazolyl)]thiourea (**17** and **16**) ($IC_{50} = 0.002\,\mu M$) and *N*-[1-(1*R*)-naphthylethyl]-*N*′-[2-(5-methylpyridyl)]thiourea (compound **5**) ($IC_{50} = 0.005\,\mu M$) were identified as the lead compounds. Among the 11 indolylethyl thiourea compounds tested, there were seven active compounds and the halopyridyl compounds *N*-[2-(3-indolylethyl)]-*N*′-[2-(5-chloropyridyl)]thiourea (**24**) and *N*-[2-(3-indolylethyl)]-*N*′-[2-(5-bromopyridyl)]thiourea (**25**) were the most active agents and inhibited the LTC_4 release with low micromolar IC_{50} values of 4.9 and 6.1 μM, respectively. The hydroxylphenyl substituted compounds *N*-[2-(4-hydroxyphenyl)ethyl]-*N*′-[2-(5-chloropyridyl)]thiourea (**37**; $IC_{50} = 12.6\,\mu M$), *N*-[2-(4-hydroxyphenyl)ethyl]-*N*′-[2-(5-bromopyridyl)]thiourea (**50**; $IC_{50} = 16.8\,\mu M$) and *N*-[2-(4-hydroxyphenyl)ethyl]-*N*′-[2-(pyridyl)]thiourea (**35**; $IC_{50} = 8.5\,\mu M$) were the most active pyridyl thiourea agents. Notably, the introduction of electron withdrawing or donating groups had a marked impact on the biological activity of these thiourea derivatives and the Hammett sigma values of their substituents were identified as predictors of their potency. In contrast, experimentally determined partition coefficient values did not correlate with the biological activity of the thiourea compounds which demonstrates that their liphophilicity is not an important factor controlling their mast cell inhibitory effects. These results establish the substituted halopyridyl, indolyl and naphthyl thiourea compounds as a new chemical class of anti-allergic agents inhibiting IgE receptor/FcεRI-mediated mast cell LTC_4 release. Further lead optimization efforts may provide the basis for new and effective treatment as well as prevention programs for allergic asthma in clinical settings.

Introduction

Mast cells participate in the pathophysiology of allergy and asthma through the release of chemical mediators, including the pro-inflammatory leukotrienes (LTs) after crosslinking of their high affinity surface IgE receptors/FcεRI.[1–4] LT synthesis in mast cells is triggered by activation of the 5-lipoxygenase (5-LO) pathway.[5] As a first step in this multistep process, the monooxygenase activity of 5-LO results in oxygenation of the 20-carbon fatty acid arachidonic acid to form 5-hydroperoxyeicosatetraenoic acid (5-HPETE). Next, the dehydrase activity of 5-LO catalyzes the conversion of 5-HPETE to an unstable epoxide intermediate (LTA_4), which is either converted by a zinc-dependent cytosolic hydrolase to leukotriene B_4 (LTB_4) or conjugated by a glutathione S transferase (viz., LTC_4 synthase) to glutathione to form the C6-peptide leukotriene C_4 (LTC_4).[6] LTB_4 as a potent chemotactic peptide can initiate a local inflammatory response by recruiting neutrophils[7,8] and eosinophils.[7,9,10] LTC_4 is converted to the other C6-peptide leukotrienes LTD_4 and LTE_4).[6] The

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C6-peptide leukotrienes LTC_4, LTD_4 and LTE_4, as potent smooth muscle contractiles and vasoactive factors comprising the slow-reacting substance of anaphylaxis, participate in the pathophysiology of reactive airway disease and asthma by (i) inducing contractions of the airway smooth muscles[11–15] increasing microvascular permeability and contributing to edema formation in the bronchial wall[16] both of which lead to bronchoconstriction, and (ii) stimulating mucus secretion in the airways[9] which can aggravate the airway obstruction. Furthermore, LTD_4 is selectively chemotactic for eosinophils[17] and LTE_4 may also promote eosinophil chemotaxis.[18] Repeated stimulation of mast cells in patients with allergic asthma may cause sustained synthesis and release of LTs contributing to the significant and persistent bronchoconstriction and inflammatory airway response during episodes of exacerbation. In recent years, several strategies aimed at inhibiting the synthesis and release of leukotrienes (e.g., use of 5-LO inhibitors) or blocking their action at the receptor level (e.g., use of specific LTD_4 antagonists) have been explored as treatment modalities for asthma.[15,19–21]

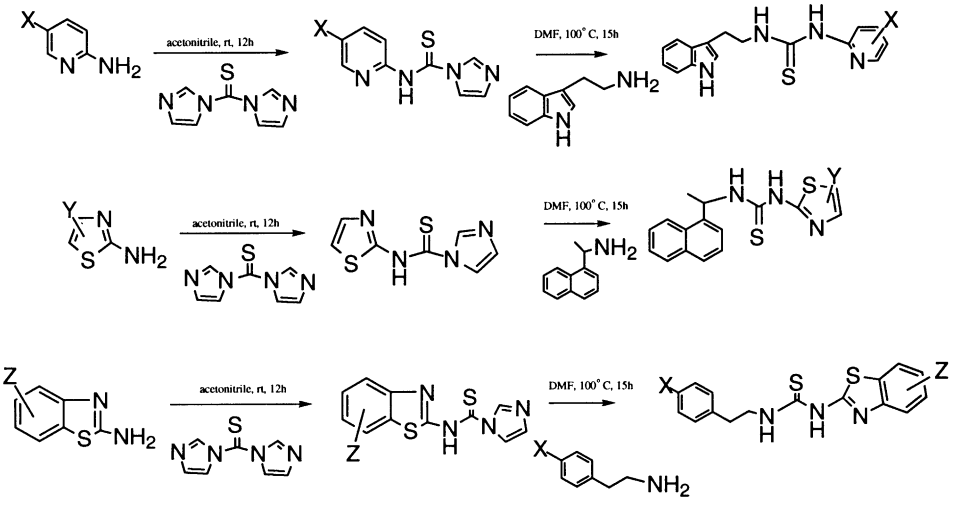
The purpose of the present study was to examine members of our thiourea compound library[26–29] for mast cell inhibitory activity in an attempt to identify thiourea compounds capable of inhibiting FcεRI-mediated LTC_4 release from mast cells.

Results and Discussion

Indolyl-substituted halopyridyl thiourea compounds were synthesized according to Scheme 1. Thiocarbonyl imidazole and 2-amino-5-halo pyridine were added to 100 mL of dry acetonitrile under nitrogen atmosphere and stirred at room temperature for 12–15 h. The precipitate was filtered, washed with cold acetonitrile, and dried thoroughly under vacuum to yield the thiocarbonyl intermediates. In the subsequent step, these intermediates were taken up in a dry flask under nitrogen, 50 mL of anhydrous dimethylformamide was added, and the contents were stirred for 30 min at room temperature. Indolylethylamine dissolved in 10 mL of dimethylformamide was added to this solution, and the reaction mixture was heated to 110 °C over an oil bath for 15 h. After this period, the reaction mixture was cooled to room temperature and poured into crushed ice/water mixture and the contents were stirred for an additional h. The precipitate was filtered, washed with cold water several times and dried under vacuum. The dried precipitate was then dissolved in chloroform and washed with brine, water and finally the separated chloroform layer was dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent yielded the target thiourea compounds. Compounds were further purified using silica gel column chromatography and finally recrystallized using ethanol as a solvent. A similar procedure was followed for other substituted compounds using either thiazolyl or benzothiazolyl precursors. The chiral thiourea derivatives were synthesized starting from their respective chiral amines and their chirality was confirmed using optical rotation values. The optical purity of the compounds was >99% consistent with the purity as measured by HPLC (see ref 30). The structures of the compounds were altered by changing the substituents on the pyridyl ring. Halo and methyl substitutions were chosen to determine the effects of electron withdrawing and donating groups, respectively, on the mast cell inhibitory activity. For the indolylethyl-substituted thioureas, we maintained the indolyl group in the structure while we changed the pyridyl, thiazolyl and benzothiazolyl groups. We substituted the pyridyl moiety with various substituents and introduced thiazolyl and benzothiazolyl moiety into their structures. In the case of phenylethyl pyridyl substituted thioureas, the substituents were changed with H, Me, Br, Cl, OH, OMe while keeping the pyridyl moiety constant with halosubstituent at position 5.

Structure–activity relationship among thiourea compounds

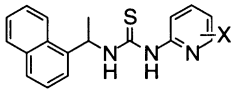
Incubation of IgE-sensitized RBL-2H3 mast cells with the specific antigen DNP-BSA for 30 min caused them to release significant amounts of LTC_4. A 1-h exposure of IgE-sensitized mast cells to some of the chiral



naphthylethylthiourea compounds prior to the antigen challenge reduced the released amounts of LTC_4 after antigen challenge in a concentration-dependent fashion with nanomolar to micromolar IC_{50} values (Tables 1 and 2). Table 1 shows the biological activity observed for chiral naphthyl thioureas. Chirality of these compounds did not influence their biological activity. Except for the methyl substituted compound **5** ($IC_{50} = 0.005\,\mu M$) and **7** ($IC_{50} = 1.6\,\mu M$), none of these compounds was active ($IC_{50} > 100\,\mu M$). Compounds **5** and **7** were more potent than the mast cell inhibitory control dimethoxyquinazoline compound WHI-P97.[24]

Table 2 shows the biological activity of chiral naphthyl thioureas when the pyridyl ring is replaced with a thiazolyl or benzothiazolyl moiety. The thiazolyl substituted compounds with methyl groups inhibited LTC_4 release from IgE/antigen-stimulated mast cells at micromolar concentrations. Notably, the ester analogues **16** and **17** exhibited potent activity with low nanomolar IC_{50} values in the nanomolar range (*R*) and (*S*) isomers of these thiazolyl-substituted compounds were equally potent implying that stereochemistry does not significantly affect their biological activity. By comparison, benzothiazolyl-substituted compounds showed only marginal activity. Introduction of methyl or methoxy substituents on the benzothiazolyl moiety eliminated the biological activity of the parent compound. Of the 22 naphthylethyl thiourea compounds tested, *N*-[1-(1-naphthylethyl]-*N*′-[2-(ethyl-4-acetylthiazolyl)]thiourea (**16** and **17**) ($IC_{50} = 0.002\,\mu M$) and *N*-[1-(1*R*)-naphthylethyl]-*N*′-[2-(5-methylpyridyl)]thiourea (**5**) ($IC_{50} = 0.005\,\mu M$) were identified as the lead compounds.

