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Antithyroid Drug Carbimazole and Its Analogues: Synthesis and Inhibition of Peroxidase-Catalyzed Iodination of L-Tyrosine

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Synthesis and biological activity of the antithyroid drug carbimazole (CBZ) and its analogues are described. The introduction of an ethoxycarbonyl group in methimazole and its selenium analogue not only prevents the oxidation to the corresponding disulfide and diselenide but also reduces the zwitterionic character. A structure−activity correlation in a series of CBZ analogues suggests that the presence of a methyl substituent in CBZ and related compounds is important for their antithyroid activity.

Introduction

Methimazole (MMI[a], **1**, Figure 1), 6-*n*-propyl-2-thiouracil (PTU, **3**), and carbimazole (CBZ, **5**) are the most commonly used drugs for treatment of hyperthyroidism.[1] These compounds block the thyroid hormone biosynthesis by inhibiting thyroid peroxidase (TPO)-catalyzed iodination of tyrosine residues in thyroglobulin.[1−3] Compound **5**, the ethoxycarbonyl derivative of **1**, is particularly important as this compound acts as a prodrug and the rapid cleavage of the ethoxycarbonyl group *in vivo* leads to the formation of **1**.[4] Recently, the selenium analogues MSeI (**2**) and PSeU (**4**) attracted considerable attention because these compounds are expected to be more nucleophilic than their sulfur analogues and they may inhibit the TPO activity by a different mechanism.[5] Whereas the antithyroid and antioxidant activities of the selenium analogues of **1** and **3** have been studied,[5,6] there is no report on the synthesis and/or biological activities of the selenium analogue of **5**.

It has been recently shown that the selenium analogue of **1** (i.e., compound **2**) does not exist in true selone form or selenol tautomeric form, but it exists as a zwitterion.[5f,6b−e] Interestingly, this compound, in contrast to the sulfur analogue, is spontaneously oxidized to the corresponding diselenide (Figure 2),[5f,6] which considerably reduces the applicability of **2** as an antithyroid agent. Therefore, the synthesis and biological evaluation of SeCBZ (**6**) is important as the introduction of $-CO_2Et$ group on the imidazole nitrogen should prevent the formation of a diselenide. In this paper, we report an easily accessible route for the synthesis of **5** and its analogues. We also report the first experimental evidence that the selenium analogue of **5** is as efficient as **5** in inhibiting the peroxidase-catalyzed iodination reaction.

Results and Discussion

One-pot synthesis of **5** and **6** was achieved by an unusual ethoxycarbonyl migration route. The low-temperature lithiation of 1-methylimidazole, followed by a sulfur or selenium insertion reactions, afforded the corresponding lithium thiolate (**8**) and selenolate (**9**). The treatment of **8** and **9** with ethylchloroformate afforded **5** and **6**, respectively, in good yield (Scheme 1). In these cases, the reactions of **8** and **9** with ethylchloroformate produce the S- and Se-substituted derivatives **10** and **11**, respectively, as intermediates. A facile migration of the ethoxycarbonyl group from sulfur or selenium to nitrogen leads to the formation of the expected compounds **5** and **6**. The methoxycarbonyl compounds **14** and **15** were synthesized by following a similar method using methylchloroformate. The final products were isolated and purified by column chromatography. All the compounds are stable in pure form in the presence of oxygen and light and can be stored for months without any noticeable decomposition. However, the N−C bond in **5** and **6** is sensitive to moisture and undergoes a slow hydrolysis in water or buffer solutions to produce **1** and **2**, respectively.

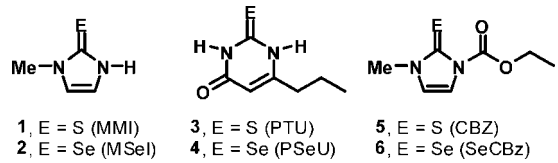

Figure 1. Chemical structures of the commonly used antithyroid drugs **1**, **3**, and **5** and their selenium analogues.

