Characterization of the Binding Site of the Histamine H_3 Receptor. 2. Synthesis, in Vitro Pharmacology, and QSAR of a Series of Monosubstituted Benzyl Analogues of Thioperamide

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A series of monosubstituted benzyl analogues of the histamine H_3 receptor antagonist thioperamide were synthesized and evaluated for their histamine H_3 receptor activity on the guinea pig jejunum. Incorporation of Cl, Br, and I at the ortho position of the benzyl moiety led to an increase of the pA_2 value, whereas the same substituents at the para position led to a decrease. However, a fluorine substituent gave a strong decrease in pA_2, regardless of the position. Molecular modeling revealed a QSAR with a correlation ($r = 0.93$) between the pA_2 and the dihedral angle between the thiourea and the benzyl moiety and the calculated electron density on the substituted carbon atom. To verify whether this QSAR model had a predictive value, the ortho *tert*-butyl and methyl analogues were synthesized and evaluated. Indeed it was shown that the predicted pA_2 values of these two compounds were in accordance with the measured pA_2 values.

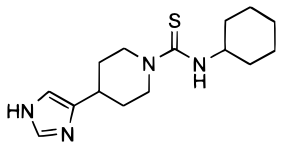
Introduction

The histamine H_3 receptor in the central nervous system (CNS) has been extensively investigated by in vitro pharmacological methods. These experiments suggest that the H_3 receptor plays an important role in regulating the function of histamine as a neurotransmitter.[1,2] The H_3 receptor acts as an autoreceptor[3] regulating the synthesis and release of histamine from histaminergic neurons, and it acts as a heteroreceptor regulating the release of noradrenaline,[4] serotonin,[5] acetylcholine,[6] and dopamine[7] from the respective systems.

This regulatory effect of the H_3 receptor can be of great importance for drug therapies in neuronal abnormalities occurring e.g. in Parkinson's disease (dopaminergic system), Alzheimer's disease (cholinergic system), schizophrenia, and depression (serotonergic system) and probably in learning and memory disorders. Both agonists and antagonists of the H_3 receptor might become useful in therapies for CNS disorders as has been proposed in several reviews.[8,9]

Not much is known however about the histamine H_3 receptor itself. It is located in the central as well as peripheral nervous systems. It has a relatively low abundancy in the brain and has not been cloned yet. Some qualitative binding models for antagonists have been described by Vollinga et al.[10] and Stark et al.,[11] and an agonist binding model has been presented by Höltje et al.[12] Recently, a general ligand-based model, based on ab initio quantum−chemical calculations, has been developed in our laboratory, reported by De Esch et al.[13]

Especially since the H_3 receptor is involved in the regulation of the release of several neurotransmitters, its role in the physiology of neuronal disorders deserves further investigation. The development of H_3 ligands suitable for positron emission tomography (PET) or single photon emission computed tomography (SPECT) by labeling these ligands with ^{18}F or ^{76}Br for PET and ^{123}I for SPECT could be of great help in such studies. We have selected thioperamide **(1)** as a template for the development of such labeled ligands. From in vitro



thioperamide, **1**

pharmacology it is known that thioperamide is both a relatively selective and a highly potent H_3 antagonist.[14] Furthermore, ex vivo binding studies have shown that thioperamide is able to cross the blood−brain barrier (BBB), e.g. after sc administration.[15] From qualitative structure−activity relationship (QSAR) studies[10,11] it is clear that the cyclohexane part of thioperamide may be replaced with a (halogenated) benzyl group without losing H_3 receptor activity. Because such derivatives have not yet been fully described,[16] we synthesized and evaluated the compounds **2a**−**o** listed in Table 1 for their histamine H_3 antagonistic activity with two goals: to investigate the SAR for the "lipophilic tail" of thio-

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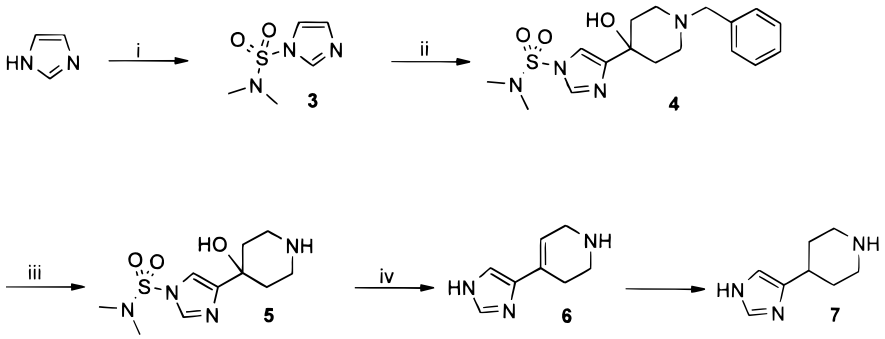
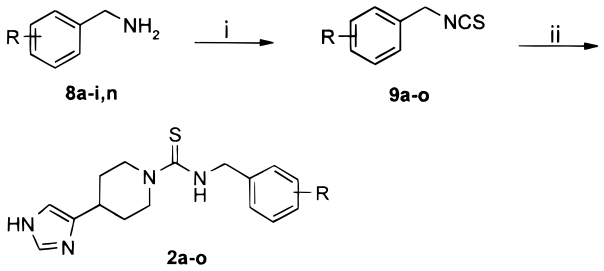
Scheme 1[a]



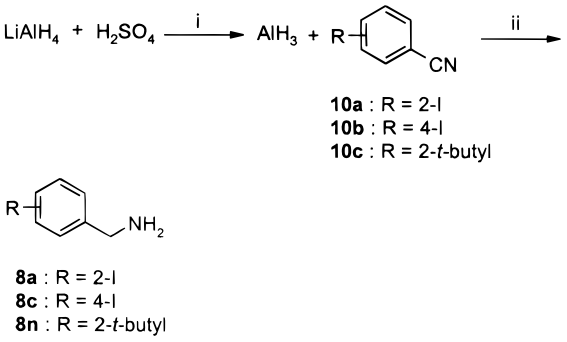
[a] (i) *N*,*N*-Dimethylsulfamoyl chloride, triethylamine, toluene, rt, 93%; (ii) (a) *n*-butyllithium, chlorotrimethylsilane, tetrahydrofuran, −65 °C, (b) *n*-butyllithium, *N*-benzyl-4-piperidone, tetrahydrofuran, −65 °C, (c) 1 M HCl, rt, 54% (a + b + c); (iii) ammonium formate, 10% Pd/C, methanol, reflux, 88%; (iv) 30% HBr, reflux, 74%; (v) H_2, 10% Pd/C, methanol, rt, 100%.

Scheme 2[a]



[a] (i) 1,1′-Thiocarbonyl-2,2′-(1*H*)-pyridone, diisopropylethylamine, dichloromethane, rt, 63−98%; (ii) **7**, diisopropylethylamine, ethanol, rt, 10−81%.

Scheme 3[a]



[a] (i) Tetrahydrofuran, 0 °C; (ii) tetrahydrofuran, rt, 45% (i + ii).

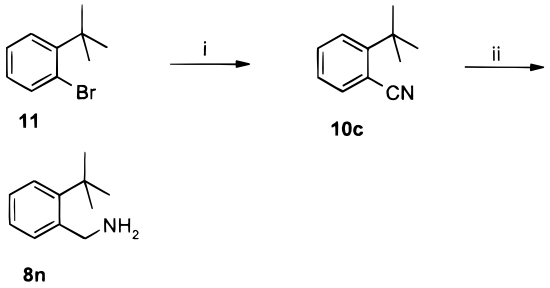
peramide and to obtain a suitable lead for further development as a PET or SPECT ligand for the histamine H_3 receptor.

Chemistry

The syntheses of the compounds **2a**−**o** are given in Schemes 1−4.