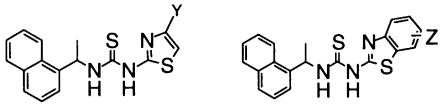
Table 1. Structure and activity of *N*-naphthyl-*N*′-pyridylthioureas



Compd	Isomer	X	Activity (μM)
1	*R*	5-Cl	>100
2	*S*	5-Br	>100
3	*S*	5-Br	>100
4	*R*	5-Cl	>100
5	*R*	5-Me	0.005
6	*S*	5-Me	>100
7	*S*	6-Me	1.6
8	*S*	4,6-diMe	>100
9	*R*	4,6-diMe	>100
10	*S*	H	>100
11	*R*	H	>100
WHI-P97	—	—	6.8[a]

[a]Ref 24.

Table 2. Structure and activity of *N*-naphthyl-*N*′-thiazolyl and benzothiazolyl thioureas



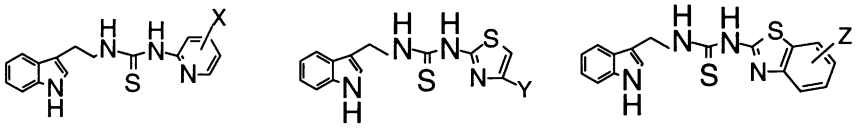
Compd	Isomer	Y	Z	Activity (μM)
12	*S*	H	NA	>100
13	*R*	H	NA	>100
14	*S*	Me	NA	83.2
15	*R*	Me	NA	25.9
16	*S*	CH_2COOEt	NA	0.002
17	*R*	CH_2COOEt	NA	0.002
18	*R*	NA	H	18.9
19	*S*	NA	H	>100
20	*S*	NA	4-Me	>100
21	*R*	NA	4-Me	>100
22	*R*	NA	6-OMe	>100

Active inhibitors of LTC_4 release were also identified among indolylethyl thiourea compounds. Table 3 shows the biological activity observed for indolyl ethyl-substituted thioureas. In the pyridyl substituted compounds, halo substitution produced active compounds. The most active compound in the series was the chloropyridyl substituted thiourea compound **24**. Thiazolyl-substituted compounds were also active albeit with less potency. Interestingly, the ester analogue of thiazolyl substituted compound **31** showed higher potency. Benzothiazolyl compounds in this series were inactive.

Table 4 shows the biological activity obtained for 29 differently substituted phenylethyl thioureas. Only the hydroxy substituted compounds exhibited mast cell inhibitory activity. Substituents such as methyl, fluoro, bromo and chloro yielded inactive compounds, irrespective of the position of substituent in the phenyl ring. We also examined the activity of thiazolyl and benzothiazolyl substituted phenylethyl thiourea compounds and found that none of the compounds in the series showed potent biological activity. Substitutions in the thiazolyl ring or the benzothiazolyl ring did not improve their potency. Table 5 shows the biological activity obtained for 33 symmetrical diphenylthiourea compounds. None of the compounds in this series inhibited mast cells, indicating that the presence of a heterocyclic moiety in the structure is critical for the mast cell inhibitory activity of thiourea compounds.

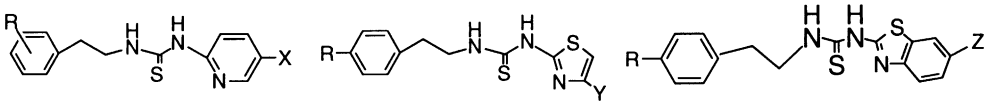
We next sought to determine if the lipophilicity of the compounds could be an important factor for their biologic activity since lipophilic compounds are likely to enter mast cells more easily resulting in higher intracellular concentrations of the compound. To this end, we estimated their partition coefficients using the octanol / water distribution ratio. An HPLC method was used to estimate the amount of compound distribution among these two phases. Table 6 shows the log P values obtained for the selective compounds. No statistically significant correlation between the Log P values and IC_{50} values was observed by regression analysis (slope $= -28.0 \pm 16.2$, t-ratio $= -1.72$, df $= 15$, $p = 0.1$) demonstrating that liphophilicity does not significantly influence the activity of these thiourea compounds. We also investigated the role played by various electron donating and electron withdrawing groups on leukotriene C4 release. A significant correlation was found for the indolyl ethyl substituted compounds: Figure 1 shows the regression between Hammett σ and the IC_{50} values observed for indolyl ethyl substituted thiourea compounds. Introducing electron withdrawing groups such as Br and Cl resulted in more potent compounds

Table 3. Structure and activity of indolylethyl-substituted thioureas



Compd	X	Y	Z	Activity (μM)
23	H	NA	NA	10
24	5Cl	NA	NA	5
25	5Br	NA	NA	6
26	5Me	NA	NA	>100
27	6Me	NA	NA	24
28	4,6 diMe	NA	NA	>100
29	NA	H	NA	36
30	NA	Me	NA	23
31	NA	CH_2COOEt	NA	17
32	NA	NA	6-OMe	100
33	NA	NA	4-Me	>100

Table 4. Structure and activity of phenylethyl substituted heterocyclic thioureas

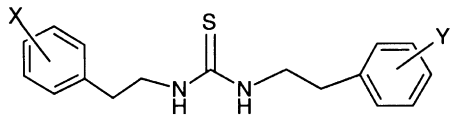


Compd	R	X	Y	Z	Activity (μM)
34	4-Br	H	NA	NA	25.1
35	4-OH	H	NA	NA	8.5
36	4-Me	H	NA	NA	28.3
37	4-OH	Cl	NA	NA	12.6
38	2,5-diOMe	Br	NA	NA	>100
39	2-OMe	Br	NA	NA	>100
40	4-OMe	Br	NA	NA	>100
41	3-OMe	Br	NA	NA	>100
42	2-F	Br	NA	NA	>100
43	3-F	Br	NA	NA	>100
44	4-F	Br	NA	NA	>100
45	4-Br	Br	NA	NA	>100
46	4-Me	Br	NA	NA	>100
47	2-Cl	Br	NA	NA	>100
48	3-Cl	Br	NA	NA	>100
49	4-Cl	Br	NA	NA	>100
50	4-OH	Br	NA	NA	16.8
51	H	H	NA	NA	>100
52	H	CF_3	NA	NA	>100
53	2,5-diOMe	CF_3	NA	NA	>100
54	2-F	CF_3	NA	NA	>100
55	3-F	CF_3	NA	NA	>100
56	4-Me	Cl	NA	NA	>100
57	OH	NA	H	NA	>100
58	4-Me	NA	CH_2COOEt	NA	>100
59	4-Me	NA	Me	NA	>100
60	4-Me	NA	H	NA	>100
61	4-Me	NA	NA	H	>100
62	4-Me	NA	NA	6-OMe	>100

that showed a statistically significant relationship between s and activity ($p<0.001$).

In summary, among the three classes of thiourea compounds studied for mast cell inhibitory activity, naphthyl substituted thiazolyl thioureas exhibited the most potent activity followed by indolylethyl and phenylethyl thiourea compounds. The mast cell inhibitory activity shown by both (*R*) and (*S*) isomers of naphthyl thiourea compounds demonstrates that stereochemistry of these compounds does not play a vital role. In the case of indolyl ethyl substituted thiourea series, the halopyridyl moiety was found to be more beneficial than both thiazolyl and benzothiazolyl units in the structure. Halo substitutions on the pyridyl ring showed improved potency. In the case of phenyl ethyl substituted thioureas, the hydroxy substituent on the phenyl ring showed improved potency compared to other substituents. In addition we found that pyridyl ring in the structure was an essential feature of these

Table 5. Structure activity of substituted symmetrical phenyl ethyl thioureas



Compd	X	Y	Activity (μM)
63	4-F	4-Cl	>100
64	H	4-OMe	>100
65	H	4-Br	>100
66	4-OMe	4-F	>100
67	4-OMe	3-Cl	>100
68	4-F	2-Cl	>100
69	4-F	3-Cl	>100
70	4-F	4-Cl	>100
71	4-F	3-F	>100
72	4F	4-F	>100
73	4-F	2-OMe	>100
74	4-F	3-OMe	>100
75	4-F	3,4-diOMe	>100
76	4-F	2,5-diOMe	>100
77	4-F	2-F	>100
78	4-F	4-Br	>100
79	4-F	4-OH	>100
80	3-F	3-F	>100
81	3-F	2-F	>100
82	3-F	4-Br	>100
83	3-F	4-OH	>100
84	3-F	2-Cl	>100
85	3-F	3-Cl	>100
86	3-F	4-Cl	80.0
87	3-F	3-OMe	>100
88	3-F	2-OMe	>100
89	3-F	4,5-diOMe	>100
90	3-F	2,5-diOMe	>100
91	3-F	4-Me	80.0
92	4-F	4-Me	>100
93	4-F	4,5-diOMe	64.3
94	4-Cl	4-Cl	>100
95	4-Cl	3-Cl	>100

Table 6. Partition coefficient values for thiourea derivatives

Compd	LogP
7	4.1
5	4.2
6	4.2
10	4.1
14	3.2
15	3.9
16	3.7
17	3.7
18	3.9
23	4.0
24	3.8
27	4.2
29	3.9
30	3.9
31	3.6
34	4.0
35	3.7
36	4.1
37	3.2
50	3.3

phenyl ethyl thiourea compounds. Substituted halopyridyl, indolyl and naphthyl thiourea compounds represent a new chemical class of anti-allergic agents inhibiting IgE/FcεRI receptor mediated mast cell LTC_4 release. The lead compounds *N*-[1-(1-naphthylethyl]-*N*′-[2-(ethyl-4-acetylthiazolyl)]thiourea and N-[1-(1*R*)-naphthylethyl]-*N*′-[2-(5-methylpyridyl)]thiourea are nanomolar inhibitors of mast cell LTC_4 release. Further lead optimization efforts may provide the basis for new and effective treatment as well as prevention programs for allergic asthma in clinical settings.

