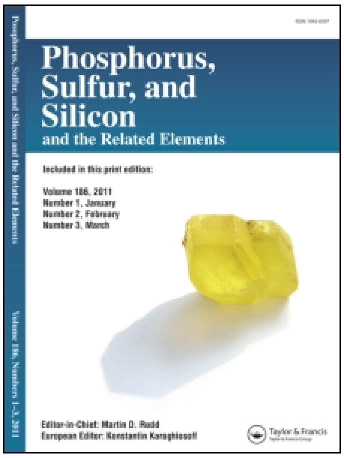

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Selenium Analogues of Anti-Thyroid Drugs

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Selenium Analogues of Anti-Thyroid Drugs

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The inhibition of lactoperoxidase (LPO)-catalyzed oxidation of ABTS by anti-thyroid drugs and related derivatives is described. The commonly used anti-thyroid agent methimazole (MMI) inhibits the LPO with an IC_{50} value of 7.0 ± 1.1 μM which is much lower than that of the other two anti-thyroid drugs, PTU and MTU. The selenium analogue of methimazole (MSeI) also inhibits LPO with an IC_{50} value of 16.4 ± 1.5 μM, which is about 4–5 times lower than that of PTU and MTU. In contrast to thiones and selones, the S- and Se-protected compounds do not show any noticeable inhibition under identical experimental conditions. While the inhibition of LPO by MMI cannot be reversed by increasing the hydrogen peroxide concentration, the inhibition by MSeI can be completely reversed by increasing the peroxide concentration. Experimental and theoretical studies were performed on a number of selones, which suggest that these compounds exist as selenolates or zwitterions in which the selenium atom carries a large negative charge. The structures of selones were studied in solution by NMR spectroscopy and the ^{77}Se NMR chemical shifts for the selones show large upfield shifts in the signals, confirming the zwitterionic structure of the selones in solution. The thermal isomerization of some S- and Se-substituted methyl and benzyl imidazole derivatives to produce the thermodynamically more stable N-substituted derivatives is described.

Keywords Anti-thyroid drugs; bioinorganic chemistry; iodine; methimazole; selenium

INTRODUCTION

Thyroid hormones, thyroxine (**T4**) and triiodothyronine (**T3**), have various physiological effects.[1–6] They exert actions in all tissues and affect essentially every metabolic pathway. Thyroid peroxidase (TPO), which is responsible for the synthesis of thyroid hormones, is synthesized on polysomes and inserted in the membrane of the endoplasmic reticulum. TPO is then transported to the Golgi, where it is subjected to terminal

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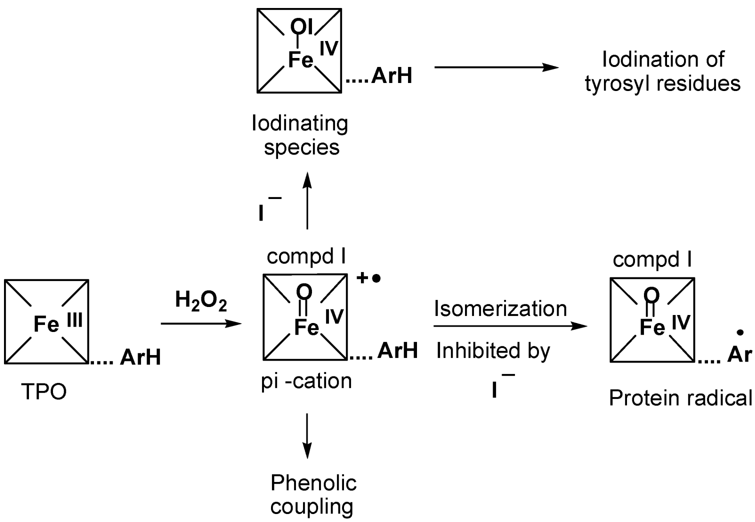
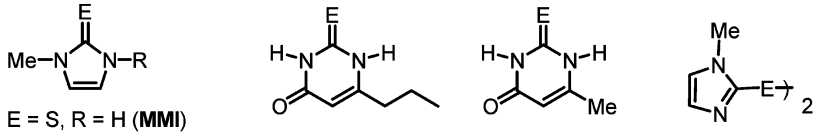