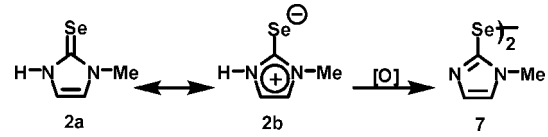

Figure 2. The spontaneous oxidation of selone **2** to the corresponding diselenide (**7**).

Compound **5** and its analogues (**6**, **14**, **15**) can also be synthesized in one pot by following a carbene route (Scheme 2). The reactions of 1-methylimidazole with ethyl- or methylchloroformate afforded the corresponding imidazolium salts (**16** and **17**), which upon reaction with triethylamine produced the *N*-heterocyclic carbenes (NHC) **18** and **19** as reactive intermediates. Addition of sulfur or selenium powder to the carbenes afforded the expected thiones and selones in very good yields except compound **15** for which the lithiation route afforded much better results. As **5**, **6**, **14**, and **15** are readily soluble in organic solvents such as chloroform, they can be easily separated from other salt-like impurities. Although the generation of imidazole-based carbenes is generally achieved by using Na_2CO_3

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[a] Abbreviations: CBZ, carbimazole; DIT, 3,5-diiodo-L-tyrosine; MIT, 3-iodo-L-tyrosine; MMI, methimazole; MSeI, 3-methyl-1*H*-imidazole-2(3*H*)-selone; PSeU, 6-*n*-propyl-2-selenouracil, PTU, 6-*n*-propyl-2-thiouracil; SeCBZ, ethyl 2,3-dihydro-3-methyl-2-selenoxoimidazole-1-carboxylate; TPO, thyroid peroxidase; LPO, lactoperoxidase; THF, tetrahydrofuran; TMS, tetramethylsilane; NBO, natural bond orbital; NPA, natural population analysis; DFT, density functional theory; B3LYP, Becke-3−Lee−Yang−Parr; NHC, *N*-heterocyclic carbenes.

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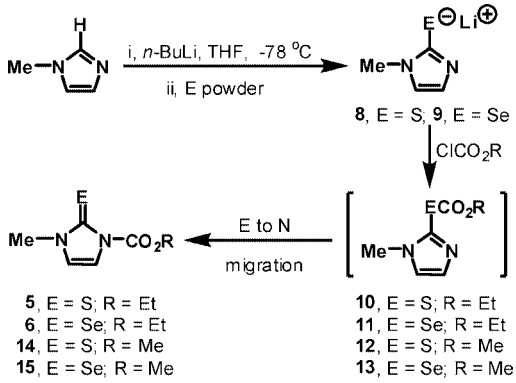
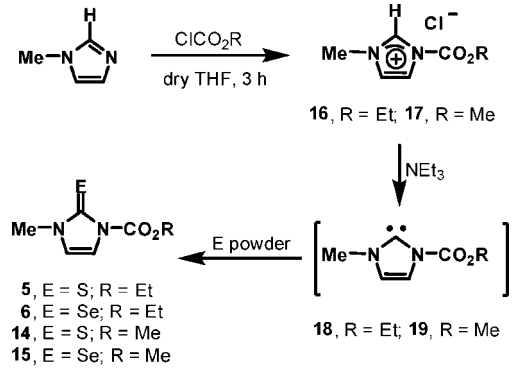
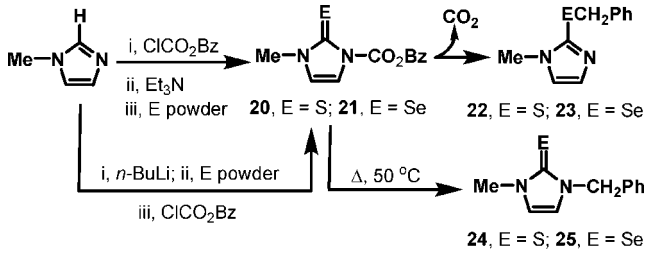
Scheme 1. One-Pot Synthesis of **5** and Its Analogues by a Lithiation and Alkoxycarbonyl Migration Route