Materials and Methods

All chemicals were purchased from Aldrich (Milwaukee, WI, USA) and were used without further purification. The chiral naphthyl amines were obtained as pure individual enantiomers and were used as such without purification. Unless otherwise noted, each reaction vessel was secured with a rubber septa, and the reaction was performed under nitrogen atmosphere. ^{1}H, ^{13}C NMR were obtained on a Varian Mercury 300 instrument at ambient temperature in DMSO-d_6. Chemical shifts are reported as δ values in parts per million downfield from tetramethylsilane (δ = 0.0 ppm) as an internal standard or from the residual dimethylsufloxide signal (δ = 2.49 ppm for ^{1}H NMR or δ = 39.7 ppm for ^{13}C NMR). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad peak. FT-IR spectra were recorded on a Nicolet Protege 460 spectrometer. Mass spectra were performed on a Hewlett Packard MALDI-TOF spectrometer (Model G2025A LD-TOF). UV spectra were recorded from a Beckmann Model # DU 7400 UV/Vis spectrometer using a cell path length of 1 cm. Melting points were determined using a Melt John's apparatus and are uncorrected. HPLC's were done using a Hewlett Packard 1100 series instrument consisting of an automatic sampler, an electronic degasser, a thermostatic control unit, a diode array detector in conjunction with a chem station software assembly. The column used was an analytical RP-18 Lichrospher column (4.6×150 mm) and eluent was 35:65, H_2O (0.1% ACOH): ACN. The flow rate was maintained at 1.0 mL/min and the detection wavelength was set at 275 nm. The column was maintained at room temperature throughout the analysis. Column chromatography was performed using silica gel obtained from the J. T. Baker Company. The solvents used for elution varied depending on the compound and included either one or a combination of the following: ethylacetate, methanol, chloroform, hexane, methylene chloride, THF and ether. Compounds were made by condensing indolyl ethyl amine and thiocarbonylimidazole derivatives of 5 and 6′-substituted amino pyridines in anhydrous dimethylformamide (Scheme 1). Indolylethylamine was purchased from Aldrich Chemical Company and was used without further purification. Thiazolyl and benzothiazolyl substituted thioureas were prepared in a similar fashion using thiocarbaimidazole derivatives of either substituted amino thiazoles or benzothiazoles respectively.

Partition coefficients

The octanol/water partition coefficients were determined by the shake flask method. A known amount of

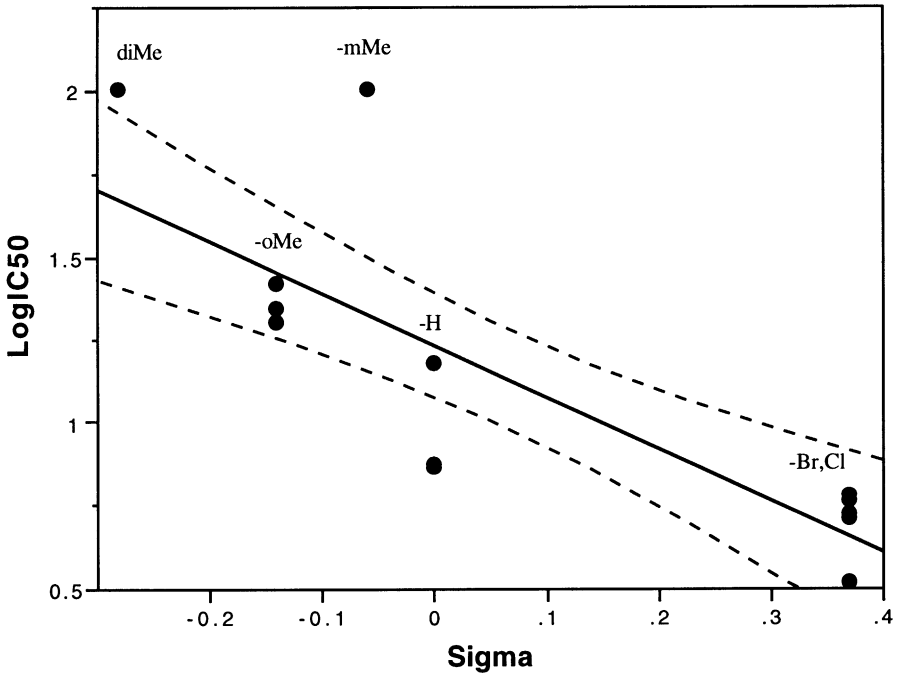


Figure 1. Structure–activity relationship for indolyethyl-substituted thioureas. Hammett sigma values predicted Log 10 transformed IC_{50} values for indolyethyl substituted thioureas (solid line, *R*-squared = 67%, slope = -1.55 ± 0.3, *t*-ratio = -5.24, df = 13, $p = 0.0003$). 95% confidence for the regression is shown by the dotted line.

the thiourea analogues was added to 3 mL of water and 3 mL of octanol in a glass vial. The mixture was shaken for 4 h at room temperature. The two phases were carefully separated and filtered through a Millipore filter and analyzed by HPLC. The wavelength of detection was kept at 254 nm. Methanol was used as eluent with a flow rate of 1 mL/min. The partition coefficient was calculated using the ratio of the area under the curve for octanol and water respectively.

Determination of optical rotation

The optical rotation of the chiral naphthyl derivatives was determined using a polarimeter (Digi Pol, Model #781, Automatic Polarimeter, Rudolph Instruments, Fairfield, NJ, USA). The active chiral thiourea derivatives were weighed and transferred into a standard flask of 10 mL capacity. Chloroform (5 mL) was used to dissolve the derivatives. The solution (1 mL) containing the respective thioruea derivatives was taken and introduced into the polarimeter tube. The optical rotation was measured at room temperature, and the values with their signs are shown in the physical constants section.

Statistical analysis

IC_{50} values were reported for each compound. The IC_{50} values were correlated with Log P values and Hamett σ using a linear regression model (JMP software, SAS institute Inc, Cary, NC, USA). Slope parameters were estimated and the *t*-ratios compared to zero slope were calculated to assess the statistical significance. *p*-Values of less than 0.05 were deemed significant.

Mast cell cultures

Stimulation of mast cells. RBL-2H3 rat mast cells were sensitized with monoclonal anti DNP IgE antibody (0.24 mg/mL) for 1 h at 37 °C in a 48-well tissue culture plate. Unbound IgE was removed by washing the cells with PIPES-buffered saline. After washing, PIPES-buffered saline containing 1 mM calcium chloride was added to the monolayers of the RBL-2H3 cells. The cells were challenged with 20 ng/mL DNP-BSA for 30 min at 37 °C. The plate was centrifuged at 200 g for 10 min at 4 °C, Supernatants were removed and saved. To study the effect of test drugs, RBL-2H3 rat mast cells were incubated with the drugs at the indicated concentrations or vehicle for 30 min prior to antigen challenge.

RBL-2H3 mast cell line and mast cell cultures. RBL-2H3 cells were supplied by Dr. R. P. Siraganian (Laboratory of Microbiology and immunology, National Institute of Dental Research, National Institute of Health). This adherent mucosal mast cell line expresses 10^5–10^6 high affinity IgE receptors/FcεRI per cell. RBL-2H3 cells serve as a convenient model to study mast cell functions.[22,23] RBL-2H3 cells were maintained as monolayers in 175 cm^2 culture flasks in Eagle's minimum essential medium with Earle's salts (without L-glutamine) supplemented with 20% fetal bovine serum and 2 mM L-glutamine.[23]

Stimulation of mast cells and mediator assays. RBL-2H3 cells were sensitized with a monoclonal anti-dinitrophenyl (DNP) IgE antibody (0.24 mg/mL) for 1 h at 37 °C in a 48-well tissue culture plate. Unbound IgE was

removed by washing the cells with phosphate buffered saline, pH 7.4. After washing the BMMC were re-suspended in RPMI-hepes buffer whereas PIPES-buffered saline containing 1 mM calcium chloride was added to the monolayers of the RBL-2H3 cells. In order to study the biologic effects of the test compounds, sensitized mast cells were further incubated with the test compounds at the indicated concentrations (or vehicle alone) for 1 h. The cells were then challenged with 20 ng/mL DNP-BSA for 30 min at 37 °C. The plates were centrifuged at 200 *g* for 10 min at 4 °C. Supernatants were removed and saved. LTC_4 levels were also determined in cell free supernatants.[24,25]

Acknowledgements

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30. Physicochemical properties of selected thiourea compounds

***N*-[1-(1*R*)-(1-Naphthylethyl)]-*N'*-[2-(5-methylpyridyl)]thiourea** (**5**). Mp 186–187 °C; ^{1}H NMR (DMSO-d_6) δ 12.22 (d, 1H, J = 8.1 Hz), 10.59 (s, 1H), 8.19 (d, 1H, J = 8.1 Hz), 7.92 (d, 2H, J = 8.4 Hz), 7.83 (d, 1H, J = 7.8 Hz), 7.56–7.46 (m, 5H), 7.06 (d, 1H, J = 8.4 Hz), 6.32 (t, 1H), 2.11 (s, 3H), 1.65 (d, 3H, J = 6.9 Hz); ^{13}C NMR (DMSO-d_6) δ 178.5, 152.0, 144.9, 139.9, 139.1, 133.6, 130.6, 128.9, 127.9, 127.0, 126.6, 125.8*, 123.4, 122.9, 112.4, 50.5, 21.6, 17.4; IR ν 3440, 3232, 3027, 2969, 1600, 1562, 1492, 1195, 798 cm^{-1}; UV (MeOH) λ 203, 222, 250, 272, 294 nm; MALDI-TOF m/z 322.8 ($C_{19}H_{19}N_3S_2 + 2H^+$). [α]: −31.0; 0.5HPLC R_t: 14.01 min% purity 99.0, elemental analysis: calcd: C: 70.99, H: 5.96, N:13.07; found: C: 71.04, H: 6.04, N: 13.17.

***N*-[1-(1*S*)-(1-Naphthylethyl)]-*N'*-[2-(5-methylpyridyl)]thiourea** (**6**). Mp 186–187 °C; ^{1}H NMR (DMSO-d_6) δ 12.23 (d, 1H, J = 7.8 Hz), 10.61 (s, 1H), 8.20 (d, 1H, J = 8.7 Hz), 7.91 (d, 2H, J = 8.0 Hz), 7.83 (d, 1H, J = 8.1 Hz), 7.59–7.46 (m, 5H), 7.06 (d, 1H, J = 8.4 Hz), 6.33 (m, 1H), 2.10 (s, 3H), 1.66 (d, 3H, J = 6.6 Hz); ^{13}C NMR (DMSO-d_6) δ 178.4, 152.0, 144.9, 139.9, 139.1, 133.6, 130.6, 128.9, 127.8, 127.0, 126.5, 125.8*, 123.4, 122.9, 112.4, 50.4, 21.6, 17.4; IR ν 3232, 3027, 2969, 1600, 1527, 1195, 779 cm^{-1}; UV (MeOH) λ 224, 249, 272, 294 nm; MALDI-TOF m/z 322.8 ($C_{19}H_{19}N_3S_2 + 2H^+$). [α]: +30.5; HPLC R_t: 13.97 min% purity 100.0, elemental analysis: calcd: C: 70.99, H: 5.96, N:13.07; found: C: 70.78, H: 6.00, N: 13.01.