Synthesis. 4-(1*H*-Imidazol-4-yl)piperidine dihydrobromide **(7)** was synthesized according to Vollinga[10] (Scheme 1). Imidazole was protected at the N-1 position with the dimethylsulfamoyl group according to literature procedures.[17,18] For the selective electrophilic addition of *N*-benzyl-4-piperidone at the 5-position, the 2-position was first protected in situ with the trimethylsilane group. After acidic workup compound **4** was isolated in moderate yield. The benzyl group was removed by a catalytic hydrogen-transfer reaction with the formate ion as hydrogen donor,[19] resulting in **5** in quantitative yield. Acidic hydrolysis of the dimethylsulfamoyl group in 30% HBr also gave elimination of the tertiary alcohol. The resulting 1,2,5,6-tetrahydropyridine **6** was hydrogenated to giving the desired compound 4-(1*H*-imidazol-4-yl)piperidine dihydrobromide **(7)** in a 24% overall yield, calculated from imidazole.

Scheme 4[a]

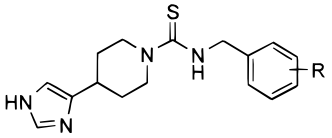


[a] (i) CuCN, dimethylformamide, 83%; (ii) see Scheme 3.

Compound **7** was reacted with substituted benzyl isothiocyanates **9a**−**o** according to Scheme 2. Benzyl isothiocyanates **9g**−**m** were commercially available, and benzyl isothiocyanates **9a**−**f,n,o** were synthesized from the commercially available substituted benzylamines **8a**−**f,n,o** and 1,1′-thiocarbonyldi[(1*H*)-pyridone][20,21] (Scheme 2), whereas 2- and 4-iodobenzylamines **(8a,c)** were obtained by the selective reduction of the corresponding 2- and 4-iodobenzonitriles **(10a,b)** with exactly 1 equiv of AlH_3, generated by the addition of 0.5 mol equiv of concentrated sulfuric acid to $LiAlH_4$ in THF[22] (Scheme 3). Other methods for the reduction of 2- and 4-iodobenzonitriles **(10a,b)** were not effective. Raney-Ni reduction in acid media did not reduce the nitrile; Raney-Ni reduction under basic conditions was possible but gave consistently deiodinated side product. The reduction with $NaBH_4$ and $CoCl_2$ gave similar results. Only by using ALH_3, deiodination could be limited to about 10%. This deiodinated product could be separated from the target compounds **8a,c** by flash column chromatography.

The 2-*tert*-butylbenzylamine **(8n)** was prepared according to Scheme 4; 2-bromo-1-*tert*-butylbenzene[23] **(11)** was reacted with CuCN to give 2-*tert*-butylbenzonitrile[24] **(10c),** which was reduced to 2-*tert*-butylbenzylamine **(8n)** with AlH_3 using the same procedure as for 2- and 4-iodobenzonitriles **(10a,b).** Compounds **2a**−**m,o** were

Table 1. Histamine H_3 Antagonistic Activity Expressed as the pA_2 Value and Molecular Modeling Results (φ and δ) of **2a**−**o**[a]



compd	R	formula	pA_2 (±SEM) ($N = 4$)	φ	δ
2a	2-I	$C_{16}H_{19}IN_4S{\cdot}0.5C_4H_4O_4$	8.13 (0.15)	−152.8	−0.58
2b	3-I	$C_{16}H_{19}IN_4S{\cdot}0.5C_4H_4O_4$	7.80 (0.14)	−131.4	−0.64
2c	4-I	$C_{16}H_{19}IN_4S{\cdot}0.5C_4H_4O_4$	6.78 (0.06)	−84.2	−0.61
2d	2-Br	$C_{16}H_{19}BrN_4S{\cdot}0.5C_4H_4O_4$	7.84 (0.18)	−162.5	−0.02
2e	3-Br	$C_{16}H_{19}BrN_4S{\cdot}0.5C_4H_4O_4$	7.47 (0.17)	−119.2	−0.08
2f	4-Br	$C_{16}H_{19}BrN_4S{\cdot}0.5C_4H_4O_4$	6.47 (0.06)	−108.8	−0.05
2g	2-Cl	$C_{16}H_{19}ClN_4S{\cdot}0.5C_4H_4O_4$	8.21 (0.09)	−168.5	0.14
2h	3-Cl	$C_{16}H_{19}ClN_4S{\cdot}0.5C_4H_4O_4$	7.41 (0.05)	−118.9	0.08
2i	4-Cl	$C_{16}H_{19}ClN_4S{\cdot}0.5C_4H_4O_4$	7.21 (0.08)	−122.2	0.11
2j	2-F	$C_{16}H_{19}FN_4S{\cdot}0.5C_4H_4O_4$	6.04 (0.14)	−118.0	0.73
2k	3-F	$C_{16}H_{19}FN_4S{\cdot}0.5C_4H_4O_4$	6.44 (0.13)	−111.9	0.65
2l	4-F	$C_{16}H_{19}FN_4S{\cdot}0.5C_4H_4O_4$	6.25 (0.14)	−118.8	0.66
2m	H	$C_{16}H_{20}N_4S{\cdot}0.5C_4H_4O_4$	7.32 (0.16)	−110.1	−0.23
2n	2-*t*-Bu	$C_{20}H_{28}N_4S$	7.54 (0.18) (calcd 7.64)	−155.7	0.21
2o	2-Me	$C_{17}H_{22}N_4S{\cdot}0.5C_4H_4O_4$	7.02 (0.10) (calcd 6.83)	−114.3	0.19

[a] φ was defined as depicted in Figure 1 to express the angle between the phenyl group and the thiourea moiety; the electron density δ was defined as the electron density of the substituted carbon atom of the phenyl ring.

isolated and recrystallized as their fumaric acid salts; **2n** was isolated and recrystallized as the free base (Table 1).

Molecular Modeling. The geometries of **2a**−**o** were optimized as follows. The starting point was the optimized geometry of the 4-[(1*H*-imidazol-4-yl)piperidinyl]-thiourea moiety (including the aspartate) as generated by De Esch et al.[13] Starting from this template, only the geometry of the added substituted benzyl moiety needed to be optimized. Starting geometries were generated and partially optimized using Chem-X (Chemical Design Ltd., Oxford, U.K.). Subsequently, the geometries were fully optimized using the Amsterdam Density Functional program package (v 2.03a) according to the same procedure as has been described previously.[13]

Pharmacology

The histamine H_3 activity of **2a**−**o** was determined using the method desribed by Vollinga et al.[25] Briefly, the pA_2 value was determined in an in vitro test system, based on the concentration-dependent inhibitory effect of H_3 agonists on electrically evoked contractile responses (acetylcholine release) of guinea pig jejunum preparations. The experiment has been performed four times in duplicate. As agonist (*R*)-α-methylhistamine was used ($pD_2 = 7.8$ (±0.2), $N = 12$). The Schild slopes were not significantly different from unity.

Results and Discussion

Compounds **2a**−**o** were obtained in moderate to good yields and have been tested for their antagonistic activity at the histamine H_3 receptor. Initially we synthesized only **2a**−**m** as model compounds for the development of a potential PET or SPECT ligand. After it became clear that a QSAR model could be derived (see further), we synthesized **2n,o** to validate this QSAR model. The pA_2 values of all the compounds are listed in Table 1.

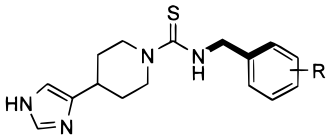


Figure 1. Dihedral angle φ (bold) used in the QSAR analysis.