Scheme 2. Synthesis of **5** and Its Analogues by Using Heterocyclic Carbenes Generated in Situ from the Corresponding Imidazolium Salts



Scheme 3. Proposed Mechanism for the Unusual Formation of Compounds **22**−**25** during the Synthesis of Compounds **20** and **21**



or K_2CO_3 as base,[7] we found that the use of triethylamine is essential for the generation of **18** and **19**. It should be noted that none of the reactions afforded the expected compounds when Na_2CO_3 or K_2CO_3 was used as the base. This is probably due to the instability of N−C bond in the presence of metal carbonates.

Replacement of the ethoxycarbonyl group in **5** and **6** with a benzyloxycarbonyl led to some interesting reactions. The reaction of 1-methylimidazole with benzylchloroformate afforded the corresponding imidazolium salt, which upon reaction with triethylamine and sulfur produced the thione **20** as white crystalline solid (Scheme 3). NMR spectroscopy and X-ray diffraction data confirmed the proposed structure of this compound. However, when **20** was stored at room temperature for a month, a spontaneous elimination of carbon dioxide followed by migration of the benzyl group to sulfur occurred, leading to the formation of compound **22**. Similarly, the selenium compound **21** also underwent CO_2 elimination and migration reactions to produce compound **23**, which was isolated and characterized. The conversion of **21** to **23** was found to be much faster than that of **20** to **22**, indicating that the thione or selone moiety plays an important role in the elimination reaction. Interestingly, when **20** and **21** were heated at 50 °C for ∼1 h, the *N*-substituted compounds **24** and **25** were obtained. These observations suggest that the CO_2 elimination leads to the formation of the S- and Se-substituted compounds, which upon heating produce the corresponding *N*-substituted compounds. This is in agreement with our previous observations that the S/Se-Me and S/Se-CH_2Ph substituted imidazole compounds undergo a heat-induced rearrangement to produce the corresponding *N*-substituted derivatives.[6d] The rearrangements involving selenium compounds are found to be much faster than that of their sulfur analogues.

Table 1. Summary of Experimental and Theoretical Data Predicting the Nature of C−S/Se Bonds in Some of the Thiones and Selones Synthesized in the Present Study

compd	C−S/Se (Å) (X-ray)[a]	C−S/Se (Å) (DFT)[b]	^{77}Se (δ, ppm)[c]	C−S/Se bond order[d]	$q_{S/Se}$[d]
1	1.685	1.676		1.48	−0.273
2	1.848	1.835	−5	1.37	−0.262
5	1.655	1.663		1.58	−0.151
6	1.821	1.800	195	1.47	−0.134
14	1.671	1.663		1.59	−0.148
15	1.820	1.799	197	1.47	−0.131

[a] Details about the X-ray structural determination[8] are given in the Supporting Information. [b] The geometries were fully optimized at B3LYP hybrid functional theory using 6-311+G(d,p) basis set.[11] [c] Experimental ^{77}Se chemical shifts ($CDCl_3$) cited with respect to Me_2Se. [d] The orbital interactions were determined using NBO analysis at B3LYP/6-311++G(2d,p) level and natural charges (q) were calculated from the natural population analysis (NPA).[10]

X-ray diffraction studies[8] and density functional theory (DFT) calculations[9] indicate that the thione and selone moieties in **5** and its analogues possess more double bond character as compared to that of **1** and **2**. For example, the C−S and C−Se bond lengths in **5** and **6** are significantly shorter than that of **1** and **2**, respectively (Table 1). The ^{77}Se chemical shifts for **6** (195 ppm) and **15** (197 ppm) are shifted downfield as compared to that of **2** (−5 ppm), indicating that the selenium moieties in **6** and **15** carry less negative charge as compared to that of **2**. The natural bond orbital (NBO) and natural population analysis (NPA)[10] indicate that **2** is more zwitterionic than **5** and its analogues. These observations suggest that the introduction of an ethoxy- or methoxycarbonyl group in **1** and **2** not only prevents the oxidation to the corresponding disulfide and diselenide but also reduces the zwitterionic character.