FIGURE 1 Mechanism for the synthesis of thyroid hormones (T4 and T3) by heme-containing Thyroid Peroxidase (TPO).

glycosylation and packaged into transport vesicles along with tyroglobulin (Tg).[7,8] The synthesis of thyroid hormones (**T4** and **T3**) is catalyzed by TPO, a heme-containing enzyme, in the presence of H_2O_2 on the apical membrane of the thyroid follicular cells. It is known that thyroid peroxidase (TPO), myeloperoxidase (MPO), eosinophil peroxidase (EPO), and lactoperoxidase (LPO) belong to the peroxidase superfamily of "mammalian peroxidases."[9–11]

TPO catalyzes two very different types of reactions in the thyroid gland: iodination and coupling (Figure 1). The iodination of tyrosyl residues in thyroglobulin may be considered as an electrophilic substitution reaction. On the other hand, the coupling of two iodinated tyrosyl residues to form **T4** may be treated as a phenolic condensation reaction. Several experiments with model iodinating systems reveal that the iodination and coupling reactions occur concurrently, suggesting that TPO catalyzes both the reactions simultaneously. The iodination is generally believed to involve a two-electron oxidation of iodide, although a radical mechanism has also been proposed.[12–16] The coupling reaction may follow either a radical pathway or an ionic mechanism. However, the iodination and coupling reactions are not completely TPO specific as LPO and MPO also catalyze these processes.[17–21]

The inhibition of Peroxidase-catalyzed oxidation reactions by thiourea compounds (**1**, **3**, **4** and **6**) has been routinely used not only to determine the potency of clinically useful anti-thyroid drugs, but



1, E = S, R = H (**MMI**)
2, E = Se, R = H (**MSeI**)
3, E = S, R = -CO_2Et (**CBZ**)
4, E = S (**PTU**)
5, E = Se (**PSeU**)
6, E = S (**MTU**)
7, E = Se (**MSeU**)
8, E = S (**MMI$_{ox}$**)
9, E = Se (**MSeI$_{ox}$**)

FIGURE 2 Chemical structures of some anti-thyroid drugs and their selenium analogues.

also to understand the mechanism by which the drugs exert their anti-thyroidal activity.[16,22–24] Although the inhibition of thyroid peroxidase (TPO) and a related enzyme, lactoperoxidase (LPO) by anti-thyroid agents has been studied extensively in recent years, the mechanism of the inhibition of heme-peroxidases or the inhibition of peroxidase-catalyzed oxidation and iodination reactions is still not clear. Magnusson et al. suggested that the inhibition of TPO or LPO by the thiourea drugs may occur through competition with hydrogen peroxide for a common form of oxidized iodine.[25] Davidson et al. proposed that anti-thyroid drugs block the iodination in vivo by reducing the concentration of oxidized iodide generated by the TPO/H_2O_2 system, thus diverting it from the natural substrate tyrosyl residues. In contrast, Engler et al. suggested that MMI (**1**) and PTU (**4**) exert their activity by reacting with the oxidized TPO heme group and thus inactivating the enzyme.[26] It is also possible that the thiourea drugs can be oxidized by the TPO/H_2O_2 system and the drugs in their oxidized forms may bind to the heme group of the enzyme. Taurog and Dorris, on the other hand, suggested that the inhibition of iodination by compounds such as PTU involves a competitive reaction between the drugs and tyrosine residues of thyroglobulin (Tg) for oxidized iodine.[22,27]

Although the selenium analogues of anti-thyroid drugs have attracted considerable attention in recent years, the inhibition of thyroid activity by these compounds appears to be more complicated as compared with their sulfur analogues (Figure 2).[28–33] The literature data derived from the inhibition of TPO by selenium compounds show that these compounds may inhibit the TPO activity by a different mechanism.[28,29] Therefore, further studies are required to understand the mechanism by which the selenium compounds exert their inhibitory action. In view of the current interest in anti-thyroid drugs and their mechanism,[30–33] we extended our approach to the synthesis and biological activities of a number of sulfur and selenium derivatives bearing the methimazole pharmacophore. In this article, we summarize our recent results on the inhibition of LPO-catalyzed oxidation and iodination by several thiones and selones related to methimazole.