From the antagonistic activities of **2a**−**m** we observed a clear influence of the substituent on the benzene ring on the pA_2 value. This is in contradiction to other, qualitative, receptor models which state that for this part of the general structure of H_3 antagonists, the "tail" of our compounds, only lipophilicity is of importance. Indeed for a series of isothiourea (clobenpropit), thiourea (burimamide), and related compounds such a relationship has been found.[26,27] In a series of imidazolyl alkyl ethers (iodoproxyfan), the 2- and 3-iodo isomers have been synthesized and tested for H_3 antagonistic activity; no significant influence of the position of the iodo substituent upon affinity for the H_3 receptor has been found.[28] From this perspective it is remarkable that the 2-iodo compound **2a** is 15 times more active then its 4-iodo isomer **2c**. The same trend was found for the brominated and chlorinated analogues, but not for the fluorine-containing derivatives. Furthermore, introduction of an iodine, bromine, or chlorine substituent in the para position leads to a decrease in H_3 antagonistic activity compared to the unsubstituted **2m**, which is in contrast to the SAR that has been found in the clobenpropit series, where para substitution increases the H_3 receptor activity. In the case of fluorine substitution, all three isomers were less active then **2m**; the three isomers are about equipotent.

These results prompted us to propose that in this series of compounds a steric factor is partly determinant for the H_3 antagonistic activity. Next to this, the results of fluorine-substituted compounds indicate the possible involvement of an electronic factor. To quantify these findings a classical QSAR method was used to establish a possible correlation between the biological activity of the compounds **2a**−**m** and steric and electronic parameters, as well as other parameters. However, no statistically significant correlations were found, which could have been caused by the relatively small size of the dataset.

Next, we performed a molecular modeling study to optimize the geometries of each of the compounds **2a**−**m** to compare these optimized geometries in correlation with the biological activities of the compounds **2a**−**m**. For this modeling study we started to optimize the geometry of the unsubstituted benzyl analogue **2m** and used the optimized structure as a template for the optimization of the other substituted analogues **2a**−**l**. Results of this molecular modeling approach, the dihedral angles φ and the electron densities δ, are given in Table 1. The dihedral angle φ was defined as depicted in Figure 1 as the angle between the phenyl group and the thiourea moiety and the electron density δ as the electron density of the substituted carbon atom of the phenyl ring. The optimized geometries of relevant compounds are shown in Figures 2−4. These modeling results show that in the case of ortho substitution (**2a,d,g**), the phenyl moiety is turned out of the plane

Figure 2. Optimized geometry of **2m** according to the method of De Esch et al.[13] This geometry was used as a starting point for the geometry optimization of **2a**−**l,n,o**.

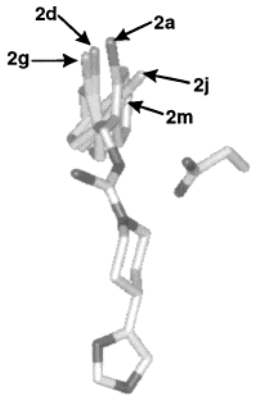


Figure 3. Optimized geometries of the 2-iodo (**2a**), 2-bromo (**2d**), 2-chloro (**2g**), and 2-fluoro (**2j**) analogues and the unsubstituted **2m.** It can clearly be seen that the 2-fluorobenzyl moiety does not turn out of the plane of the benzyl moiety of **2m**, while the substituted benzyl moieties of **2a,d,g** do turn out of the plane.

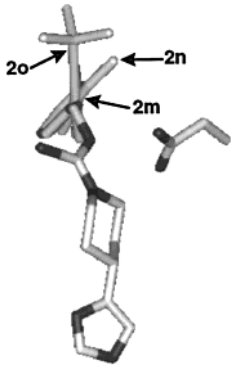


Figure 4. Optimized geometries of the 2-*tert*-butyl (**2n**) and 2-methyl (**2o**) analogues added to the optimized geometries of Figure 3. From this view it can be seen that the 2-*tert*-butylbenzyl moiety of **2n** turns out of the plane of the benzyl moiety of **2m**, whereas the 2-methylbenzyl moiety of **2o** does not.

when compared to the unsubstituted benzyl compound **2m** (Figure 3). We tried to correlate the dihedral angle between the thiourea moiety and the phenyl group for **2a**−**m** with the pA_2 value and obtained the following equation, where φ is the dihedral angle:

$$pA_2 = -0.020(\pm 0.006)\varphi + 4.645(\pm 0.832) \quad (1)$$

$$(n = 13,\ r = 0.64,\ s = 0.26,\ F = 9.79)$$

In eq 1 compounds **2a**−**m** were included. However it is clear from the modeling study that the fluorine-substituted compounds **2j**−**l** do not contribute to this correlation. Omitting **2j**−**l** from eq 1 improved the correlation indeed:

$$pA_2 = -0.016(\pm 0.003)\varphi + 5.382(\pm 0.428) \quad (2)$$

$$(n = 10,\ r = 0.87,\ s = 0.26,\ F = 24.26)$$

The correlation found in eq 2 indicates that the dihedral angle φ is of importance for the H_3 antagonistic activity of **2a**−**i,m**. However, the results from the fluorine compounds **2j**−**l** had been omitted. To include **2j**−**l** we also investigated the influence of electronic effect of the substituent, expressed as the electron density on the substituted carbon atom (see Table 1). This electron density δ alone correlates with the pA_2 according to eq 3:

$$pA_2 = -0.96(\pm 0.34)\delta + 7.20(0.15) \quad (3)$$

$$(n = 13,\ r = 0.65,\ s = 0.55,\ F = 7.88)$$

Combination of the dihedral angle φ and the electron density on the substituted carbon atom δ revealed a very good correlation with the H_3 antagonistic activity of the compounds:

$$pA_2 = -0.02(\pm 0.003)\varphi - 0.93(\pm 0.17)\delta + 4.72(\pm 0.44) \quad (4)$$

$$(n = 13,\ r = 0.93,\ s = 0.28,\ F = 31.57)$$

To validate these findings we synthesized compounds **2n,o**. We selected the *tert*-butyl substituent, because this substituent combines a large steric hindrance effect to give a large dihedral angle φ, with a relatively small electronic contribution upon the electron density δ in comparison to **2m**. The methyl group was selected because it has only a marginal effect on the electron density δ and on the dihedral angle φ in comparison with **2m** (Figure 4). The predicted pA_2 values of these two compounds are for **2n** 7.64 and for **2o** 6.83. The measured values, 7.54 and 7.02, respectively, compare with the predicted values, and thus we conclude that the QSAR model is valid. When the measured values of compounds **2n,o** are included in eq 4, the final correlation of the pA_2 with φ and δ becomes:

$$pA_2 = -0.02(\pm 0.003)\varphi - 0.93(\pm 0.16)\delta + 4.81(\pm 0.42) \quad (5)$$

$$(n = 15,\ r = 0.93,\ s = 0.26,\ F = 36.57)$$

Conclusion

We have shown that for the series **2a**−**o** a QSAR model is valid and that this relationship is in contradiction to other SAR studies with related series of H_3 antagonists found in the literature. We conclude that the 'different' results of Vollinga[10] and Stark[11,28] can be explained by the existence of two separate "lipophilic" pockets, as has been proposed by De Esch et al.[13] We further conclude that the fluorine-containing compounds **2j**−**l** are not suited for development as PET ligands, since the H_3 antagonistic activity is too low. The 2- or

3-iodo-substituted derivatives **2b,c** are candidates for SPECT ligands, because they show good H_3 antagonistic activity.