***N*-[1-(1*S*)-(1-Naphthylethyl)]-*N'*-[2-(4-methylthiazolyl)]thiourea** (**14**). Mp 186–187 °C; ^{1}H NMR (DMSO-d_6) δ: 11.50 (s, 1H), 10.17 (s, 1H), 8.15 (q, 1H), 7.95 (t, 1H), 7.86 (t, 1H), 7.55 (m, 4H), 6.61 (d, 1H, J = 8.7 Hz), 6.20 (m, 1H), 2.16 (d, 3H, J = 4.8 Hz), 1.64 (t, 3H); ^{13}C NMR (DMSO-d_6) δ: 177.2, 161.2, 138.7, 133.5, 130.4, 128.8, 127.8, 126.5, 125.8, 125.6, 123.2, 122.8, 106.2, 49.9, 21.2, 16.7; IR ν 3448, 3170, 3020, 2969, 1581, 1531, 1502, 1207, 777 cm^{-1}; UV (MeOH) λ 224, 266, 294 nm; MALDI-TOF MS m/z 329.0 ($C_{17}H_{17}N_3O_2 + 2H^+$). [α]: +21.5; HPLC R_t: 11.65 min.% purity 99.0, elemental analysis: calcd: C: 62.35, H: 5.23, N:12.83; found: C: 62.46, H:. 5.30, N: 12.81.

***N* - [1 - (1*R*) - (1 - Naphthylethyl)] - *N'* - [2 - (4 - methylthiazolyl)]thiourea** (**15**). Mp 186–187 °C; ^{1}H NMR (DMSO-d_6) δ: 11.52 (s, 1H), 10.17 (s, 1H), 8.15 (d, 1H, J = 8.4 Hz), 7.94 (d, 1H, J = 8.1 Hz), 7.85 (d, 1H, J = 7.5 Hz), 7.52 (m, 4H), 6.61 (s, 1H), 6.21 (m, 1H), 2.16 (s, 3H), 1.64 (d, 3H, J = 6.6 Hz); ^{13}C NMR (DMSO-d_6) δ: 177.9, 162.0, 139.4, 134.1, 131.0, 129.4, 128.4, 127.1, 126.5, 126.2, 123.8, 123.4, 106.8, 50.6, 21.8, 17.3; IR ν 3423, 3170, 3018, 2968, 1581, 1531, 1502, 1205, 779 cm^{-1}; UV (MeOH) λ 207, 224, 284, 293 nm; MALDI-TOF MS m/z 329.2 ($C_{17}H_{17}N_3O_2 + 2H^+$). [α]: −21.2; HPLC R_t: 12.31 min% purity 100.0.

***N* - [1 - (1*S*) - (1 - Naphthylethyl)] - *N'* - [2 - (ethyl - 4 - acetylthiazolyl)]thiourea** (**16**) Mp 107–109 °C; ^{1}H NMR (DMSO-

d_6) δ 11.54 (s, 1H), 10.10 (s, 1H), 8.15 (t, 1H), 7.96 (t, 1H), 7.86 (t, 1H), 7.61–7.50 (m, 4H), 6.89 (s, 1H), 6.21 (s, 1H), 4.05–4.00 (m, 2H), 3.64 (s, 2H), 1.62 (d, 3H, $J=3.9$ Hz), 1.16–1.09 (m, 3H); ^{13}C NMR (DMSO-d_6) δ 177.2, 170.3, 161.5, 143.9, 139.3, 134.1, 131.0, 129.4, 128.4, 127.2, 126.5, 126.2, 123.7, 123.3, 109.9, 61.1,. 50.5, 31.2, 21.9, 14.9; IR ν 3444, 3185, 3047, 2927, 1577, 1554, 1519, 1230 cm^{-1}; MALDI-TOF m/z 401.0 ($C_{20}H_{21}N_3O_2S_2+2H^+$); [α]: +22.8; HPLC R_t: 6.91 min% purity 100.0, elemental analysis: calcd: C: 60.13, H: 5.30, N:10.52; found: C: 60.06, H: 5.30, N: 10.50.

***N*-[1-(1*R*)-(1-Naphthylethyl)]-*N*′-[2-(ethyl-4-acetylthiazolyl)]thiourea (17)**. Mp 105–107 °C; ^{1}H NMR (DMSO-d_6) δ 11.54 (s, 1H), 10.09 (s, 1H), 8.14 (d, 1H, $J=7.8$ Hz), 7.95 (d, 1H, $J=7.8$ Hz), 7.86 (t, 1H), 7.62–7.50 (m, 4H), 6.89 (s, 1H), 6.20 (t, 1H), 4.02 (q, 2H), 3.63 (s, 2H), 1.62 (d, 3H, $J=5.4$ Hz), 1.12 (t, 3H); ^{13}C NMR (DMSO-d_6) δ 176.5, 169.7, 160.8, 143.3, 138.7, 133.5, 130.4, 128.8, 127.8, 126.5, 125.9, 125.6, 123.1, 122.7, 109.4, 60.5, 49.9, 36.6, 21.3, 14.3; IR ν 3463, 3166, 2981, 1743, 1573, 1535, 1508, 1380, 1211, 1164, 794 cm^{-1}; MALDI-TOF m/z 401.2 ($C_{20}H_{21}N_3O_2S_2+2H^+$); [α]: −25.5; HPLC R_t: 9.89 min% purity 99.9, elemental analysis: calcd: C: 60.13, H: 5.30, N:10.52; found: C: 60.40, H: 5.36, N: 10.53.

***N*-[1-(1*R*)-(1-Naphthylethyl)]-*N*′-[2-(benzothiazolyl)]thiourea (18)**. Mp 174–175 °C; ^{1}H NMR (DMSO-d_6) δ 11.86 (s, 1H), 10.30 (s, 1H), 8.17 (d, 1H, $J=8.4$ Hz), 7.95 (d, 1H, $J=8.1$ Hz), 7.87 (d, 2H, $J=7.8$ Hz), 7.62–7.51 (m, 5H), 7.38 (t, 1H), 7.25 (t, 1H), 6.24 (m, 1H), 1.69 (d, 3H, $J=6.3$ Hz); ^{13}C NMR (DMSO-d_6) δ 178.6, 161.6, 138.6, 133.5, 130.5, 128.8, 127.9, 126.5, 126.3, 125.9, 125.6, 123.6, 123.2, 121.8, 118.950.2, 50.1, 21.1; IR ν 3563, 3182, 3039, 2973, 1565, 1523, 1199 cm^{-1}; MALDI-TOF m/z 367.2 ($C_{20}H_{17}N_3S_2+4H^+$); [α]: −39.5; HPLC R_t: 18.84 min% purity 99.7, elemental analysis: calcd: C: 66.09, H: 4.71, N:11.56; found: C: 65.89, H: 4.75, N: 11.36.

***N*-[1-(1*S*)-(1-Naphthylethyl)]-*N*′-[2-(benzothiazolyl)]thiourea (19)**. Mp 193–194 °C; ^{1}H NMR (DMSO-d_6) δ 11.88 (s, 1H), 10.31 (s, 1H), 8.18 (d, 1H, $J=8.4$ Hz), 7.94 (d, 1H, $J=8.1$ Hz), 7.87 (dd, 2H, $J=3.9$, 4.5, 7.5 Hz), 7.62–7.50 (m, 5H), 7.37 (t, 1H), 7.25 (t, 1H), 6.25 (m, 1H), 1.69 (d, 3H, $J=6.3$ Hz); ^{13}C NMR (DMSO-d_6) δ 178.3, 162.4, 139.2, 134.1, 131.1, 129.4, 128.5, 127.2, 126.9, 126.5, 126.3, 124.3, 123.8, 123.5, 122.4, 119.7, 50.8, 21.7; IR ν 3452, 3166, 3031, 1573, 1523, 1203 cm^{-1}; MALDI-TOF m/z 364.8 ($C_{20}H_{17}N_3S_2+2H^+$); [α]: +38.9; HPLC R_t: 18.84 min% purity 99.9, elemental analysis: calcd: C: 66.09, H: 4.71, N:11.56; found: C: 66.12, H: 4.67, N: 11.53.

***N*-[2-(3-Indolylethyl)]-*N*′-[2-(pyridyl)]thiourea (23)**. Mp 188.5 °C; ^{1}H NMR (DMSO-d_6) δ 11.67 (s, 1H), 10.88 (s, 1H), 10.51 (s, 1H), 7.96 (t, 1H), 7.74–7.64 (m, 2H), 7.35 (d, 1H, $J=8.1$ Hz), 7.25 (s, 1H), 7.12–7.04 (m, 2H), 6.99–6.95 (m, 2H) 3.88 (q, 2H), 3.05 (t, 2H); ^{13}C NMR (DMSO-d_6) δ 179.8, 154.3, 145.9, 139.4, 136.9, 127.7, 123.9, 121.7, 119.1, 118.9, 118.2, 113.0, 112.1, 112.0, 102.8, 46.4, 25.0; IR ν 3326, 3236, 3056, 2912, 1604, 1564, 1537, 1481, 1317, 1238, 1176, 1149, 1091, 771, 754 cm^{-1}; UV (MeOH) λ 223, 267, 285, 291 nm; MALDI-TOF MS m/z 296.2 ($C_{16}H_{16}N_4S^+$).

***N*-[2-(3-Indolylethyl)]-*N*′-[2-(5-chloropyridyl)]thiourea (24)**. Mp 168 °C (dec.); ^{1}H NMR (DMSO-d_6) δ 11.20 (t, 1H), 10.91 (s, 1H), 10.67 (s, 1H), 7.93 (d, 1H, $J=2.7$ Hz), 7.84–7.80 (d, 1H, $J=9.0$ Hz), 7.64–7.61 (d, 1H, $J=7.5$ Hz), 7.37–7.34 (d, 1H, $J=7.8$ Hz), 7.28 (d, 1H, $J=1.5$ Hz), 7.14–7.11 (d, 1H, $J=8.4$ Hz), 7.09–7.04 (dd, 1H, $J=6.7$, 8.1 Hz), 6.99–6.93 (dd, 1H, $J=8.1$, 6.9 Hz), 3.87 (q, 2H), 3.04 (t, 2H); ^{13}C NMR (DMSO-d_6) δ 179.4, 152.6, 144.1, 139.3, 136.9, 127.7, 124.2, 124.1, 121.7, 119.1, 118.9, 114.6, 112.1, 111.9, 46.5, 24.8; IR ν 3357, 3209, 3155, 3082, 3037, 2916, 2870, 1662, 1597, 1556, 1531, 1467, 1321, 1263, 1228, 1192, 1109, 737, 590 cm^{-1}; UV (MeOH) λ 203, 208, 210, 220, 264, 267, 274 nm; MALDI-TOF MS m/z 332.0 ($C_{16}H_{15}ClN_4S+2H^+$).