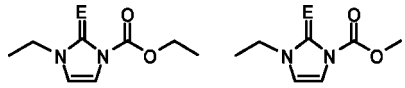
To understand the antithyroid effect of **5** and its analogues, we have studied the effect of **5**, **6**, **14**, and **15** on lactoperoxidase (LPO)-catalyzed iodination of L-tyrosine by using a HPLC method.[12] The half-maximal inhibitory concentrations (IC_{50} values) for the inhibition of LPO-catalyzed iodination were obtained at various concentrations of the thiones and selones and are summarized in Table 2. As expected, compound **1** exhibited a strong inhibition with an IC_{50} value of 11.8 ± 1.1 μM. The activity of **5** (entry b) was almost identical to that of **1**, indicating that the cleavage of N−C bond occurs during the inhibition experiments.[13] This is in agreement with the observations of Nakashima and Taurog that **5** is as potent as **1** in blocking TPO-catalyzed iodination of thyroglobulin.[4a] The IC_{50} value obtained for **6** (entry c) indicates that the replacement of sulfur with selenium does not affect the inhibitory activity of **5**, although the mechanism of inhibition by **5** may differ from that of the selenium analogue. Although the activity of **14** (entry d) having a −CO_2Me substituent was identical to that of **5**, such

Table 2. IC_{50} Values for the Inhibition of LPO-Catalyzed Iodination of L-Tyrosine by Various Thiones and Selones[a]

entry	compd	IC_{50} (μM)	entry	compd	IC_{50} (μM)
a	1	11.8 ± 1.1	f	26	20.5 ± 1.9
b	5	10.4 ± 0.6	g	27	21.3 ± 0.3
c	6	10.1 ± 0.3	h	28	19.6 ± 1.2
d	14	10.7 ± 1.8	i	29	25.3 ± 1.1
e	15	19.7 ± 1.4			

[a] Experimental conditions: the reactions were carried out in 67 mM phosphate buffer at pH 7.5; KI: 300 μM; L-tyrosine: 300 μM; hydrogen peroxide: 800 μM; lactoperoxidase: 12.9 nM.

change in the substituent in **6** reduces the inhibitory activity. For example, the IC_{50} value of **15** (entry e) was found to be almost two times higher than that of **6** (entry c). On the other hand, the replacement of the N-Me group in **5** and **6** with an N-Et substituent significantly reduces the activity of both sulfur and selenium compounds.



26, E = S; **27**, E = Se **28**, E = S; **29**, E = Se

The IC_{50} values observed for compounds **26** (entry f) and **27** (entry g) are much higher than that of **5** and **6**. Similarly, the replacement of N-Me group in **14** and **15** with N-Et substituent led to a considerable increase in the IC_{50} values (entries h and i), indicating that the presence of a methyl substituent is important for an efficient inhibition. While the N-Et substituted sulfur compounds **26** and **28** are only slightly more active than their selenium analogues **27** and **29**, respectively, the N-Me derivative **14** is almost two times more active than the corresponding selenium compound **15**. These differences may be ascribed to the various degree of polarization of C═S/C═Se bonds by different substituents. It should be noted that the difference in the activities between sulfur and selenium compounds can be remarkably high when there is no cleavable N−C bond. For example, although the *N*,*N*-disubstituted sulfur compound **24** lacking a free N−H group was almost inactive as an inhibitor of LPO-catalyzed reactions, the selenium analogue **25** has been shown to have significant activity.[6d]

Conclusions

We have described a simple and efficient method for the synthesis of the antithyroid drug **5**, its selenium analogue **6**, and some related derivatives. The introduction of an ethoxycarbonyl group in compounds **1** and **2** not only prevents the oxidation to the corresponding disulfide and diselenide but also reduces the zwitterionic character. Our results on the inhibition of LPO-catalyzed iodination of L-tyrosine indicates that the cleavage of alkoxycarbonyl group in **5**, **6** and related compounds leads to the formation of reactive zwitterions, which act as peroxidase inhibitors. A structure−activity correlation in **5** analogues suggests that the presence of a methyl substituent in **5** is important for an efficient inhibition of peroxidase-catalyzed iodination reactions.