Experimental Section

^{1}H NMR spectra were recorded on a Bruker AC 200 (at 200.13 MHz); chemical shifts (δ) are determined relative to the solvent and converted to the TMS scale using $\delta = 2.50$ for DMSO-d_6, 3.35 for CD_3OD, and 7.26 for $CDCl_3$. Abbreviations used in description of NMR spectra: s = singlet, d = doublet, t = triplet, dd = double doublet, dt = double triplet, m = multiplet, bs = broad singlet. Melting points were measured on a Mettler FP-5 mounted with a FP-52 microscope and are uncorrected. Flash column chromatography was performed with Baker silica gel 60. Thin-layer chromatography (TLC) was performed on Merck TLC plates (silica gel 60, F_{254}, 0.25 mm); amines were detected using ninhydrin. Amides were detected using the Reindol−Hoppe coloring procedure, giving purple spots for NH- or NH_2-containing compounds. For all end products elemental analyses were within 0.4% of the theoretical values. The commercial available benzyl isothiocyanates were purchased from Lancaster and all other chemicals from Aldrich; solvents were purchased from Riedel−de Haen. Dichloromethane was distilled from CaH_2 and stored over CaO. Tetrahydrofuran was distilled from $LiAlH_4$ and stored over Na wire. *n*-Hexane was distilled before use. All reactions were carried out under a nitrogen atmosphere.

1-Benzyl-4-[1-(*N*,*N*-dimethylsulfamoyl)imidazol-4-yl]-4-hydroxypiperidine, 4. Compound **3** (26.28 g, 0.15 mol) was dissolved in 500 mL of tetrahydrofuran and cooled to −65 °C. 100 mL (0.16 mol) of a 1.6 M solution of *n*-butyllithium in hexanes was added dropwise keeping the temperature between −65 and −60 °C and was stirred for another 15 min at −65 °C. Then 20.11 mL (0.15 mol) of chlorotrimethylsilane was added dropwise at −65 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. This solution was cooled again to −65 °C and 100 mL (0.16 mol) of a 1.6 M solution of *n*-butyllithium in hexanes was added keeping the reaction temperature between −65 and −60 °C. The reaction mixture was stirred for 45 min before 26.52 mL (0.15 mol) of *N*-benzyl-4-piperidone was added dropwise at −65 °C. The reaction was allowed to warm to room temperature overnight. Next, the reaction mixture was poured into 1250 mL of water and THF was evaporated under reduced pressure. The aqueous residue was extracted three times with 700 mL of dichloromethane. The dichloromethane layers were dried over Na_2SO_4 and evaporated under reduced pressure. The residue was suspended in 300 mL of 1 M hydrochloric acid, stirred for 30 min at ambient temperature and extracted two times with 150 mL of diethyl ether. The aqueous layer was basified (pH > 10) with K_2CO_3 and extracted three times with 150 mL of dichloromethane. The dichloromethane layers were dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash column chromatography with ethyl acetate/triethylamine (9/1) as the eluent to give 29.52 g of **4** (81 mmol, 54%) as a yellow oil. R_f (ethyl acetate/triethylamine: 9/1) = 0.29. ^{1}H NMR ($CDCl_3$): δ = 2.72−3.51 (m, 8H, piperidine-H), 2.97 (s, 6H, CH_3), 4.37 (s, 1H, OH), 4.42 (s, 2H, CH_2), 7.28 (s, 1H, im-H4), 7.38−7.60 (m, 5H, phenyl-H), 7.81 (s, 1H, im-H2).

4-[1-(*N*,*N*-Dimethylsulfamoyl)imidazol-4-yl]-4-hydroxypiperidine, 5. Compound **4** (25.00 g, 69 mmol) was dissolved in 250 mL of methanol and 2.50 g of 10% Pd/C and 28.00 g (0.45 mol) of ammonium formate were added. The reaction mixture was refluxed for 6 h. After cooling to room temperature the reaction mixture was filtered over Celite and the filtrate was evaporated under reduced pressure to yield 15.75 g (61 mmol, 88%) of **5**. This product was pure enough to use in the next reaction step. R_f (ethyl acetate/methanol: 9/1) = 0.27. ^{1}H NMR ($CDCl_3$): δ = 1.80−1.98 (m, 2H, piperidine-H3$_{ax}$,5$_{ax}$), 2.03−2.19 (m, 2H, piperidine-H3$_{eq}$,5$_{eq}$), 2.81−2.88 (m, 2H, piperidine-H2$_{ax}$,6$_{ax}$), 2.97 (s, 6H, CH_3), 2.94−3.16 (m, 3H, piperidine-H2$_{eq}$,6$_{eq}$ and OH), 6.92 (s, 1H, imidazole-H4), 7.70 (s, 1H, imidazole-H2).

4-(1*H*-Imidazol-4-yl)-1,2,5,6-tetrahydropyridine Dihydrobromide, 6. Compound **5** (15.00 g, 58 mmol) was refluxed for 3 h in 50 mL of 30% HBr. The hydrobromic acid was removed under reduced pressure and the residue was dissolved in 150 mL of ethanol, 1 mL of concentrated sulfuric acid was added and the reaction mixture was refluxed for 2 h. After the solvent was removed under reduced pressure, the solid material was washed three times with 50 mL of acetone yielding 13.34 g (43 mmol, 74%) of **6**. R_f (methanol/triethylamine: 9/1) = 0.42. Mp = 291−292 °C. ^{1}H NMR (D_2O): δ = 2.65−2.80 (m, 2H, tetrahydropyridine-H5), 3.52 (t, J = 6.7 Hz, 2H, tetrahydropyridine-H6), 3.90 (s, 2H, tetrahydropyridine-H2), 6.58−6.72 (m, 1H, tetrahydropyridine-H3), 7.52 (s, 1H, imidazole-H4), 8.74 (s, 1H, imidazole-H2).

4-(1*H*-Imidazol-4-yl)piperidine Dihydrobromide, 7. Compound **6** (13.00 g, 42 mmol) was dissolved in 25 mL of methanol and 1 mL of water, 1.30 g of 10% Pd/C was added and the reaction mixture was hydrogenated for 4 h at 50 bar H_2 in a bomb at room temperature. The catalyst was removed by filtration over Celite and the filtrate was evaporated to give 13.15 g (42 mmol) of **7.** R_f (methanol/triethylamine: 9/1) = 0.38. Mp = 275−278 °C. ^{1}H NMR (D_2O): δ = 1.70−2.00 (m, 2H, piperidine-H3$_{ax}$,5$_{ax}$), 2.20−2.40 (m, 2H, piperidine-H3$_{eq}$,5$_{eq}$), 3.11−3.32 (m, 3H, piperidine-H2$_{ax}$,4,6$_{ax}$), 3.45−3.61 (m, 2H, piperidine-H2$_{eq}$,6$_{eq}$), 7.48 (s, 1H, imidazole-H4), 8.61 (s, 1H, imidazole-H2).

2-*tert*-Butylbenzonitrile, 10c. Compound **11** (5.00 g, 23 mmol) was added to 2.38 g (26 mmol) of CuCN in 5 mL of dimethylformamide. The reaction mixture was refluxed for 4 h. After cooling to room temperature 5 mL of diethylamine and 15 mL of water were added. This aqueous layer was extracted five times with 25 mL of diethyl ether. The combined diethyl ether layers were extracted with 25 mL of a 10% NaCN in water solution and subsequently with 15 mL of water. The organic layer was dried, the solvent evaporated and the product was obtained from the residu by Kugelrohr distillation at 60−70 °C (at 10 mmHg) as a colorless oil. Yield = 3.07 g (19 mmol, 83%). ^{1}H NMR ($CDCl_3$): δ = 1.48 (s, 9H, *tert*-butyl), 7.15−1.31 (m, 1H, phenyl-H5), 7.40−7.56 (m, 2H, phenyl-H3,4), 7.63 (d, J = 8.0 Hz, 1H, phenyl-H6).