***N*-[2-(3-Indolylethyl)]-*N*′-[2-(5bromopyridyl)]thiourea (25)**. Mp: 211–212 °C; ^{1}H NMR (DMSO-d_6) δ 11.18 (t, 1H), 10.90 (s, 1H), 10.65 (s, 1H), 7.97 (s, 1H), 7.90 (m, 1H), 7.62 (d, 1H, $J=7.5$ Hz), 7.35 (d, 1H, $J=7.5$ Hz), 7.27 (s, 1H), 7.08 (s, 1H), 7.05 (t, 1H), 6.95 (t, 1H), 3.86 (q, 2H), 3.03 (t, 2H); ^{13}C NMR (DMSO-d_6) δ 178.1, 152.3, 145.7, 141.3, 136.4, 127.1, 123.5, 121.1, 118.5, 118.4, 114.4, 111.8, 111.5, 111.3, 45.9, 24.2; IR ν 3347, 3207, 3035, 2941, 1591, 1556, 1529, 1456, 1189, 736 cm^{-1}; MALDI-TOF m/z 376 ($C_{16}H_{15}BrN_4S+2H^+$); HPLC R_t: 6.60 min.

***N*-[2-(Indolylethyl)]-*N*′-[2-(5-methylpyridyl)]thiourea (26)**. Mp: 209–210 °C; ^{1}H NMR (DMSO-d_6) δ 11.63 (t, 1H), 10.90 (s, 1H), 10.45 (s, 1H), 7.79 (s, 1H), 7.64 (d, 1H, $J=7.5$ Hz), 7.52 (d, 1H, $J=7.0$ Hz), 7.36 (m, 1H), 7.26 (s, 1H), 7.10–6.94 (m, 3H), 3.89 (q, 2H), 3.05 (t, 2H), 2.16 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 179.0, 151.8, 144.6, 139.6, 136.4, 127.1, 126.5, 123.4, 121.1, 118.4 (d), 112.0, 111.5 (d), 45.7, 24.5, 17.5; IR ν 3320, 3251, 3054, 2931, 1527, 1488, 1257, 748 cm^{-1}; UV (MeOH) λ 209, 211, 223, 269, 292 nm; MALDI-TOF m/z 312.1 ($C_{17}H_{18}N_4S+2H^+$).

***N*-[2-(3-Indolylethyl)]-*N*′-[2-(6-methylpyridyl)]thiourea (27)**. Mp: 188–189 °C; ^{1}H NMR (DMSO-d_6) δ 11.83 (t, 1H), 10.84 (s, 1H), 10.43 (s, 1H), 7.62–7.52 (m, 2H), 7.34 (d, 1H, $J=7.8$ Hz), 7.20 (s, 1H), 7.05 (t, 1H), 6.96–6.88 (m, 2H), 6.76 (d, 1H, $J=7.5$ Hz), 3.97 (q, 2H), 3.04 (t, 2H), 2.05 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 179.4, 154.6, 153.3, 139.1, 136.5, 127.3, 123.0, 121.2, 118.5 (d), 116.9, 111.6 (d), 109.4, 45.3, 24.8, 23.5; IR ν 3417, 3224, 3047, 2985, 1612, 1542, 1450, 1226 cm^{-1}; MALDI-TOF m/z 311.6 ($C_{17}H_{18}N_4S+H^+$); HPLC R_t: 5.64 min.

***N*-[2-(3-Indolylethyl)]-*N*′-[2-(4,6-dimethylpyridyl)]thiourea (28)**. Mp: 195–196 °C; ^{1}H NMR (DMSO-d_6) δ 11.91 (t, 1H), 10.84 (s, 1H), 10.37 (s, 1H), 7.61 (d, 1H, $J=8.1$ Hz), 7.34 (d, 1H, $J=7.8$ Hz), 7.20 (d, 1H, $J=1.5$ Hz), 7.06 (t, 1H), 6.95 (t, 1H), 6.72 (s, 1H), 6.59 (s, 1H), 3.97 (q, 2H), 3.04 (t, 2H), 2.15 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 179.4, 154.0, 153.4, 149.7, 136.4, 127.2, 122.9, 121.1, 118.5, 118.3, 118.0, 111.5, 111.4, 109.3, 45.2, 24.7, 23.2, 20.9; IR ν 3507, 3261, 3035, 2917, 1618, 1591, 1537, 1456, 1346, 1211, 833 cm^{-1}; MALDI-TOF m/z 326.5 ($C_{18}H_{20}N_4S+2H^+$); HPLC R_t: 10.13 min.

***N*-[2-(2-Indolylethyl)]-*N*′-[2-(thiazolyl)]thiourea (29)**. Mp 212–213 °C; ^{1}H NMR (DMSO-d_6) δ 11.56 (s, 1H), 10.86 (s, 1H), 9.73 (s, 1H), 7.62 (d, 1H, $J=7.5$ Hz), 7.35 (s, 1H), 7.31 (t, 1H), 7.20 (s, 1H), 7.07 (d, 1H, $J=6.9$ Hz), 7.03 (s, 1H), 6.96 (t, 1H), 3.81 (q, 2H), 3.00 (t, 2H); ^{13}C NMR (DMSO-d_6) δ 178.4, 162.3, 136.9, 127.7, 123.8, 121.7, 119.1, 118.9, 112.7, 112.1, 111.8, 102.8, 45.9, 24.9; IR ν 3386, 3164, 3076, 3035, 1560, 1514, 1184, 750 cm^{-1}; UV (MeOH) λ 204, 207, 221, 285 nm; MALDI-TOF MS m/z 304.2 ($C_{14}H_{14}N_4S_2+2H^+$).

***N*-[2-(Indolylethyl)]-*N*′-[2-(4-methylthiazolyl)]thiourea (30)**. Mp: 177–178 °C; ^{1}H NMR (DMSO-d_6) δ 11.53 (s, 1H), 10.89 (s, 1H), 9.94 (s, 1H), 7.62 (d, 1H, $J=7.6$ Hz), 7.34 (d, 1H, $J=7.0$ Hz), 7.22 (s, 1H), 7.06 (t, 1H), 6.97 (t, 1H), 6.60 (s, 1H), 3.85 (q, 2H), 3.01 (t, 2H), 2.12 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 178.3, 161.7, 137.0, 127.7, 123.8, 121.7, 119.1, 118.9, 112.1, 111.8, 106.6, 45.8, 25.0, 17.4; IR ν 3407, 3174, 3025, 2917, 1560, 1508, 1213, 742 cm^{-1}; UV (MeOH) λ 201, 208, 212, 223, 289, 292 nm; MALDI-TOF MS m/z 318.4 ($C_{15}H_{16}N_4S_2+2H^+$).

***N*-[2-(Indolylethyl)]-*N*′-[2-(ethyl-4-acetylthiazolyl)]thiourea (31)**. Mp: 144–145 °C; ^{1}H NMR (DMSO-d_6) δ 11.61 (s, 1H), 10.87 (s, 1H), 9.45 (s, 1H), 7.61 (d, 1H, $J=7.5$ Hz), 7.35 (d, 1H, $J=7.5$ Hz), 7.20 (d, 1H, $J=2.1$ Hz), 7.07 (t, 1H), 6.97 (dd, 1H, $J=8.0$, 6.5 Hz), 6.84 (s, 1H), 4.07 (q, 2H), 3.82 (q, 2H), 3.60 (s, 2H), 3.00 (t, 2H), 1.17 (t, 3H); ^{13}C NMR (DMSO-d_6) δ 177.6, 169.9, 160.9, 143.2, 136.3, 127.1, 123.1, 121.1, 118.4 (d), 111.5, 111.2, 109.1, 60.6, 45.1, 36.6, 24.4, 14.4; IR ν 3371, 3170, 3018, 1727, 1569, 1203, 742 cm^{-1}; UV (MeOH) λ 207,

223, 289, 291 nm; MALDI-TOF MS m/z 390.0 ($C_{18}H_{20}N_4O_2S_2+H^+$).

***N*-[2-(4-Bromophenylethyl)]-*N′*-[2-(pyridyl)]thiourea (34)**. Mp: 146–148 °C; ^{1}H NMR (DMSO-d_6) δ: 11.65 (d, 1H), 10.57 (s, 1H), 8.05 (m, 1H), 7.71 (m, 1H), 7.48 (m, 2H), 7.25 (m, 2H) 7.11 (m, 1H), 6.98 (t, 1H), 3.82 (q, 2H), 2.90 (t, 2H); ^{13}C NMR (DMSO-d_6) δ: 179.5, 153.7, 145.3, 138.9, 138.6, 131.2 (d), 119.5, 117.8, 112.5, 46.1, 33.7; IR ν 3237, 3104, 3018, 2931, 1602, 1537, 1479, 1319, 1010, 773 cm^{-1}; UV (MeOH) λ 206, 213, 223, 247, 266, 293 nm; MALDI-TOF MS m/z 337.2 ($C_{14}H_{14}BrN_3S+H^+$).

***N*-[2-(4-Hydroxyphenylethyl)]-*N′*-[2-(pyridyl)]thiourea (35)**. Mp: 192.5 °C; ^{1}H NMR (DMSO-d_6) δ 11.64 (t, 1H), 10.51 (s, 1H), 9.22 (s, 1H), 8.05 (d, 1H, J = 4.8 Hz), 7.74–7.68 (td, 1H), 7.08 (q, 2H), 7.00–7.96 (m, 1H), 6.69 (m, 2H), 3.74 (q, 2H), 2.79 (t, 2H); ^{13}C NMR (DMSO-d_6) δ 179.9, 156.4, 154.3, 145.9, 139.5, 130.3, 118.3, 115.8, 113.1, 102.8, 47.4, 34.2; IR ν 3245, 3008, 2935, 1606, 1511, 1211, 1149, 1108 769 cm^{-1}; UV (MeOH) λ 202, 248, 268, 291 nm; MALDI-TOF MS m/z 274.9 ($C_{14}H_{15}N_3OS+2H^+$).

***N*-[2-(4-Methylphenylethyl)]-*N′*-[2-(pyridyl)]thiourea (36)**. Mp: 143–145 °C; ^{1}H NMR (DMSO-d_6) δ 11.67 (t, 1H), 10.54 (s, 1H), 8.05 (dd, 1H, J = 5.1 Hz), 7.72 (dd, 1H, J = 8.7, 6.9 Hz), 7.17 (d, 2H, J = 8.1 Hz), 7.10 (d, 3H, J = 8.1 Hz), 6.99 (dd, 1H, J = 6.9 Hz), 3.80 (m, 2H), 2.87 (t, 2H), 2.25 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 179.4, 153.7, 145.3, 138.9, 136.0, 135.3, 129.0, 128.7, 117.7, 112.5, 46.6, 33.9, 20.9; IR ν 3203, 3018, 2925, 1565, 1479, 1317, 1228, 1166, 1147, 772 cm^{-1}; UV (MeOH) λ 205, 209, 266 nm; MALDI-TOF MS m/z 271.1 ($C_{15}H_{17}N_3S^+$).