Experimental Section

Synthesis of 5. Method A. To a cooled (−78 °C) solution of 1-methylimidazole (0.19 mL, 2.43 mmol) in freshly distilled dry THF (30 mL) was added via syringe *n*-butyllithium (1.52 mL, 1.6 M in hexanes). The mixture was stirred at this temperature for 30 min and then allowed to come to room temperature (25 °C), at which time elemental sulfur (0.08 g, 2.60 mmol) was added. The resulting mixture was stirred for 12 h and then cooled to 0 °C. To this, ethyl chloroformate (0.23 mL, 2.43 mmol) was added dropwise and stirring was continued for additional 12 h. The reaction mixture was filtered through a pad of celite. The solvent was evaporated under reduced pressure to obtain a reddish solid. The compound was extracted with chloroform and filtered through celite. The desired compound was obtained from the filtrate, which was purified by column chromatography using ethyl acetate/petroleum ether (1:1.5) to yield a white solid; yield 0.4 g (88%); mp 119−121 °C. ^{1}H NMR ($CDCl_3$, ppm): δ 1.43 (t, 3H of $-OCH_2CH_3$), 3.58 (s, 3H of $-NCH_3$), 4.48 (q, 2H of OCH_2CH_3), 6.63 (d, $J = 2.8$ Hz, 1H of CH of imidazole ring), 7.19 (d, $J = 2.8$, 1H of CH of imidazole ring). ^{13}C NMR ($CDCl_3$, ppm): δ 14.2, 35.1, 64.5, 114.5, 118.9, 149.0, 165.2; Anal. ($C_7H_{10}N_2O_2S$) C, H, N.

Method B. To a cooled (0 °C) solution of 1-methylimidazole (0.19 mL, 2.43 mmol) in freshly distilled dry THF (30 mL), ethyl chloroformate (0.23 mL, 2.43 mmol) was added via syringe. The mixture was stirred for 3 h and then cooled to 0 °C. After the addition of triethylamine (0.34 mL, 2.43 mmol), the solution was allowed to reach room temperature (25 °C). After stirring for 3 h at this temperature, elemental sulfur (0.08 g, 2.60 mmol) was added. The resulting mixture was stirred for 24 h and then filtered through a pad of celite. The solvent was evaporated under reduced pressure to obtain a gray solid. The compound was extracted with chloroform and filtered through celite. The desired compound was obtained from the filtrate as a white solid, which was further purified by column chromatography using ethyl acetate/petroleum ether (1:1.5) as eluent to obtain compound **5** as a white crystalline solid. Yield: 0.44 g (97%). All the analytical data for compound **5** obtained by this method were identical with that of method A.