RESULTS AND DISCUSSION

Inhibition of LPO-catalyzed Oxidation of ABTS by Anti-thyroid Drugs

The enzyme inhibition experiments were carried out with lactoperoxidase (LPO) since it is readily available in purified form. Furthermore, LPO has been shown to behave very similarly to TPO with respect to iodination of thyroglobulin, the natural substrate, and other iodide acceptors.[34] Edelhock et al. have reported the inactivation of LPO by thiourea-based drugs using LPO-N-acetyltyrosylamide assay.[35] We have employed 2,2′-azino-bis-3-ethylbenthiazoline-6-sulphonic acid (ABTS) and H_2O_2 as substrates to determine the half-maximal inhibitory concentration (IC_{50}) of test compounds.[36] The LPO activities at different concentration of MMI (**1**) and MSeI (**2**) are summarized in Figure 3 and the corresponding concentration-inhibition plots and IC_{50} values are given in Figure 4 and Table I, respectively.

We carried out the experiment with the reduced species (**2**), which was obtained by reducing the diselenide (**9**) with $NaBH_4$ in an aqueous solution. The extraction of the aqueous solution with dichloromethane, followed by drying over anhydrous Na_2SO_4 and evaporation of the

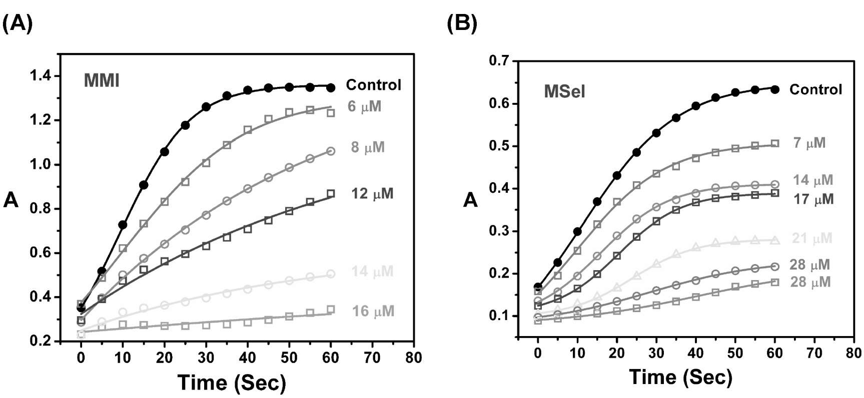


FIGURE 3 Inhibition of LPO-catalyzed oxidation of ABTS by MMI (A) and MSeI (B) at pH 7 and 30°C. The incubation mixture contained 0.5 μg/mL LPO, 1.4 mM ABTS, 0.067 M phosphate buffer (pH 7) and 28.67 μM H_2O_2. The reaction was initiated by the addition of H_2O_2. The initial formation of ABTS radical cation was monitored by an UV-Vis spectrophotometer at 411 nm.

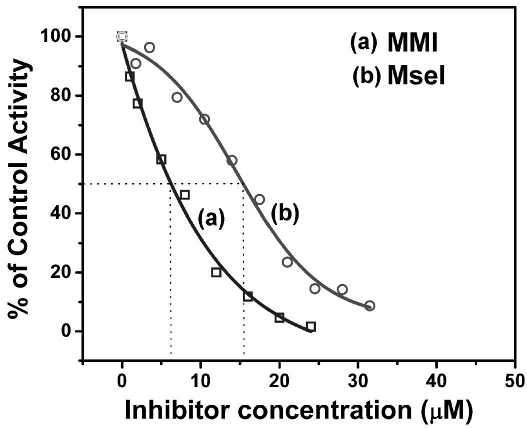


FIGURE 4 Concentration-inhibition curves for the inhibition of LPO-catalyzed oxidation of ABTS by MMI and MSeI at pH 7.0 and 30°C. The incubation mixture contained 0.5 μg/mL LPO, 1.4 mM ABTS, 0.067 M phosphate buffer (pH 7) and 28.67 μM H_2O_2. The reaction was initiated by addition of H_2O_2.