***N*-[2-(4-Hydroxyphenylethyl)]-*N′*-[2-(5-chloropyridyl)]thiourea (37)**. Mp: 192–193 °C; ^{1}H NMR (DMSO-d_6) δ 11.18 (s, 1H), 10.60 (s, 1H), 9.08 (s, 1H), 7.97 (t, 1H), 7.70–7.65 (m, 1H), 7.12 (dd, 1H, J = 9, 6.0 Hz), 7.02 (m, 2H), 6.70–6.66 (m, 2H), 3.75 (q, 2H), 2.78 (t, 2H); ^{13}C NMR (DMSO-d_6) δ 179.7, 156.4, 152.7, 143.8, 138.9, 130.1, 129.5, 124.3, 115.8, 114.6, 47.4, 34.2; IR ν?3226, 3174, 3030, 2937, 1591, 1560, 1519, 1483, 1230 cm^{-1}; UV (MeOH) λ 209, 215, 224, 273, 304 nm; MALDI-TOF MS m/z 309.4 ($C_{14}H_{14}ClN_3OS_2+2H^+$).

***N*-[2-(4-hydroxyphenylethyl]-*N′*-[2-(5-bromopyridyl)]thiourea (50)**. Mp: 159 °C; ^{1}H NMR (DMSO-d_6) δ 11.30 (bs, 1H), 10.17 (bs, 1H), 8.78 (bs, 1H), 8.03–8.02 (s, 1H), 7.67–7.65 (d, 1H, J = 6.0 Hz), 7.11–7.09 (d, 1H, J = 6.0 Hz), 7.03–7.99 (d, 1H, J = 3.0 Hz), 6.82–6.80 (d, 2H, J = 6.0 Hz), 3.96–3.90 (q, 2H), 2.92–2.83 (t, 2H), ^{13}C NMR ($CDCl_3$) δ 178.9, 155.4, 151.9, 145.4, 140.3, 129.2, 128.9, 114.9, 113.9, 111.6, 46.7, 33.5, IR ν 3224, 3159, 3089, 3041, 2933, 2870, 1595, 1558, 1533, 1514, 1332, 1306, 1265, 1227, 1186, 1136, 1094, 1007, 910, 862, 827, 708 cm^{-1}; UV (MeOH) λ 205, 208, 274, 305 nm, MALDI-TOF m/z 353.0 ($C_{14}H_{14}N_3OSBr+H^+$). Anal: C, H,N, Br, S.

***N*-[2-(4-Hydroxyphenylethyl)]-*N′*-[2-(thiazolyl)]thiourea (57)**. Mp: 160–161 °C; ^{1}H NMR (DMSO-d_6) δ 11.57 (s, 1H), 9.66 (s, 1H), 9.22 (s, 1H), 7.33 (d, 1H, J = 3.6 Hz), 7.06 (t, 3H), 6.68 (d, 2H, J = 8.1 Hz), 3.68 (q, 2H), 2.76 (t, 2H); ^{13}C NMR (DMSO-d_6) δ 178.5, 162.3, 156.4, 137.3, 130.3, 129.5, 115.9, 112.7, 46.9, 34.1; IR ν 3437, 3050, 1581, 1556, 1518 cm^{-1}; UV (MeOH) λ 209, 219, 225, 260, 289 nm; MALDI-TOF MS m/z 280.6 ($C_{12}H_{13}N_3OS_2+H^+$).

***N* - [2 - (4 - Methylphenylethyl)] - *N′* - [2 - (ethyl - 4 - acetylthiazolyl)]thiourea (58)**. Mp: 132–133 °C; ^{1}H NMR (DMSO-d_6) δ 11.60 (s, 1H), 9.47 (s, 1H), 7.13 (q, 4H), 6.85 (s, 1H), 4.08 (q, 2H), 3.72 (q, 2H), 3.60 (s, 2H), 2.82 (t, 2H), 2.25 (s, 3H), 1.14 (t, 3H); ^{13}C NMR (DMSO-d_6) δ 177.6, 169.8, 160.8, 143.2, 135.8, 135.3, 129.1, 128.6, 109.1, 60.5, 45.9, 42.4, 36.5, 33.8, 20.9, 14.3; IR ν 3448, 3170, 3006, 2937, 1731, 1573, 1508, 1220, 713 cm^{-1}; UV (MeOH) λ 206, 208, 214, 260, 293 nm; MALDI-TOF MS m/z 364.9 ($C_{17}H_{21}N_3O_2S_2+H^+$).

***N*-[2-(4-Methylphenylethyl)]-*N′*-[2-(4-methylthiazolyl]thiourea (59)**. Mp: 161–162 °C; ^{1}H NMR (DMSO-d_6) δ 11.56 (s, 1H), 9.89 (s, 1H), 7.11 (q, 5H), 6.60 (s, 1H), 3.76 (m, 2H), 2.84 (t, 2H), 2.24 (s, 3H), 2.14 (d, 3H); ^{13}C NMR (DMSO-d_6) δ 178.0, 161.2, 146.1, 135.9, 135.3, 129.1, 128.6, 106.1, 46.1, 33.8, 20.9, 16.8; IR ν 3463, 3174, 3022, 2921, 1571, 1508, 1203, 715 cm^{-1}; UV (MeOH) λ 207, 215, 259, 293 nm; MALDI-TOF MS m/z 292.8 ($C_{14}H_{17}N_3S_2+H^+$).

***N*-[2-(4-Methylphenyl)ethyl)]-*N′*-[2-(thiazolyl)]thiourea (60)**. Mp: 162–163 °C; ^{1}H NMR (DMSO-d_6) δ 11.59 (s, 1H), 9.66 (s, 1H), 7.33–7.32 (m, 1H), 7.15–7.08 (m, 5H), 3.73 (q, 2H), 2.83 (t, 2H), 2.24 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 178.0, 161.8, 136.7, 135.8, 135.3, 129.1, 128.7, 112.1, 46.1, 33.9, 20.9; IR ν 3448, 3170, 3000, 2946, 1565, 1511, 1280, 1157, 702 cm^{-1}; MALDI-TOF m/z 279.1 ($C_{13}H_{15}N_3S_2+2H^+$); HPLC R_t: 6.99 min.

***N*-[2-(4-Methylphenylethyl)]-*N′*-[2-(benzothiazolyl)]thiourea (61)**. Mp: 186–87 °C; ^{1}H NMR (DMSO-d_6) δ 11.89 (s, 1H), 10.09 (s, 1H), 7.86 (d, 1H, J = 6.6 Hz), 7.53 (d, 1H, J = 6.0 Hz), 7.38 (t, 1H), 7.26–7.09 (m, 5H), 3.81 (m, 2H), 2.88 (t, 2H), 2.24 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 178.3, 161.1, 148.9, 147.9, 135.8, 135.3, 129.1, 128.7, 126.3, 123.7, 121.8, 119.5, 46.2, 33.7, 20.9; IR ν 3178, 3039, 2931, 1573, 1519, 1234, 748 cm^{-1}; MALDI-TOF m/z 329.3 ($C_{17}H_{17}N_3S_2+2H^+$).

***N* - [2 - (4 - Methylphenylethyl)] - *N′* - [2 - (6 - methoxybenzothiazolyl)]thiourea (62)**. Mp: 202–203 °C; ^{1}H NMR (DMSO-d_6) δ 11.73 (s, 1H), 10.15 (s, 1H), 7.49 (d, 1H, J = 2.4 Hz), 7.45 (d, 1H, J = 8.7 Hz), 7.19 (d, 2H, J = 8.1 Hz), 7.10 (d, 2 H, J = 8.1 Hz), 7.00 (dd, 1H, J = 2.4, 8.7 Hz), 3.80 (q, 2H), 3.77 (s, 3H), 2.89 (t, 2H), 2.25 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 177.9, 158.1, 156.1, 142.9, 135.8, 135.3, 131.2, 129.1, 128.7, 120.2, 114.6, 105.3, 55.8, 46.2, 33.7, 20.9; IR ν 3178, 3047, 2931, 1558, 1535, 1473, 1218 cm^{-1}; MALDI-TOF m/z 358.8 ($C_{18}H_{19}N_3OS_2+2H^+$).

***N*-[2-(4-Chlorophenethyl)]-*N′*-[2-(4-fluorophenethyl)]-thiourea (63)**. Yield: 84%; UV ($CHCl_3$) λ_{max}: 254 nm; IR (KBr) ν 3266, 3210, 3050, 2931, 2860, 1556, 1510, 1349, 1218, 1095, 1014, 819, 694, 665, 594, 486 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.17–6.84 (m, 8H), 5.91 (s, 2H), 3.49 (q, 4H), 2.74–2.69 (t, 4H); ^{13}C NMR ($CDCl_3$) δ 181.5, 130.1, 129.9, 128.7, 115.6, 115.3, 45.3, 45.2, 34.4, 34.2; ^{19}F NMR ($CDCl_3$) δ −40.37; MALDI-TOF found: 337.9 (M + 1), calcd: 336.9.

***N*-[2-(2-Chlorophenethyl)]-*N′*-[2-(4-fluorophenethyl)]-thiourea (68)**. Yield: 60%; UV ($CHCl_3$) λ_{max}: 254 nm; IR (KBr) ν 3353, 3264, 3062, 2933, 2865, 1710, 1550, 1510, 1442, 1355, 1222, 1157, 1053, 827, 754, 680, 530 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.37–7.96 (m, 8H), 5.90 (s, 1H), 5.80 (s, 1H), 3.64 (q, 4H), 3.02–2.98 (t, 2H), 2.88–2.83 (t, 2H); ^{13}C NMR ($CDCl_3$) δ 181.7, 133.8, 131.0, 130.1, 130.0, 129.6, 128.3, 127.2, 115.7, 115.4, 45.5, 43.7, 34.3, 32.9; ^{19}F NMR ($CDCl_3$) δ.48; MALDI-TOF found: 338.5 (M + 2), calcd: 336.9.