Synthesis of 6. Method A. To a cooled (−78 °C) solution of 1-methylimidazole (0.97 mL, 12.18 mmol) in freshly distilled dry THF (70 mL) was added via syringe *n*-butyllithium (7.60 mL, 1.6 M in hexanes). The mixture was stirred at this temperature for 35 min and then allowed to come to room temperature (25 °C), at which time elemental selenium (1.44 g, 18.27 mmol) was added. The resulting mixture was stirred for an additional 12 h and then cooled to 0 °C. Ethyl chloroformate (1.16 mL, 12.18 mmol) was added dropwise, and the stirring was contined for 12 h. The reaction mixture was filtered through a pad of celite. The solvent was evaporated under reduced pressure to obtain a yellow solid. The compound was extracted with chloroform and filtered through a pad of celite. The desired compound was obtained from the filtrate, which was purified by column chromatography using ethyl acetate/petroleum ether (1:1.5) to obtain a pale-yellow solid; yield 1.8 g (60%); mp 128−130 °C. ^{1}H NMR ($CDCl_3$, ppm): δ 1.46 (t, 3H of $-OCH_2CH_3$), 3.69 (s, 3H of $-NCH_3$), 4.52 (q, 2H of OCH_2CH_3), 6.80 (d, $J = 2.4$, 1H of CH of imidazole ring), 7.40 (d, $J = 2.4$, 1H of CH of imidazole ring). ^{13}C NMR ($CDCl_3$, ppm): δ 14.2, 37.5, 65.0, 117.1, 120.7, 149.1, 159.8 [C═Se, $^1J_{Se-C} = 246$ Hz]. ^{77}Se NMR ($CDCl_3$, ppm): δ 195; HRMS *m*/*z* (TOF) calcd for $C_7H_{10}N_2O_2Se$ $[M + Na]^+$, 256.9805; found, 256.9801. Anal. ($C_7H_{10}N_2O_2Se$) C, H, N.

Method B. To a cooled (0 °C) solution of 1-methylimidazole (0.97 mL, 12.18 mmol) in freshly distilled dry THF (70 mL), ethyl chloroformate (1.16 mL, 12.18 mmol) was added dropwise via syringe. A white precipitate was obtained immediately. The reaction mixture was allowed to stir for additional 3 h. The reaction mixture was then cooled to 0 °C, and triethylamine (1.69 mL, 12.18 mmol) was added dropwise. The cooling bath was removed, and after 3 h of stirring, elemental selenium (1.44 g, 18.27 mmol) was added. The resulting mixture was stirred at room temperature (25 °C) for 24 h and then filtered through a pad of celite. The solvent was evaporated under reduced pressure to yield a pale-yellow solid. The compound was extracted with chloroform and filtered through a pad of celite. The desired compound was obtained from the filtrate, which was purified by column chromatography using ethyl acetate/petroleum ether (1:1.5) to get a pale-yellow solid; yield 2.1 g (74%). All the analytical data for compound **6** obtained by this method were identical with that of method A.

Synthesis of 14. Method A. To a cooled (−78 °C) solution of 1-methylimidazole (0.97 mL, 12.18 mmol) in freshly distilled dry

THF (70 mL) was added via syringe *n*-butyllithium (7.60 mL, 1.6 M in hexanes). The mixture was stirred at this temperature for 30 min and then allowed to come to room temperature (25 °C), at which time elemental sulfur (0.44 g, 14 mmol) was added. The resulting mixture was stirred for 12 h and then cooled to 0 °C. To this, methyl chloroformate (0.94 mL, 12.18 mmol) was added dropwise and stirring was continued for additional 12 h. The reaction mixture was filtered through a pad of celite. The solvent was evaporated under reduced pressure to obtain a reddish solid. The compound was extracted with chloroform and filtered through celite. The desired compound was obtained from the filtrate, which was purified by column chromatography using ethyl acetate/petroleum ether (1:1.5) to yield compound **14** as a white solid; yield 1.6 g (76%); mp 132−134 °C. ^{1}H NMR ($CDCl_3$, ppm): δ 3.59 (s, 3H of $-NCH_3$), 4.03 (s, 3H of $-OCH_3$), 6.65 (d, J = 1.2, 1H of CH of imidazole ring), 7.21 (s, 1H of CH of imidazole ring). ^{13}C NMR ($CDCl_3$, ppm): δ 35.1, 54.7, 114.4, 119.0, 149.7, 165.1. HRMS *m*/*z* (TOF) calcd for $C_6H_8N_2O_2S$ $[M + Na]^+$, 195.0204; found, 195.0210. Anal. ($C_6H_8N_2O_2S$) C, H, N.