organic solvent afforded **2** as pale yellow solid. Similarly to the inhibition of LPO by MMI, the LPO activity decreased with an increase in the concentration of MSeI (Figure 3, B). As expected, MMI exhibited high inhibitory activity towards LPO with an IC_{50} value of 7.0 ± 1.1 μM, which is much lower than that observed with PTU and MTU. The selenium analogue (MSeI) also inhibited LPO, and the IC_{50} value was found to be almost 4–5 times lower than that of PTU and MTU. The higher

TABLE I Inhibition of LPO Activity by Compounds 1, 2, 4, 6, 12, and 13

No.	Compd.	IC_{50}(μM)[a]
1	MMI (**1**)	7.0 ± 1.1
2	MSeI (**2**)	16.4 ± 1.5
3	PTU (**4**)	45.0 ± 2.1
4	MTU (**6**)	47.8 ± 0.1
5	**12**	24.4 ± 1.9
6	**13**	22.6 ± 2.8
7	**14**	Inactive
8	**15**	Inactive
9	**16**	Inactive

[a]Concentration of the compound causing 50% inhibition. Each IC_{50} value was calculated from at least three independent experiments.

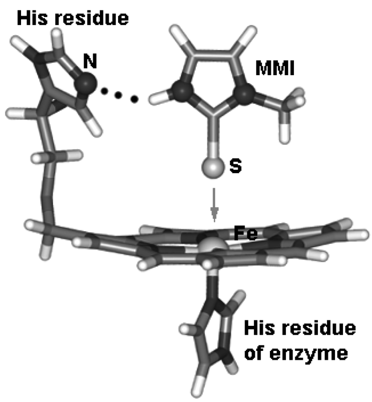


FIGURE 5 A hypothetical model for the coordination of thiourea drugs to the Fe-center of TPO.

activity of MMI as compared with PTU and MTU is in agreement with the previous studies on the inhibition of TPO.[22,26] Since the activation of the iron center in TPO must proceed through an interaction of Fe(III) with H_2O_2, the inhibition of TPO may occur through a competitive coordination of the drug to iron, assisted by hydrogen bonding with a histidine residue of the TPO enzyme (Fig. 5).[37,38] Under these conditions, MMI might compete more successfully than PTU with H_2O_2, because the hydrogen-bond (hard) basicity pk_{HB} value of MMI (2.11) is much higher than that of PTU ($\sim$1.32). Similar to PTU, the methyl derivative **6** (MTU) is also expected to be a weak inhibitor of TPO. On the other hand, the nucleophilicity of the selenium moiety in compound **2** that exists predominantly in its zwitterionic form is expected to be much higher than that of the sulfur analogue. However, the lower activity of MSeI as compared with MMI indicates that the selenium analogue of MMI may inhibit LPO by a different mechanism. Although compound **2** is exhibits high inhibition activity towards LPO-catalyzed oxidation reaction, the selenium protected compounds **10** and **11** do not show any significant inhibition activity. However, these compounds exhibits good activity after thermal isomerization to form compounds **12** and **13** (Fig. 6).

During the summer, when the temperature was about 32°C, the Se-substituted compounds **10** and **11** underwent thermal isomerization to produce the corresponding N-substituted derivatives **12** and **13**, respectively (Fig. 6). The migration of methyl and benzyl groups from selenium to nitrogen atom was readily occurred when the samples were heated to 40–50°C. The isomerization was followed by ^{1}H, ^{13}C and ^{77}Se NMR spectroscopy and the thermodynamically stable final products were characterized by single crystal X-ray studies.

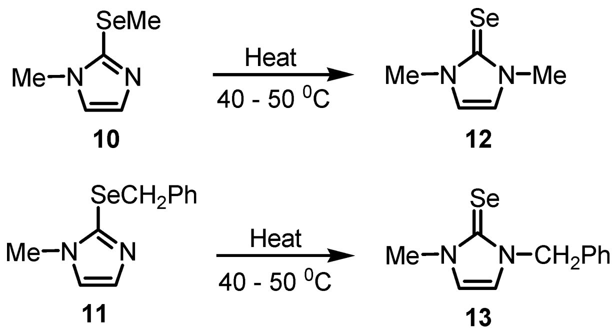


FIGURE 6 Heat-induced isomerization in monoselenides: Migration of methyl and benzyl groups from selenium to nitrogen.