***N*-[2-(3-Chlorophenethyl)]-*N′*-[2-(4-fluorophenethyl)]-thiourea (69)**. Yield: 79%; UV ($CHCl_3$) λ_{max}: 254 nm; IR (KBr) ν 3259, 3062, 2935, 2861, 1560, 1508, 1309, 1222, 1004, 829, 783, 684, 514 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.26–6.96 (m, 8H), 5.86 (s, 1H), 5.85 (s, 1H), 3.63–3.61 (q, 4H), 2.87–2.81 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.7, 163.2, 160.0, 140.3, 134.4, 133.8, 130.1, 130.02, 129.97, 128.7, 126.9, 115.7, 115.4, 45.3, 45.1, 34.7, 34.2; ^{19}F NMR ($CDCl_3$) δ −40.37; MALDI-TOF found: 337.3 (M + 1), calcd: 336.9.

***N*-[2-(3-Fluorophenethyl)]-*N′*-[2-(4-fluorophenethyl)]-thiourea (71)**. Yield: 92%; UV ($CHCl_3$) λ_{max}: 255 nm; IR (KBr) ν 3259, 3058, 2929, 2860, 1556, 1510, 1446, 1384, 1309, 1220, 1141, 1118, 1002, 937, 831, 784, 690, 511 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30–6.87 (m, 8H), 5.95 (s, 2H), 3.62–3.61 (q, 4H), 2.88–2.80 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.6, 164.4, 163.2, 161.2, 160.0, 140.7, 133.8, 130.2, 130.1, 130.0, 124.3, 115.6, 115.3, 113.7, 113.4, 45.3, 45.1, 34.8, 34.2 ; ^{19}F NMR ($CDCl_3$) δ −40.44, −34.18; MALDI-TOF found: 322.8 (M + 2), calcd: 320.4.

***N*-[2-(4-Fluorophenethyl)]-*N′*-[2-(4-fluorophenethyl)]-thiourea (72)**. Yield: 93%; UV ($CHCl_3$) λ_{max}: 254 and 273 nm; IR

(KBr) ν 3259, 3058, 2927, 2854, 1600, 1556, 1510, 1450, 1311, 1218, 1118, 1010, 823, 757, 680, 523, 499 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27–6.96 (m, 8H), 5.84 (s, 2H), 3.61–3.59 (q, 4H), 2.85–2.81 (t, 4H); ^{13}C NMR ($CDCl_3$) δ 181.6, 163.2, 160.0, 130.1, 130.0, 115.6, 115.4, 45.4, 34.2; ^{19}F NMR ($CDCl_3$) δ −40.38; MALDI-TOF found: 321.4 (M + 1), calcd: 320.4.

***N*-[2-(4-Fluorophenethyl)]-*N′*-[2-(2-methoxyphenethyl)]-thiourea (73)**. Yield: 80%; UV ($CHCl_3$) λ_{max}: 255, 273, and 279 nm; IR (KBr) ν 3303, 3232, 3068, 2935, 2867, 1600, 1564, 1510, 1315, 1245, 1220, 1155, 1118, 1031, 825, 763, 684, 499 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27–6.84 (m, 8H), 6.27 (s, 1H), 5.88 (s, 1H), 3.75 (s, 3H), 3.68 (s, 2H), 3.45 (s, 2H), 2.90–2.82 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.3, 163.2, 160.0, 157.1, 130.6, 130.2, 130.1, 128.3, 121.1, 115.6, 115.3, 110.5, 55.4, 45.9, 45.4, 34.4, 29.8; ^{19}F NMR ($CDCl_3$) δ −40.61; MALDI-TOF found: 333.5 (M + 1), calcd: 332.4.

***N*-[2-(4-Fluorophenethyl)]-*N′*-[2-(3-methoxyphenethyl)]-thiourea (74)**. Yield: 84%; UV ($CHCl_3$) λ_{max}: 255, 274, and 283 nm; IR (KBr) ν 3263, 3064, 2939, 2861, 1600, 1556, 1508, 1384, 1311, 1259, 1222, 1166, 1122, 1037, 1002, 833, 669, 576, 514 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27–6.73 (m, 8H), 5.71 (s, 2H), 3.79 (s, 3H) 3.62–3.60 (q, 4H), 2.86–2.80 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.7, 163.3, 159.9, 139.8, 133.8, 130.1, 130.0, 129.8, 120.9, 115.7, 115.4, 114.5, 112.0, 55.2, 45.4, 45.2, 34.1, 34.3; ^{19}F NMR ($CDCl_3$) δ −40.49; MALDI-TOF found: 334.6 (M + 2), calcd: 332.4.

***N*-[2-(4-Fluorophenethyl)]-*N′*-[2-(3,4-dimethoxyphenethyl)]-thiourea (75)**. Yield: 73%; UV ($CHCl_3$) λ_{max}: 255 and 273 nm; IR (KBr) ν 3259, 3058, 2942, 2854, 1600, 1556, 1510, 1450, 1311, 1218, 1118, 1016, 823, 757, 682, 532, 499 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.13–6.68 (m, 7H), 6.04 (s, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.64 (q, 4H), 2.83–2.78 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.6, 163.0, 159.8, 148.1, 147.4, 133.9, 130.7, 130.0, 129.9, 120.4, 115.4, 115.1, 111.6, 111.1, 55.7, 45.3, 34.5, 34.2; ^{19}F NMR ($CDCl_3$) δ −40.57; MALDI-TOF found: 364.8 (M + 2), calcd: 362.5.

***N*-[2-(2-Fluorophenethyl)]-*N′*-[2-(3-fluorophenethyl)]-thiourea (77)**. Yield: 75%; UV ($CHCl_3$) λ_{max}: 255 nm; IR (KBr) ν 3411, 3261, 3062, 2935, 2865, 1616, 1587, 1552, 1490, 1450, 1386, 1348, 1230, 1188, 1141, 1002, 937, 891, 757, 692, 520, 457 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30–6.89 (m, 8H), 5.92 (s, 1H), 5.84 (s, 1H), 3.66 (q, 4H), 2.93–2.86 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.7, 164.5, 162.7, 161.2, 159.5, 140.8, 131.1, 131.0, 130.2, 130.1, 128.7, 128.6, 125.1, 124.4, 115.7, 115.5, 115.4, 115.2, 113.8, 113.5, 45.1, 44.2, 34.8, 28.7; ^{19}F NMR ($CDCl_3$) δ −42.88, −42.85, −42.81, −42.79, −37.25, −37.23; MALDI-TOF found: 321.9 (M + 1), calcd: 320.4.

***N*-[2-(4-Fluorophenethyl)]-*N′*-[2-(4-bromophenethyl)]-thiourea (78)**. Yield: 93%; UV ($CHCl_3$) λ_{max}: 256 nm; IR (KBr) ν 3406, 3251, 3060, 2927, 2863, 1600, 1548, 1508, 1346, 1222, 1157, 1072, 1010, 823, 657, 497 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43–6.96 (m, 8H), 5.86 (s, 2H), 3.60 (q, 4H), 2.84–2.80 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.6, 163.2, 160.0, 137.2, 133.7, 131.7, 130.4, 130.1, 130.0, 120.5, 115.6, 115.4, 45.4, 45.1, 34.5, 34.2; ^{19}F NMR ($CDCl_3$) δ −40.37; MALDI-TOF found: 382.5 (M + 1), calcd: 381.3.

***N*-[2-(4-Fluorophenethyl)]-*N′*-[2-(4-hydroxyphenethyl)]-thiourea (79)**. Yield: 90%; UV ($CHCl_3$) λ_{max}: 256, 273, and 284 nm; IR (KBr) ν 3272, 3066, 2923, 2850, 1600, 1556, 1510, 1440, 1346, 1220, 1105, 1014, 825, 759, 505 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27–6.76 (m, 8H), 5.74 (s, 2H), 5.61 (s, 1H), 3.59 (q, 4H), 2.84–2.75 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.4, 163.3, 160.0, 154.6, 133.8, 130.2, 130.1, 123.8, 115.1, 115.4, 45.4, 34.3, 34.1; ^{19}F NMR ($CDCl_3$) δ −40.40; MALDI-TOF found: 319.8 (M + 1), calcd: 318.4.

***N*-[2-(3-Fluorophenethyl)]-*N*′-[2-(3-fluorophenethyl)]-thiourea (80)**. Yield: 83%; UV ($CHCl_3$) λ_{max}: 255 nm; IR (KBr) ν 3415, 3257, 3062, 2933, 2863, 1616, 1589, 1552, 1488, 1450, 1348, 1251, 1141, 1012, 937, 892, 783, 690, 520, 455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30–6.87 (m, 8H), 5.96 (s, 2H), 3.64–3.63 (q, 4H), 2.88–2.83 (t, 4H); ^{13}C NMR ($CDCl_3$) δ 181.6, 164.4, 161.2, 140.7, 130.2, 130.1, 124.3, 115.6, 115.3, 113.7, 113.4, 45.1, 34.8; ^{19}F NMR ($CDCl_3$) δ −37.17, −37.15; MALDI-TOF found: 321.4 (M + 1), calcd: 320.4.

***N*-[2-(2-Fluorophenethyl)]-*N′*-[2-(3-fluorophenethyl)]-thiourea (81)**. Yield: 75%; UV ($CHCl_3$) λ_{max}: 255 nm; IR (KBr) ν 3411, 3261, 3062, 2935, 2865, 1616, 1587, 1552, 1490, 1450, 1386, 1348, 1230, 1188, 1141, 1002, 937, 891, 757, 692, 520, 457 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30–6.89 (m, 8H), 5.92 (s, 1H), 5.84 (s, 1H), 3.66 (q, 4H), 2.93–2.86 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.7, 164.5, 162.7, 161.2, 159.5, 140.8, 131.1, 131.0, 130.2, 130.1, 128.7, 128.6, 125.1, 124.4, 115.7, 115.5, 115.4, 115.2, 113.8, 113.5, 45.1, 44.2, 34.8, 28.7; ^{19}F NMR ($CDCl_3$) δ −42.88, −42.85, −42.81, −42.79, −37.25, −37.23; MALDI-TOF found: 321.9 (M + 1), calcd: 320.4.

***N*-[2-(3-Fluorophenethyl)]-*N′*-[2-(4-bromophenethyl)]-thiourea (82)**. Yield: 91%; UV ($CHCl_3$) λ_{max}: 255 nm; IR (KBr) ν 3405, 3259, 3060, 2931, 2863, 1616, 1589, 1552, 1488, 1448, 1346, 1251, 1141, 1072, 1010, 937, 891, 810, 784, 690, 520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43–6.87 (m, 8H), 5.86 (s, 2H), 3.61 (q, 4H), 2.88–2.79 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.7, 164.5, 140.7, 137.1, 131.7, 130.4, 130.3, 130.1, 124.3, 120.5, 115.6, 115.4, 113.7, 113.5, 45.1, 34.8, 34.5; ^{19}F NMR ($CDCl_3$) δ −37.10; MALDI-TOF found: 383.1 (M + 2), calcd: 381.3.