Method B. To a cooled (0 °C) solution of 1-methylimidazole (0.97 mL, 12.18 mmol) in freshly distilled dry THF (70 mL) was added methyl chloroformate (0.94 mL, 12.18 mmol). A white precipitate was formed immediately. The reaction mixture was stirred for 3 h at room temperature (25 °C), cooled to 0 °C, and then triethylamine (1.69 mL, 12.18 mmol) was added dropwise. The cooling bath was removed, and the mixture was stirred for 3 h at room temperature. To this, elemental sulfur (0.40 g, 12.5 mmol) was added. The resulting mixture was stirred at room temperature for 24 h and then filtered through a pad of celite. The solvent was evaporated under reduced pressure to obtain a yellow solid. The compound was extracted with chloroform and filtered through celite. The desired compound was obtained from the filtrate as a yellow solid, which was purified by column chromatography using ethyl acetate/petroleum ether (1:1.5) to get a white solid; yield 1.7 g (81%). All the analytical data for compound **14** obtained by this method were identical with that of method A.

Synthesis of 15. To a cooled (−78 °C) solution of 1-methylimidazole (0.97 mL, 12.18 mmol) in freshly distilled dry THF (70 mL) was added via syringe *n*-butyllithium (7.60 mL, 1.6 M in hexanes). The mixture was stirred at this temperature for 30 min and then allowed to come to room temperature (25 °C), at which time elemental selenium (1.44 g, 18.27 mmol) was added. The resulting mixture was stirred for 12 h and then cooled to 0 °C. After the addition of methyl chloroformate (0.94 mL, 12.18 mmol), the stirring was continued for additional 12 h. The reaction mixture was filtered through a pad of celite. The solvent was evaporated under reduced pressure to yield a reddish solid. The compound was extracted with chloroform and filtered through celite. The desired compound was obtained from the filtrate as a pale-yellow solid, which was purified by column chromatography using ethyl acetate/petroleum ether (1:1.5) to yield a pale-yellow solid; yield 1.6 g (60%); mp 125−127 °C. ^{1}H NMR ($CDCl_3$, ppm): δ 3.67 (s, 3H of $-NCH_3$), 4.03 (s, 3H of $-OCH_3$), 6.81 (d, J = 2.8 Hz, 1H of CH of imidazole ring), 7.38 (d, J = 2.8 Hz, 1H of CH of imidazole ring). ^{13}C NMR ($CDCl_3$, ppm): δ 37.5, 54.9, 117.1, 120.9, 149.7, 159.8[C=Se, $^1J_{Se-C}$ = 246 Hz]. ^{77}Se ($CDCl_3$, ppm): δ 197; HRMS *m*/*z* (TOF) calcd for $C_6H_8N_2O_2Se$ $[M + Na]^+$, 242.9649; found, 242.9726. Anal. ($C_6H_8N_2O_2Se$) C, H, N.

Synthesis of 20. To a cooled (0 °C) solution of 1-methylimidazole (0.97 mL, 12.18 mmol) in freshly distilled dry THF (70 mL), dropwise benzyl chloroformate (12.05 mL, 12.18 mmol) was added via syringe. A white precipitate was obtained immediately. The mixture was stirred for 3 h at room temperature (25 °C) and then cooled to 0 °C. To this, triethylamine (1.69 mL, 12.18 mmol) was added dropwise and then the reaction mixture was allowed to attain room temperature. After stirring for 3 h, elemental sulfur (0.40 g, 12.5 mmol) was added. The resulting mixture was stirred at room temperature for 24 h and then filtered through a pad of celite. The solvent was evaporated under reduced pressure to obtain an oily liquid. The compound was extracted with chloroform and filtered through celite. The desired compound was obtained from the filtrate as an oily liquid, which was purified by column chromatography using ethyl acetate/petroleum ether (1:1.5) to get a white solid; yield 2.4 g (79%). ^{1}H NMR ($CDCl_3$, ppm): δ 3.57 (s, 3H of $-NCH_3$), 5.43 (s, 2H of $-OCH_2Ph$), 6.61 (d, J = 4 Hz, 1H of CH of imidazole ring), 7.19 (d, J = 4 Hz, 1H of CH of imidazole ring), 7.38 (m, 3H of phenyl ring), 7.48 (m, 2H of phenyl ring). ^{13}C NMR ($CDCl_3$, ppm): δ 35.1, 69.8, 114.4, 118.9, 128.7, 134.2, 148.9, 165.3. HRMS *m*/*z* (TOF) calcd for $C_{12}H_{12}N_2O_2S$ $[M + Na]^+$, 271.0517; found, 271.0504. Anal. ($C_{12}H_{12}N_2O_2S$) C, H, N.