2-Iodobenzylamine Hydrochloride, 8a. $LiAlH_4$ (1.60 g, 42 mmol) of was suspended in 25 mL of THF. The mixture was cooled to 0 °C and 2.10 g (21 mmol) of concentrated sulfuric acid was added dropwise with vigorous stirring. The suspension was stirred for 1 h at 0 °C, before a solution of 4.06 (20 mmol) of 2-iodobenzonitrile in 10 mL of THF was added dropwise. Stirring was continued for 1 h and the reaction was stopped by the addition of 10 mL of water followed by the addition of 25 mL of 2.5 M of NaOH. The reaction mixture was filtered and the organic layer was separated. The water layer was extracted two times with 20 mL of diethyl ether. The combined organic layers were dried over Na_2SO_4 and evaporated. The product was purified by flash column chromatography with dichloromethane/hexane (1/1) as the eluent, yielding 2.10 g (9.0 mmol, 45%) of **8a**. R_f (dichloromethane/*n*-hexane: 1/1) = 0.15. ^{1}H NMR ($CDCl_3$): δ = 1.50 (s, 2.2H, NH_2·HCl), 3.82 (s, 2H, CH_2), 6.91 (m, 1H, phenyl-H5), 7.30 (m, 2H, phenyl-H4,6), 7.78 (d, J = 7.9 Hz, phenyl-H3).

4-Iodobenzylamine Hydrochloride, 8c. Compound **8c** was prepared from 4-iodobenzonitrile according to the same procedure as for **8a** yielding 2.78 g (12 mmol, 60%). R_f (dichloromethane/*n*-hexane: 1/1) = 0.27. ^{1}H NMR ($CDCl_3$): δ = 1.50 (bs, 1.9H, NH_2), 3.78 (s, 2H, CH_2), 7.00 (d, J = 8.4 Hz, 2H, phenyl-H2,6), 7.59 (d, J = 8.4 Hz, phenyl-H3,5).

2-*tert*-Butylbenzylamine, 8n. Compound **8n** was prepared from 3.01 g (19 mmol) of **10c** according to the same procedure as for **8a** yielding 2.44 g (15 mmol, 79%) of **8n**. ^{1}H NMR ($CDCl_3$): δ = 1.50 (s, 9H, *tert*-butyl), 4.06 (s, 2H, CH_2), 7.13 (m, 2H, phenyl-H3,6), 7.35 (m, 2H, phenyl-H4,5).

2-Iodobenzyl Isothiocyanate, 9a. 1,1′-Thiocarbonyl-2,2′-(1*H*)-pyridone (0.71 g, 3.0 mmol) was dissolved in 15 mL of dichloromethane and 0.60 mL (3.5 mmol) of diisopropylethylamine was added. To this mixture was added dropwise a

solution of 0.59 g (2.5 mmol) of **8a** and 1.80 mL (10.5 mmol) of diisopropylethylamine in 10 mL of dichloromethane at ambient temperature. The mixture was stirred for a additional 30 min after which the reaction mixture was washed twice with 15 mL of brine and once with 15 mL of 1 M HCl. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The product was purified with flash column chromatography with dichloromethane as the eluent, yielding 0.65 g (2.4 mmol, 80%) of **9a**. ^{1}H NMR ($CDCl_3$): δ = 4.59 (s, 2H, CH_2), 6.94−7.09 (m, 1H, phenyl-H5), 7.35−7.47 (m, 2H, phenyl-H4,6) 7.83−7.96 (m, 1H, phenyl-H3).

3-Iodobenzyl Isothiocyanate, 9b. Compound **8b** (0.2 g, 0.75 mmol) was reacted according to the same procedure as for **9a** to yield 0.19 g (0.69 mmol, 92%) of **9b**. ^{1}H NMR ($CDCl_3$): δ = 4.67 (s, 2H, CH_2), 7.13−7.25 (m, 2H, phenyl-H5,6), 7.63 (m, 2H, phenyl-H2,4).

4-Iodobenzyl Isothiocyanate, 9c. Compound **8c** (0.19 g, 0.71 mmol) was reacted according to the same procedure as for **9a** to yield 0.13 g (0.45 mmol, 63%) of **9c**. ^{1}H NMR ($CDCl_3$): δ = 4.54 (s, 2H, CH_2), 7.00 (d, J = 7.8 Hz, 2H, phenyl-H2,6), 7.39 (d, J = 7.8 Hz 2H, phenyl-H3,5).

2-Bromobenzyl Isothiocyanate, 9d. Compound **8d** (0.19 g, 0.88 mmol) was reacted according to the same procedure as for **9a** to yield 0.18 g (0.77 mmol, 88%) of **9d**. ^{1}H NMR ($CDCl_3$): δ = 4.68 (s, 2H, CH_2), 7.25 (m, 2H, phenyl-H4,6), 7.45 (m, 2H, phenyl-H3,5).

3-Bromobenzyl Isothiocyanate, 9e. Compound **8e (**0.22 g, 0.99 mmol) was reacted according to the same procedure as for **9a** to yield 0.22 g (0.97 mmol, 98%) of **9e**. ^{1}H NMR ($CDCl_3$): δ = 4.65 (s, 2H, CH_2), 7.20 (m, 2H, phenyl-H5,6), 7.49 (m, 2H, phenyl-H2,4).

4-Bromobenzyl Isothiocyanate, 9f. Compound **8f (**0.18 g, 0.80 mmol) was reacted according to the same procedure as for **9a** to yield 0.17 g (0.77 mmol, 96%) of **9f**. ^{1}H NMR ($CDCl_3$): δ = 4.61 (s, 2H, CH_2), 7.19 (d, J = 7.9 Hz, 2H, phenyl-H2,6), 7.45 (d, J = 7.9 Hz, 2H, phenyl-H3,5).

2-*tert*-Butylbenzyl Isothiocyanate, 9n. Compound **8n** 1.00 g (6.1 mmol) was reacted according to the same procedure as for **9a** to yield 1.23 g (6.0 mmol, 98%) of **9n**. ^{1}H NMR ($CDCl_3$): δ = 1.32 (s, 9H, *tert*-butyl), 4.92 (s, 2H, CH_2), 7.20 (m, 2H, phenyl-H3,6), 7.38 (m, 2H, phenyl-H3,5).

***N*-(2-Iodobenzyl)-*N*′-[4-(1*H*-imidazol-4-yl)piperidinyl]-thiourea Hemifumarate, 2a.** Compound **7** (0.25 g, 0.80 mmol) and 0.3 mL (1.6 mmol) of diisopropylethylamine were dissolved in 10 mL of ethanol. To this solution was added dropwise a solution of 0.22 g (0.80 mmol) of **9a** in 10 mL of ethanol. The reaction mixture was stirred at room temperature for 18 h. The solvent was evaporated under reduced pressure and the product was isolated by flash column chromatography with ethyl acetate/methanol/triethylamine (7/2/1) as the eluent to yield 259 mg (0.61 mmol). The free base was dissolved in as little methanol as possible and then a saturated solution of fumaric acid in diethyl ether was added dropwise until the pH was around 4. The precipitate was filtered off and recrystallized from methanol/acetone to yield 158 mg (0.33 mmol, 41%) of **2a**. R_f (ethyl acetate/methanol/triethylamine: 7/2/1) = 0.35. Mp = 150−152 °C. ^{1}H NMR (DMSO-d_6): δ = 1.43−1.61 (m, 2H, piperidine-H3$_{ax}$,5$_{ax}$), 1.90−2.08 (m, 2H, piperidine-H3$_{eq}$,5$_{eq}$), 3.07−3.25 (m, 4H, piperidine-H2,6), 3.61 (s, 1H, piperidine-H4), 4.64 (bs, 1H, thiourea-NH), 4.77 (d, 2H, ^2J = 13 Hz, CH_2), 6.52 (s, 1H, fumaric acid), 6.97 (t, ^3J = 7.5, 1H, phenyl-H5), 7.08 (d, ^3J = 6.8 Hz, 1H, phenyl-H4), 7.31 (d, ^3J = 7.4 Hz, 1H, phenyl-H6), 7.49 (s, 1H, imidazole-H5), 7.78 (d, ^3J = 6.8 Hz, 1H, phenyl-H3), 8.37 (bs, 1H, imidazole-NH), 9.07 (s, 1H, imidazole-H2). ^{13}C NMR (MeOD): δ 32.7 (piperidine-4), 35.6 (CH_2), 49.4 (piperidine-5), 49.7 (piperidine-3), 50.1 (piperidine-6), 55.4 (piperidine-2), 98.5 (phenyl-2), 115.7 (imidazole-5), 129.2 (phenyl-4), 129.7 (phenyl-6), 135.8 (imidazole-4), 138.4 (imidazole-2), 140.4 (phenyl-3), 142.1 (phenyl-1). Anal. ($C_{16}H_{19}IN_4S\cdot0.5C_4H_4O_4$) C, H, N.