***N*-[2-(3-Fluorophenethyl)]-*N′*-[2-(4-hydroxyphenethyl)]-thiourea (83)**. Yield: 31%; UV ($CHCl_3$) λ_{max}: 254 nm; IR (KBr) ν 3276, 3066, 2935, 2863, 1614, 1589, 1556, 1513, 1448, 1346, 1247, 1141, 1110, 1008, 908, 829, 784, 732, 692, 520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27–6.73 (m, 8H), 6.38 (s, 1H), 5.94 (s, 1H), 5.85 (s, 1H), 3.61 (m, 2H), 3.50 (m, 2H), 2.83–2.79 (t, 2H), 2.75–2.70 (t, 2H); ^{13}C NMR ($CDCl_3$) δ 181.1, 154.6, 141.8, 130.2, 130.1, 129.7, 124.3, 115.7, 115.3, 113.7, 113.4, 45.4, 34.8, 34.0; ^{19}F NMR ($CDCl_3$) δ −37.20, −37.18; MALDI-TOF found: 319.6 (M + 1), calcd: 318.4.

***N*-[2-(2-Chlorophenethyl)]-*N′*-[2-(3-fluorophenethyl)]-thiourea (84)**. Yield: 90%; UV ($CHCl_3$) λ_{max}: 256 nm; IR (KBr) ν 3405, 3261, 3064, 2935, 2863, 1616, 1589, 1552, 1488, 1446, 1384, 1346, 1299, 1251, 1195, 1141, 1053, 1002, 937, 908, 784, 754, 732, 692, 520, 455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36–6.88 (m, 8H), 6.05 (s, 1H), 5.93 (s, 1H), 3.66 (q, 4H), 3.01–2.97 (t, 2H), 2.90–2.85 (t, 2H); ^{13}C NMR ($CDCl_3$) δ 181.6, 164.5, 161.2, 140.7, 135.7, 133.8, 131.0, 130.2, 130.1, 129.6, 128.3, 127.1, 124.3, 115.6, 115.4, 113.7, 113.4, 45.2, 43.7, 34.8, 32.9; ^{19}F NMR ($CDCl_3$) δ −37.19; MALDI-TOF found: 338.6 (M + 2), calcd: 336.9.

***N*-[2-(3-Chlorophenethyl)]-*N′*-[2-(3-fluorophenethyl)]-thiourea (85)**. Yield: 96%; UV ($CHCl_3$) λ_{max}: 254 nm; IR (KBr) ν 3409, 3257, 3060, 2933, 2863, 1616, 1589, 1552, 1488, 1448, 1346, 1251, 1141, 1080, 1010, 937, 887, 783, 692, 520, 443 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29–6.87 (m, 8H), 6.07 (s, 2H), 3.62 (q, 4H), 2.87–2.81 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.6, 164.4, 161.1, 140.8, 140.7, 140.3, 134.3, 130.2, 130.1, 129.9, 128.7, 126.83, 126.78, 124.3, 115.6, 115.3, 113.7, 113.4, 45.0, 34.7; ^{19}F NMR ($CDCl_3$) δ −37.10; MALDI-TOF found: 337.3 (M + 1), calcd: 336.9.

***N*-[2-(4-Chlorophenethyl)]-*N′*-[2-(3-fluorophenethyl)]-thiourea (86)**. Yield: 93%; UV ($CHCl_3$) λ_{max}: 254 nm; IR (KBr) ν 3409, 3251, 3060, 2917, 2848, 1614, 1589, 1550, 1490, 1448, 1346, 1253, 1139, 1091, 1014, 937, 811, 783, 690, 520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30–6.87 (m, 8H), 5.91 (s, 2H), 3.62 (q, 4H), 2.88–2.80 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.7, 164.4, 161.2, 140.7, 136.6, 132.5, 130.2, 130.1, 130.0, 128.8, 124.3, 115.6, 115.4, 113.7, 113.5, 45.1, 34.8, 34.4; ^{19}F NMR ($CDCl_3$) δ −37.13; MALDI-TOF found: 338.2 (M + 1), calcd: 336.9.

***N*-[2-(3-Fluorophenethyl)]-*N′*-[2-(3-methoxyphenethyl)]-thiourea (87)**. Yield: 95%; UV ($CHCl_3$) λ_{max}: 255 nm; IR (KBr) ν 3258, 3057, 2937, 2834, 1585, 1548, 1487, 1451, 1385, 1346, 1257, 1152, 1043, 910, 783, 731, 693, 571, 520, 456 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 7.29–6.72 (m, 8H), 5.93 (s, 2H), 3.77 (s, 3H), 3.75–3.61 (q, 4H), 2.85–2.80 (t, 4H); ^{13}C NMR ($CDCl_3$) δ 181.5, 164.4, 161.2, 159.7, 140.8, 139.8, 130.2, 130.0, 129.7, 124.3, 120.9, 115.6, 115.3, 114.4, 113.6, 113.4, 111.9, 55.1, 45.2, 35.0, 34.8; ^{19}F NMR ($CDCl_3$) δ −37.23, −37.20; MALDI-TOF found: 333.8 (M + 1), calcd: 332.4.

***N*-[2-(3-Fluorophenethyl)]-*N′*-[2-(2-methoxyphenethyl)]-thiourea (88)**. Yield: 94%; UV ($CHCl_3$) λ_{max}: 254 nm; IR (KBr) ν 3349, 3253, 3062, 2917, 2836, 1587, 1552, 1492, 1346, 1290, 1243, 1029, 937, 892, 754, 690, 520, 457 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.29–6.84 (m, 8H), 6.38 (s, 1H), 6.00 (s, 1H), 3.75 (s, 3H), 3.78–3.45 (q, 4H), 2.93–2.83 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.2, 164.4, 161.2, 157.0, 141.0, 130.5, 130.1, 130.0, 128.2, 126.4, 124.4, 121.0, 115.7, 11534, 113.6, 113.3, 110.4, 55.3, 45.5, 34.9, 29.8; ^{19}F NMR ($CDCl_3$) δ −37.36; MALDI-TOF found: 332.9 (M + 1), calcd: 332.4.

***N*-[2-(3-Fluorophenethyl)]-*N′*-[2-(2,5-dimethoxyphenethyl)]-thiourea (90)**. Yield: 80%; UV ($CHCl_3$) λ_{max}: 252 and 293 nm; IR (KBr) ν 3345, 3253, 3060, 2996, 2935, 2833, 1614, 1589, 1552, 1500, 1448, 1346, 1282, 1224, 1139, 1045, 867, 784, 692, 520, 457 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.29–6.70 (m, 7H), 6.45 (s, 1H), 6.01 (s, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 3.50–3.46 (q, 4H), 2.93–2.80 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.2, 164.4, 161.2, 153.7, 151.2, 145.0, 130.1, 130.0, 124.4, 116.7, 115.6, 115.4, 113.6, 113.3, 112.1, 111.4, 55.9, 55.6, 45.5, 34.9, 31.5, 29.3; ^{19}F NMR ($CDCl_3$) δ −37.34; MALDI-TOF found: 363.6 (M + 1), calcd: 362.5.

***N*-[2-(3-Fluorophenethyl)]-*N′*-[2-(4-methylphenethyl)]-thiourea (91)**. Yield: 60%; UV ($CHCl_3$) λ_{max}: 254 nm; IR (KBr) ν 3228, 3060, 2966, 2933, 2865, 1569, 1486, 1448, 1386, 1346, 1249, 1141, 1008, 937, 871, 810, 788, 759, 692, 505 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.29–6.85 (m, 8H), 5.92 (s, 1H), 5.86 (s, 1H), 3.60 (q, 4H), 2.85–2.78 (m, 4H), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 181.5, 164.4, 161.2, 140.7, 136.3, 134.9, 130.1, 130.0, 129.4, 128.5, 124.3, 115.6, 115.3, 113.6, 113.4, 45.3, 45.0, 34.8, 34.6, 21.0; ^{19}F NMR ($CDCl_3$) δ −37.19; MALDI-TOF found: 317.5 (M + 1), calcd: 316.4.

***N*-[2-(4-Fluorophenethyl)]-*N′*-[2-(4-methylphenethyl)]-thiourea (92)**. Yield: 72%; UV ($CHCl_3$) λ_{max}: 253 nm; IR (KBr) ν 3423, 3264, 3156, 3049, 2928, 2862, 1600, 1543, 1510, 1383, 1343, 1224, 1158, 1097, 1022, 904, 826, 736, 650, 555, 500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.26–6.95 (m, 8H), 5.79 (s, 2H), 3.59 (q, 4H), 2.86–2.78 (m, 4H), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 181.5, 163.2, 160.0, 136.3, 134.9, 133.8, 130.1, 130.0, 129.4, 128.5, 115.6, 115.3, 45.4, 34.6, 34.3, 21.0; ^{19}F NMR ($CDCl_3$) δ −40.47; MALDI-TOF found: 317.4 (M + 1), calcd: 316.4.

***N*-[2-(4-Chlorophenethyl)]-*N′*-[2-(4-chlorophenethyl)]-thiourea (94)**. Yield: 48%; UV ($CHCl_3$) λ_{max}: 253 nm; IR (KBr) ν 3267, 3062, 2938, 2916, 2853, 1584, 1489, 1406, 1349, 1273, 1125, 1096, 1002, 907, 807, 729, 651, 514, 440 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.29–7.09 (m, 8H), 5.77 (s, 2H), 3.62–3.60 (q, 4H), 2.85–2.80 (t, 4H); ^{13}C NMR ($CDCl_3$) δ 181.8, 136.6, 132.5, 130.0, 128.8, 45.2, 34.4; MALDI-TOF found: 353.3, calcd: 353.3.

***N*-[2-(3-Chlorophenethyl)]-*N′*-[2-(4-chlorophenethyl)]-thiourea (95)**. Yield: 77%; UV ($CHCl_3$) λ_{max}: 254 nm; IR (KBr) ν 3409, 3253, 3062, 2931, 2865, 1663, 1597, 1550, 1491, 1431, 1346, 1292, 1203, 1092, 1015, 908, 816, 783, 732, 684, 534 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.28–7.05 (m, 8H), 5.96 (s, 2H), 3.62 (q, 4H), 2.86–2.80 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 181.7, 140.3, 136.6, 134.3, 132.4, 130.0, 128.7, 126.9, 45.1, 34.7, 34.4; MALDI-TOF found: 354.7 (M + 1), calcd: 353.3.