Compounds **12** and **13** were also synthesized by independent methods and compared with the isomerized products. It is important to note that the doublets observed for the imidazolyl ring hydrogens in **11** (Se-substituted) have smaller coupling constants (∼1 Hz) than those of the C-N isomer (selone) (2.2 Hz). In addition, the resonance for $–CH_2–$ hydrogens occurs further upfield in **11** (δ: 4.16 ppm) than in **13** (δ: 5.35 ppm). Thus, the coupling constants and chemical shifts of the $–CH_2–$ resonance can be used to distinguish between a C–Se– versus a C–N– bonded isomer in this family of compounds. However, the ^{77}Se satellites observed in the ^{1}H NMR spectra and the ^{77}Se NMR chemical shifts are found to be quite informative. The singlet signal observed in the ^{1}H NMR spectra of compounds **10** and **11** for the methyl and $–CH_2–$ groups showed ^{77}Se satellites for the expected selenium coupling to the protons. The ^{77}Se NMR chemical shifts for the products (**12**: -6 ppm, **13**: -3 ppm) are much upfield shifted as compared with the starting materials **10** and **11**, which exhibited signals at 117 ppm and 282 ppm, respectively. The migration of alkyl or benzylic groups from selenium to nitrogen appears to be faster than that involves sulfur. This type of tautomerization is expected to be faster in the case of MSeI (**2**) and such processes may account for the facile oxidation of **2** to the diselenide **9**.

It should be mentioned that the selones **12** and **13** were also obtained in trace amounts during our syntheses of Se-substituted methyl and benzylic derivatives (**10**, **11**). The formation of these unexpected products can be ascribed to the presence of the lithium selenolate in different isomeric forms. The low-temperature metallation of 1-methylimidazole with n-BuLi affords the lithiated species, which in turn reacts with elemental selenium to produce the corresponding lithium selenolate. The straightforward reactions of this species with methyl iodide and benzyl chloride afforded the Se-substituted methyl (**10**) and benzyl (**11**)

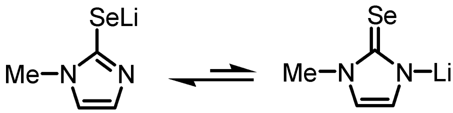
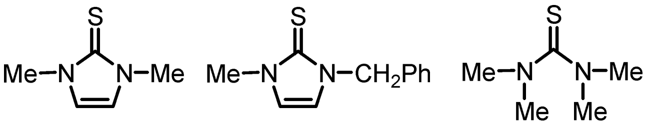


FIGURE 7 Proposed pathway for the formation of compound **12** and **13**.

derivatives, respectively. However, the migration of Li from selenium to nitrogen would yield the corresponding selone having a little charge on selenium and a large negative charge on the nitrogen (Figure 7), which further reacts with methyl iodide and benzyl chloride to produce the selones **12** and **13**, respectively.

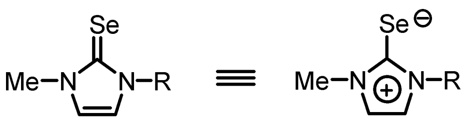


14 **15** **16**

SCHEME 1 Chemical structures of compounds **14–16**.

On the other hand, the N3-methylated derivative of MMI and TMTU (compounds **14–16**, Scheme 1) do not inhibit the LPO-catalyzed oxidation reaction, because the N–C bonds in this compound are stable and cannot be cleaved under acidic conditions. Surprisingly, the replacement of sulfur in compound **14** with selenium (compound **12**) led to almost a complete inhibition of LPO activity with an IC_{50} value of 24.4 μM, which is slightly higher than that of MSeI (16.4 μM), but this compound is much more active than the 2-thiouracil derivatives (**4** and **6**). An almost identical activity was observed with compound **13** (22.6 μM), which also does not have any free N–H moiety.