***N*-(3-Iodobenzyl)-*N*′-[4-(1*H*-imidazol-4-yl)piperidinyl]-thiourea Hemifumarate, 2b.** Compound **9b** (88 mg, 0.31 mmol) was reacted with **7** (100 mg, 0.31 mmol) according to the same procedure as for **2a** to yield 75 mg (0.15 mmol, 48%) of **2b**. R_f (ethyl acetate/methanol/triethylamine: 7/2/1) = 0.32. Mp = 131−133 °C. ^{1}H NMR (DMSO-d_6): δ = 1.45−1.66 (m, 2H, piperidine-H3$_{ax}$,5$_{ax}$), 1.93−2.07 (m, 2H, piperidine-H3$_{eq}$,5$_{eq}$), 3.08−3.58 (m, 5H, piperidine-H2,4,6), 4.68−4.80 (m, 2.8H, CH_2, thiourea-NH), 6.43 (s, 1H, fumaric acid), 7.12 (t, ^3J = 7.7 Hz, 1H, phenyl-H5), 7.31 (d, ^3J = 7.7 Hz, 1H, phenyl-H6), 7.47 (s, 1H, imidazole-H5), 7.58 (d, ^3J = 7.8 Hz, 1H, phenyl-H4), 7.65 (s, 1H, phenyl-H2), 8.39 (bs, 1H, imidazole-NH), 9.00 (s, 1H, imidazole-H2). ^{13}C NMR (CD_3OD): δ = 32.3 (piperidine-4), 34.6 (CH_2), 49.1 (piperidine-3,5), 50.5 (piperidine-6), 55.9 (piperidine-2), 108.6 (phenyl-3), 120.8 (imidazole-5), 128.4 (phenyl-4), 129.5 (phenyl-5), 129.8 (phenyl-6), 133.6 (phenyl-2), 136.1 (phenyl-4), 138.9 (phenyl-2), 143.8 (phenyl-1). Anal. ($C_{16}H_{19}IN_4S\cdot0.5C_4H_4O_4$) C, H, N.

***N*-(4-Iodobenzyl)-*N*′-[4-(1*H*-imidazol-4-yl)piperidinyl]-thiourea Hemifumarate, 2c.** Compound **9c** (125 mg, 0.45 mmol) was reacted with 140 mg (0.45 mmol) of **7** according to the same procedure as for **2a** to yield 111 mg (0.23 mmol 51%) of **2c**. R_f (ethyl acetate/methanol/triethylamine: 7/2/1) = 0.43. Mp = 140−144 °C. ^{1}H NMR (CD_3OD): δ = 1.60−1.70 (m, 2H, piperidine-H3$_{ax}$,5$_{ax}$), 1.90−2.14 (m, 2H, piperidine-H3$_{eq}$,5$_{eq}$), 2.85−3.12 (m, 1H, piperidine-H4), 3.13−3.27 (m, 4H, piperidine-H2,6), 4.84 (s, 2H, CH_2), 6.54 (s, 1H, fumaric acid), 6.94 (s, 1H, imidazole-H5), 7.12 (d, ^3J = 8.0 Hz, 2H, phenyl-H2,6), 7.63 (d, ^3J = 8.0 Hz, 2H, phenyl-H3,5), 7.86 (s, 1H, imidazole-H2), 8.39 (bs, 1H, imidazole-NH). ^{13}C NMR (CD_3OD): δ = 32.7 (piperidine-4), 35.5 (CH_2), 49.3 (piperidine-3,5), 50.2 (piperidine-2,6), 92.6 (phenyl-4), 115.8 (imidazole-5), 130.7 (phenyl-2,6), 135.7 (imidazole-4), 138.4 (phenyl-3,5), 140.8 (imidazole-2), 141.7 (phenyl-1), 182.7 (C=S). MS: 427 (M + 1), 303, 169, 164, 152, 146, 113. Anal. ($C_{16}H_{19}IN_4S\cdot0.5C_4H_4O_4$) C, H, N.

***N*-(2-Bromobenzyl)-*N*′-[4-(1*H*-imidazol-4-yl)piperidinyl]-thiourea Hemifumarate, 2d.** Compound **9d** (71 mg, 0.31 mmol) was reacted with 100 mg (0.31 mmol) of **7** according to the same procedure as for **2a** to yield 72 mg (0.16 mmol, 52%) of **2d**. R_f (ethyl acetate/methanol/triethylamine: 7/2/1) = 0.37. Mp = 151−154 °C. ^{1}H NMR (DMSO-d_6): δ = 1.65−1.82 (m, 2H, piperidine-H3$_{ax}$,5$_{ax}$), 2.01−2.19 (m, 2H, piperidine-H3$_{eq}$,5$_{eq}$), 2.95−3.15 (m, 1H, piperidine-H4), 3.16−3.29 (m, 4H, piperidine-H2,6), 4.85 (s, 2H, CH_2), 6.45 (s, 1H, fumaric acid), 7.10−7.20 (m, 1H, phenyl-H5), 7.24−7.32 (m, 2H, phenyl-H4,6), 7.38 (s, 1H, imidazole-H5), 7.55 (d, ^3J = 8.0 Hz, phenyl-H3), 8.85 (s, 1H, imidazole-H2). MS: 381 (M + 1), 299, 203, 167, 152, 115, 95, 78. Anal. ($C_{16}H_{19}BrN_4S\cdot0.5C_4H_4O_4$) C, H, N.

***N*-(3-Bromobenzyl)-*N*′-[4-(1*H*-imidazol-4-yl)piperidinyl]-thiourea Hemifumarate, 2e.** Compound **9e** (71 mg, 0.31 mmol) was reacted with 100 mg (0.31 mmol) of **7** according to the same procedure as for **2a** to yield 67 mg (0.15 mmol, 48%) of **2e**. R_f (ethyl acetate/methanol/triethylamine: 7/2/1) = 0.35. Mp = 138−139 °C. ^{1}H NMR (CD_3OD): δ = 1.55−1.70 (m, 2H, piperidine-H3$_{ax}$,5$_{ax}$), 2.00−2.10 (m, 2H, piperidine-H3$_{eq}$,5$_{eq}$), 2.91−3.15 (m, 1H, piperidine-H4), 3.13−3.26 (m, 4H, piperidine-H2,6), 4.84 (s, 2H, CH_2), 6.45 (s, 1H, fumaric acid), 6.96 (s, 1H, imidazole-H5), 7.06 (t, ^3J = 7.7 Hz, 1H, phenyl-H5), 7.32 (d, ^3J = 7.7 Hz, 1H, phenyl-H6), 7.57 (d, ^3J = 7.8 Hz, phenyl-H4), 7.69 (s, 1H, phenyl-H2), 7.91 (s, 1H, imidazole-H2). ^{13}C NMR (CD_3OD): δ = 34.7 (CH_2), 48.9 (piperidine-3), 49.1 (piperidine-5), 49.4 (piperidine-6), 49.8 (piperidine-2), 116.0 (piperidine-5), 123.2 (phenyl-3), 127.4 (phenyl-6), 130.8 (phenyl-5), 131.1 (phenyl-4), 131.5 (phenyl-2), 135.4 (piperidine-4), 140.2 (piperidine-2), 143.6 (phenyl-1), 182.8 (C=S). MS: 381 (M + 1), 363, 320, 299, 259, 205, 194, 152. Anal. ($C_{16}H_{19}BrN_4S\cdot0.5C_4H_4O_4$) C, H, N.