Compound 22.[6b,d] ^{1}H NMR ($CDCl_3$, ppm): δ 3.23 (s, 3H of $-NCH_3$), 4.15 (s, 2H of $-SCH_2-$), 6.86 (s, 1H of CH of imidazole ring), 7.11 (d, 2H of phenyl ring), 7.23 (m, 3H of phenyl ring) 7.38 (s, 1H of CH of imidazole ring). HR-MS *m*/*z* (TOF) found for $C_{11}H_{12}N_2S$ $[M + Na]^+$: 227.0617.

Compound 23.[6b,d] ^{1}H NMR ($CDCl_3$, ppm): δ 3.21 (s, 3H of $-NCH_3$), 4.14 (s, 2H of $-SCH_2-$), 6.89 (s, 1H of CH of imidazole ring), 6.98 (m, 2H of phenyl ring), 7.06 (s, 2H of phenyl ring), 7.12 (m, 3H of phenyl ring). ^{13}C NMR ($CDCl_3$, ppm): δ 33.3, 34.1, 123.0, 127.1, 128.5, 128.6, 130.5, 134.6, 138.8. ^{77}Se ($CDCl_3$, ppm): δ 282.

Lactoperoxidase Assay. LPO-catalyzed iodination of L-tyrosine and inhibition by antithyroid drugs were determined by a HPLC method. As the formation of 3,5-diiodo-L-tyrosine was also observed in the reaction, only the initial 5−10% of the conversion was followed where only a trace amount of the diiodo compound was produced. The decrease in the concentration of monoiodo tyrosine with increase of the concentration of inhibitor was followed by measuring the peak area at 275 nm. The effect of antithyroid drugs on the iodination reaction was determined at various concentrations of the drugs under identical experimental conditions. The half-maximal inhibitory concentrations (IC_{50} values) for the inhibition of LPO-catalyzed iodination of L-tyrosine by the test compounds were also determined by following the same procedure. The incubation mixtures for the HPLC analysis contained KI (300 μM), L-tyrosine (300 μM), hydrogen peroxide (800 μM), and LPO enzyme (12.9 nM) in 67 mM phosphate buffer (pH 7.5). The mixture was incubated at room temperature (25 °C) and aliquots (50 μL) injected into the HPLC column and eluted with 75% of 0.1% TFA in water−25% MeCN solvent system using a C_{18} reverse-phase column. The inhibition curves were obtained by plotting the percentage control activity against the concentration of inhibitor.

Computational Studies. All calculations were performed using Gaussian98 suite of quantum chemical program.[9] The hybrid Becke 3−Lee−Yang−Parr (B3LYP) exchange correlation functional was applied for DFT calculations.[11] All structures were characterized as potential energy minima at the B3LYP/6-311++G(d,p) level by verifying that all vibrational frequencies were real. NBO analysis[10] was performed at the B3LYP/6-311++G(2d,p) level.

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Supporting Information Available: LPO inhibition plots, details of theoretical calculations, spectral data, and elemental analytical data for the target compounds and initial rates for the hydrolysis of N−C bonds in thiones and selones. This material is available free of charge via the Internet at http://pubs.acs.org.

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