Although compounds **12** and **13** lack the essential N–H group, the higher inhibitory activity of these compounds as compared with their sulfur analogues can be ascribed to the existence of **12** and **13** in zwitterionic structures where the selenium moiety acts as a selenolate rather than a selone (Figure 8). Similarly to MSeI (**2**), the negatively charged selenium moiety may scavenge the H_2O_2 substrate, which effectively



12, R = Me; **13**, R = Bz

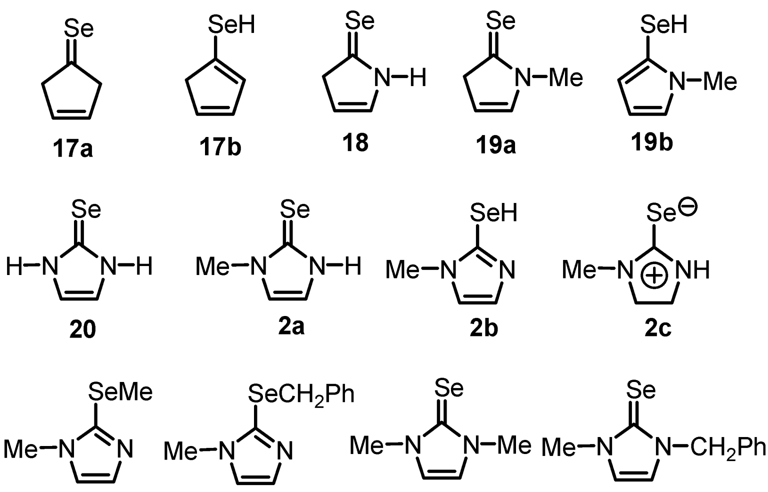
FIGURE 8 Proposed structures of compounds **12** and **13**. Both compounds exist predominantly in zwitterionic form, which may have only a partial C–Se double bond character.

present in the model system (ABTS assay) or this compound may interfere with the oxidized LPO species, leading to a reversible inactivation. Interestingly, the Se-substituted derivatives **10** and **11**, on the other hand, do not show any noticeable inhibition of the LPO-catalyzed oxidation, but they show high inhibition after the thermal isomerization.

To understand the effect of peroxide (H_2O_2) on the reaction rate and the inhibition, the LPO activity was determined at various concentrations of hydrogen peroxide. In addition, the effect of hydrogen peroxide on the inhibition of LPO-catalyzed iodination by selenium analogue of anti-thyroid drugs (**2**, **12**, and **13**) was evaluated by carrying out the experiments at various concentrations of H_2O_2. The initial rates (v_0) derived from various concentrations of H_2O_2 were plotted against the concentrations of H_2O_2. Although the LPO activity was inhibited by selones (**2**, **12** and **13**) at lower concentrations of H_2O_2, the enzyme's activity could be completely recovered by increasing H_2O_2 concentration (up to certain concentration of selones). These results suggest that the concentration of H_2O_2 has a dramatic effect on the inhibition of iodination reaction by selones. The inhibition curves at different concentrations of inhibitors (selones) were characterized by a lag phase whose length is related to the amount of inhibitors (selones) present in the reaction mixture. After the lag phase, the rate of formation of MIT was increased to the control value with an increase in the concentration of H_2O_2. The control experiments indicate that the lag phase is probably due to the hydrogen peroxidase depletion and not an enzyme inactivation. These observations support our conclusions on the inhibition of LPO-catalyzed oxidation reactions that the selenium analogue of anti-thyroid drugs (**2**, **12**, and **13**) reversibly inhibits the enzyme's activity.

Theoretical Studies on Selones

All calculations were performed using Gaussian98 suite of quantum chemical programs.[39] The hybrid Becke 3-Lee-Yang-Parr (B3LYP) exchange correlation functional was applied for DFT calculations.[40,41] Geometries were fully optimized at B3LYP level of theory using the 6-311++G(d,p) basis sets. All stationary points were characterized as minima by corresponding Hessian indices. The NMR calculations were done at B3LYP/6-311++G(2d,p) level on B3LYP/6-311++G(d,p) level optimized geometries using the GIAO method.[42–48] Orbital interactions were analyzed using the Natural Bond Orbital (NBO) method at the B3LYP/6-311++G(2d,p) level and charges were calculated from Natural Population Analysis (NPA).[49] In general, theoretical investigations on selones are highly limited to the compounds having simple substituents, mainly due to the requirement of large basis sets for the calculations.[50–52] The relatively larger size and more polarizability of selenium as compared with those of sulfur have led to the assumption that the compounds with selone moiety are less stable than their sulfur analogues. In addition to structure optimizations, we performed NBO analysis to understand further the nature of Se atoms in selones and calculated bond order between C–Se of all selones. The reactivity and reaction patterns of selones, in general, vary considerably depending upon the substituents adjacent to the selenocarbonyl group. Therefore, the heteroatom-substituted selones are more polar than selenoaldehydes and selenoketones.[53] In view of this, we have undertaken further studies to understand the effect of substituents on selenocarbonyl moiety.