***N*-(4-Bromobenzyl)-*N*′-[4-(1*H*-imidazol-4-yl)piperidinyl]-thiourea Hemifumarate, 2f.** Compound **9f** (71 mg, 0.31 mmol) was reacted with 100 mg (0.31 mmol) of **7** according to the same procedure as for **2a** to yield 98 mg (0.22 mmol, 71%) of **2f**. R_f (ethyl acetate/methanol/triethylamine: 7/2/1) = 0.39. Mp = 145−147 °C. ^{1}H NMR (CD_3OD): δ = 1.50−1.72 (m, 2H, piperidine-H3$_{ax}$,5$_{ax}$), 1.89−2.07 (m, 2H, piperidine-H3$_{eq}$,5$_{eq}$), 2.85−3.02 (m, 1H, piperidine-H4), 3.12−3.24 (m, 4H, piperidine-H2,6), 4.88 (s, 2H, CH_2), 6.49 (s, 1H, fumaric acid), 6.88 (s, 1H, imidazole-H5), 7.26 (d, ^3J = 7.3 Hz, 2H, phenyl-H2,6), 7.44 (d, ^3J = 7.3 Hz, 1H, phenyl-H3,5), 7.70 (s, 1H, imidazole-

H2). ^{13}C NMR (CD_3OD): δ = 29.5 (CH_2), 31.5 (piperidine-4), 48.0 (piperidine-3,5), 52.0 (piperidine-2,6), 112.7 (phenyl-4), 115.0 (imidazole-5), 128.6 (phenyl-3,5), 131.1 (phenyl-2,6), 134.5 (phenyl-1), 139.8 (imidazole-4), 145.6 (imidazole-2), 181.4 (C=S). MS: 381 (M + 1), 296, 256, 242, 217, 211, 203, 196, 164, 152, 146, 97. Anal. ($C_{16}H_{19}BrN_4S\cdot0.5C_4H_4O_4$) C, H, N.

***N*-(2-Chlorobenzyl)-*N*′-[4-(1*H*-imidazol-4-yl)piperidinyl]-thiourea Hemifumarate, 2g.** Compound **9g** (57 mg, 0.31 mmol) was reacted with 100 mg (0.31 mmol) of **7** according to the same procedure as for **2a** to yield 75 mg (0.19 mmol, 62%) of **2g**. R_f (ethyl acetate/methanol/triethylamine: 7/2/1) = 0.41. Mp = 124−125 °C. ^{1}H NMR (CD_3OD): δ = 1.55−1.78 (m, 2H, piperidine-H3$_{ax}$,5$_{ax}$), 1.88−2.07 (m, 2H, piperidine-H3$_{eq}$,5$_{eq}$), 3.04−3.34 (m, 3H, piperidine-H2$_{ax}$,4,6$_{ax}$), 4.70−4.90 (m, 2H, piperidine-H2$_{eq}$,6$_{eq}$), 4.85 (s, 2H, CH_2), 6.42 (s, 1H, fumaric acid), 7.21−7.41 (m, 4H, phenyl-H), 7.45 (s, 1H, imidazole-H5), 8.25 (s, 1H, imidazole-H2). Anal. ($C_{16}H_{19}ClN_4S\cdot0.5C_4H_4O_4$) C, H, N.

***N*-(3-Chlorobenzyl)-*N*′-[4-(1*H*-imidazol-4-yl)piperidinyl]-thiourea Hemifumarate, 2h.** Compound **9h** (57 mg, 0.31 mmol) was reacted with 100 mg (0.31 mmol) of **7** according to the same procedure as for **2a** to yield 98 mg (0.25 mmol, 81%) of **2h**. R_f (ethyl acetate/methanol/triethylamine: 7/2/1) = 0.38. Mp = 130−133 °C. ^{1}H NMR (CD_3OD): δ = 1.56−1.72 (m, 2H, piperidine-H3$_{ax}$,5$_{ax}$), 1.78−2.01 (m, 2H, piperidine-H3$_{eq}$,5$_{eq}$), 2.85−3.11 (m, 1H, piperidine-H4), 3.28−3.34 (m, 2H, piperidine-H2$_{ax}$,6$_{ax}$), 4.77 (m, 2H, piperidine-H2$_{eq}$,6$_{eq}$), 4.93 (s, 2H, CH_2), 6.40 (s, 1H, fumaric acid), 6.81 (s, 1H, imidazole-H5), 7.14−7.30 (m, 3H, phenyl-H4,5,6), 7.34−7.40 (m, 1H, phenyl-H2), 7.57 (s, 1H, imidazole-H2). Anal. ($C_{16}H_{19}ClN_4S\cdot0.5C_4H_4O_4$) C, H, N.

***N*-(4-Chlorobenzyl)-*N*′-[4-(1*H*-imidazol-4-yl)piperidinyl]-thiourea Hemifumarate, 2i.** Compound **9i** (57 mg, 0.31 mmol) was reacted with 100 mg (0.31 mmol) of **7** according to the same procedure as for **2a** to yield 71 mg (0.18 mmol, 58%) of **2i**. R_f (ethyl acetate/methanol/triethylamine: 7/2/1) = 0.45. Mp = 119−123 °C. ^{1}H NMR (CD_3OD): δ = 1.56−1.70 (m, 2H, piperidine-H3$_{ax}$,5$_{ax}$), 1.90−2.10 (m, 2H, piperidine-H3$_{eq}$,5$_{eq}$), 2.90−3.20 (m, 1H, piperidine-H4), 3.23−3.30 (m, 4H, piperidine-H2,6), 4.83 (s, 2H, CH_2), 6.42 (s, 1H, fumaric acid), 6.82 (s, 1H, imidazole-H5), 7.20 (d, J = 7.9 Hz, 2H, phenyl-H2,6), 7.43 (d, J = 7.9 Hz, 2H, phenyl-H3,5), 7.59 (s, 1H, imidazole-H2). Anal. ($C_{16}H_{19}ClN_4S\cdot0.5C_4H_4O_4$) C, H, N.

***N*-(2-Fluorobenzyl)-*N*′-[4-(1*H*-imidazol-4-yl)piperidinyl]-thiourea Hemifumarate, 2j.** Compound **9j** (167 mg, 1.00 mmol) was reacted with 313 mg (1.00 mmol) of **7** according to the same procedure as for **2a** to yield 176 mg (0.47 mmol, 42%) of **2j**. R_f (ethyl acetate/methanol/triethylamine: 7/2/1) = 0.48. Mp = 111−114 °C. ^{1}H NMR (CD_3OD): δ = 1.62−1.88 (m, 2H, piperidine-H3$_{ax}$,5$_{ax}$), 2.10−2.31 (m, 2H, piperidine-H3$_{eq}$,5$_{eq}$), 3.10−3.34 (m, 5H, piperidine-H2,4,6), 4.70 (s, 2H, CH_2), 6.49 (s, 1H, fumaric acid), 7.05−7.48 (m, 5H, phenyl-H + imidazole-H5), 8.34 (s, 1H, imidazole-H2). ^{13}C NMR (CD_3OD): δ = 31.7 (piperidine-4), 38.8 (CH_2), 48.9 (piperidine-3,5), 50.3 (piperidine-6), 55,9 (piperidine-2), 115.7 (imidazole-5), 116,2 (phenyl-3), 125.1 (phenyl-5), 126.0 (phenyl-4), 129.9 (phenyl-6), 131.9 (phenyl-1), 135.2 (imidazole-4), 138.7 (imidazole-2). MS: 319 (M + 1), 287, 285, 234, 194, 164, 152, 126, 115, 102, 186. Anal. ($C_{16}H_{19}FN_4S\cdot0.5C_4H_4O_4$) C, H, N.

***N*-(3-Fluorobenzyl)-*N*′-[4-(1*H*-imidazol-4-yl)piperidinyl]-thiourea Hemifumarate, 2k.** Compound **9k** (167 mg, 1.00 mmol) was reacted with 313 mg (1.00 mmol) of **7** according to the same procedure as for **2a** to yield 154 mg (0.41 mmol, 41%) of **2j**. R_f (ethyl acetate/methanol/triethylamine: 7/2/1) = 0.38. Mp = 128−129 °C. ^{1}H NMR (CD_3OD): δ = 1.56−1.78 (m, 2H, piperidine-H3$_{ax}$,5$_{ax}$), 1.90−2.11 (m, 2H, piperidine-H3$_{eq}$,5$_{eq}$), 3.08−3.25 (m, 5H, piperidine-H2,4,6), 4.83 (s, 2H, CH_2), 6.49 (s, 1H, fumaric acid), 6.89−7.38 (m, 5H, phenyl-H + imidazole-H5), 8.57 (s, 1H, imidazole-H2). MS: 319 (M + 1), 164, 152, 130, 86, 77. Anal. ($C_{16}H_{19}FN_4S\cdot0.5C_4H_4O_4$) C, H, N.

***N*-(4-Fluorobenzyl)-*N*′-[4-(1*H*-imidazol-4-yl)piperidinyl]-thiourea Hemifumarate, 2l.** Compound **9l** (167 mg, 1.00 mmol) was reacted with 313 mg (1.00 mmol) of **7** according to the same procedure as for **2a** to yield 210 mg (0.56 mmol, 56%) of **2m**. R_f (ethyl acetate/methanol/triethylamine: 7/2/1) = 0.42. Mp = 120−124 °C. ^{1}H NMR (CD_3OD): δ = 1.55−1.83 (m, 2H, piperidine-H3$_{ax}$,5$_{ax}$), 2.10−2.29 (m, 2H, piperidine-H3$_{eq}$,5$_{eq}$), 3.02−3.44 (m, 5H, piperidine-H2,4,6), 4.81 (s, 2H, CH_2), 6.40 (s, 1H, fumaric acid), 7.19−7.57 (m, 5H, phenyl-H + imidazole-H5), 8.55 (s, 1H, imidazole-H2). MS: 319 (M + 1), 164, 152, 146, 113, 96, 86. Anal. ($C_{16}H_{19}FN_4S\cdot0.5C_4H_4O_4$) C, H, N.

***N*-Benzyl-*N*′-[4-(1*H*-imidazol-4-yl)piperidinyl]thiourea Hemifumarate, 2m.** Compound **9m** (149 mg, 1.00 mmol) was reacted with 313 mg (1.00 mmol) of **7** according to the same procedure as for **2a** to yield 125 mg (0.35 mmol, 35%) of **2m**. R_f (ethyl acetate/methanol/triethylamine: 7/2/1) = 0.30. Mp = 161−165 °C. ^{1}H NMR (CD_3OD): δ = 1.60−1.78 (m, 2H, piperidine-H3$_{ax}$,5$_{ax}$), 2.15−2.36 (m, 2H, piperidine-H3$_{eq}$,5$_{eq}$), 2.99−3.30 (m, 5H, piperidine-H2,4,6), 4.51 (s, 2H, CH_2), 6.46 (s, 1H, fumaric acid), 6.99 (s, 1H, imidazole-H5), 7.25−7.48 (m, 4H, phenyl-H), 8.34 (s, 1H, imidazole-H2). MS: 301 (M + 1), 180, 154, 152, 144, 126, 112, 98, 86, 78. Anal. ($C_{16}H_{20}N_4S\cdot0.5C_4H_4O_4$) C, H, N.

***N*-(2-*tert*-Butylbenzyl)-*N*′-[4-(1*H*-imidazol-4-yl)piperidinyl]thiourea, 2n.** Compound **9n** (1.03 g, 5.00 mmol) was reacted with 1.57 g (5.0 mmol) of **7** according to the same procedure as for **2a** to yield 170 mg (0.48 mmol, 10%) of **2n**. The free base was recrystallized from ethyl acetate. R_f (ethyl acetate/methanol: 3/1) = 0.39. Mp = 197−199 °C. ^{1}H NMR ($CDCl_3$): δ = 1.35 (s, 9H, *tert*-butyl), 1.51−1.75 (m, 2H, piperidine-H3$_{ax}$,5$_{ax}$), 1.95−2.15 (m, 2H, piperidine-H3$_{eq}$,5$_{eq}$), 2.61−2.96 (m, 1H, piperidine-H4), 3.01−3.23 (m, 2H, piperidine-H2$_{ax}$,6$_{ax}$), 4.50−4.65 (m, 2H, piperidine-H2$_{eq}$,6$_{eq}$), 4.91 (d, ^3J = 4.3 Hz, CH_2), 5.50 (bs, 0.9H, NH), 6.63 (s, 1H, imidazole-H5), 7.05−7.25 (m, 3H, phenyl-H4,5,6), 7.30−7.40 (m, 1H, phenyl-H3), 7.48 (d, ^4J = 1.2 Hz, imidazole-H2). ^{13}C NMR (CD_3OD): δ = 20.4 (CH_3), 30.6 (CH_2), 33.1 (piperidine-4), 35.6 (*tert*-butyl-C), 47.5 (piperidine-3,5), 49.5 (piperidine-2,6), 113.5 (imidazole), 126.4 (phenyl), 127.7 (phenyl), 131.5 (phenyl), 134.5 (phenyl), 135.6 (imidazole-4), 138.6 (phenyl-2), 148.6 (phenyl-1), 181.0 (C=S). Anal. ($C_{20}H_{28}N_4S$) C, H, N.

***N*-(2-Methylbenzyl)-*N*′-[4-(1*H*-imidazol-4-yl)piperidinyl]-thiourea Hemifumarate, 2o.** Compound **9o** (163 mg, 1.00 mmol) was reacted with 313 mg (1.00 mmol) of **7** according to the same procedure as for **2a** to yield 204 mg (0.55 mmol, 55%) of **2o**. R_f (ethyl acetate/methanol/triethylamine: 7/2/1) = 0.30. Mp = 171−172 °C. ^{1}H NMR (DMSO-d_6): δ = 1.41−1.65 (m, 2H, piperidine-H3$_{ax}$,5$_{ax}$), 2.14−2.33 (m, 2H, piperidine-H3$_{eq}$,5$_{eq}$), 2.72 (s, 3H, CH_3), 2.81−3.00 (m, 1H, piperidine-H4), 3.10−3.20 (m, 2H, piperidine-H2$_{ax}$,6$_{ax}$), 4.60−4.80 (m, 4H, piperidine-H2$_{eq}$,6$_{eq}$ and CH_2), 6.53 (s, 1H, fumaric acid), 6.82 (s, 1H, imidazole-H5), 7.11−7.30 (m, 4H, phenyl-H), 7.62 (s, 1H, imidazole-H2), 8.01 (bs, 1H, NH). Anal. ($C_{17}H_{22}N_4S\cdot0.5C_4H_4O_4$) C, H, N.

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