SCHEME 2 Chemical structures of some selones.

The exocyclic C–Se bond length in compound **17a**, which is not containing any heteroatom in the ring, is 1.774 Å and considered as a true selone in the present discussion. The C–Se bond order for this compound is close to two (1.87). However introducing one nitrogen atom into the ring (Compound **18**, Scheme 2) increases the C–Se bond length significantly from 1.775 Å to 1.805 Å as well as bond order decreases dramatically from 1.87 to 1.58 (Table II), indicates delocalization of π-electron from C–Se bond to C–N bond (resonance structure I is possible). Furthermore, incorporation of one more nitrogen atom at 3- position of the heterocycle (Compound **20**, Scheme 2) increases C–Se bond length further from 1.805 Å to 1.831 Å. The bond order for compound **20** is 1.38 which is no longer contains C–Se double bond. In this case

TABLE II Summary of DFT Calculations on Selenium Compounds at B3LYP/6-311+G(d,p) Level and GIAO ^{77}Se NMR Chemical Shifts Calculated at B3LYP/6-311+G(d,p)//B3LYP/6-311++G(2d,p) Level using Gaussian03 suite of Quantum Chemical Calculations Along with Experimental ^{77}Se NMR Chemical Shifts.

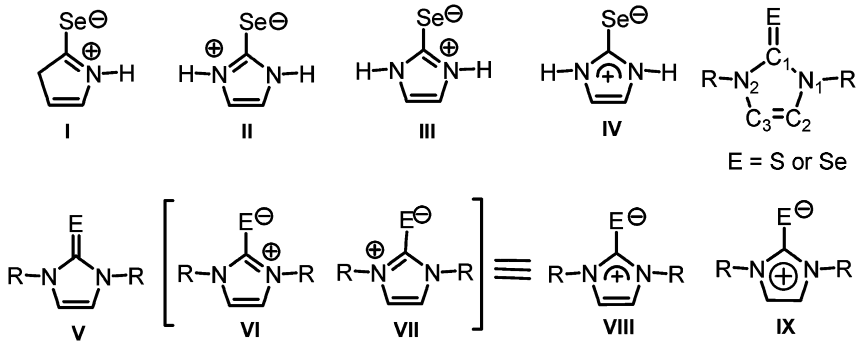
Compd.	C−Se bond length (Å) (Calc.)	C−Se bond length (Å) (Exp.)	C−Se bond order	Charge on Se (NBO)	^{77}Se NMR (ppm) (Exp.)	^{77}Se NMR (ppm) (Calc.)[a]
17a	1.774	—	1.87	0.098	—	2094
17b	1.915	—	1.03	0.138	—	—
18	1.805	—	1.58	−0.101	—	632
19a	1.812	—	1.55	−0.124	—	652
19b	1.908	—	1.02	0.123	—	—
20	1.831	—	1.38	−0.252	—	10
2a	1.835	1.848	1.37	−0.262	−5	23
2b	1.917	—	1.02	0.132	—	—
2c	1.835	—	1.37	−0.261	—	—
12	1.838	1.843	1.36	−0.269	−6	39
13	1.844	1.843	1.34	−0.272	−3	−2

[a]The chemical shifts (δ) are cited with respect to dimethyl selenide. The calculated chemical shift for dimethyl selenide in B3LYP/6-311+G(d,p)//B3LYP/6-311++G(2d,p) level is 1637.6348. [b]^{77}Se NMR for all compounds were taken in $CDCl_3$ except compound 73, which is not soluble in $CDCl_3$ taken in D_2O.

π-electrons are more delocalized among the four atoms (two resonance structures are possible II and III).

Replacement of H atom with methyl substituent has a little effect on the ^{77}Se NMR as well as charge on the selenium atom since the bigger selenium atom has a p orbital which overlaps less effectively with the ring π-orbital. Thus, the charge on the selenium atom in compounds **18** and **19a** has a very little difference; and the same is true for compounds **12** and **13**. NBO calculation shows that the charge on selenium moiety in compound **17a** is positive (0.098), whereas that for compound **18** is negative (−0.101) and the corresponding charge for compound **20** is even more negative (−0.252). This clearly indicates that compound **20** does not contain a true C−Se double bond; in fact, it can best be represented as zwitterionic structure having negative charge on selenium and positive charge on carbon atom (IV, Scheme 3).

The X-ray structure of 1,3-Dimethyl-2(3H)-imidazolethione (**14**) was first reported by Ansel et al. and best on the C−N bond lengths and C−C bond length [C(thionyl)−N: 1.350 Å; C(ethylenic)−N: 1.41 Å and C=C: 1.31 Å] in the imidazole ring they have proposed that the electronic structure of compound **14** would best be represented by a resonance hybrid of structures (V) and (VIII) (Scheme 3).[54] However, Tomlin et al.



SCHEME 3 Chemical structures of some selones showing resonance structures of the compounds.

reported the crystal structure of the same compound (**14**) and based on the bond distances found in their study [C(thionyl)–N: 1.346 Å; C(ethylenic)–N: 1.39 Å and C=C: 1.329 Å], they have proposed more delocalized zwitterionic structure (IX).[55] Crystal structure of **2** clearly shows that there are no significant differences in the lengths of the two unique C–N bonds (Table 3). This strongly suggests that the n electrons are delocalized and aromatic character exists in the heterocyclic ring. The structure of compound **2** can, therefore, be represented as zwitterionic **2c**.

Similarly, the crystal structures of all N,N-disubstituted thiones and selones (**12**, **13**, **14** and **15**) indicate that these compounds do not have a

TABLE III C–C and C–N bond lengths in the imidazole ring of some thione and selone compounds

Compd.	C–N bond length (Å)
1[a]	C1–S: 1.685; N1–C1: 1.353; N1–C2: 1.382; N2–C1: 1.342; N2–C3: 1.369; C2–C3: 1.322
2	C1–Se: 1.848; N1–C1: 1.350; N1–C2: 1.375; N2–C1: 1.346; N2–C3: 1.376; C2–C3: 1.336
14[b]	C1–S: 1.695; N1–C1: 1.350; N1–C2: 1.410; N2–C1: 1.350; N2–C3: 1.410; C2–C3: 1.310
14[c]	C1–S: 1.681; N1–C1: 1.346; N1–C2: 1.390; N2–C1: 1.346; N2–C3: 1.390; C2–C3: 1.329
12[d]	C1–Se: 1.843; N1–C1: 1.342; N1–C2: 1.371; N2–C1: 1.342; N2–C3: 1.371; C2–C3: 1.346
13	C1–Se: 1.843; N1–C1: 1.349; N1–C2: 1.371; N2–C1: 1.351; N2–C3: 1.365; C2–C3: 1.330

[a]Raper et al.;[56] [b]Ansell et al.;[54] [c]Tomlin et al.[55]

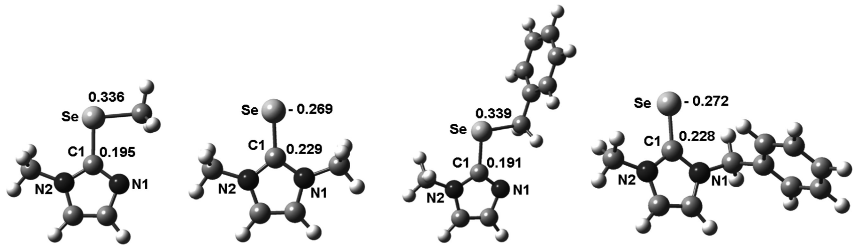


FIGURE 9 Optimized structure of compounds **10**, **11**, **12** and **13** showing the charges on selenium, carbon and nitrogen atoms. The structure optimization and NBO analysis were performed at B3LYP/6-311+G(d,p)/6-311++G(2d,p) level of theory.

true C=S or C=Se double bond. The C=S bond length in the thiones are in the range of 1.678 to 1.695 Å, which are shorter than the single bond value of 1.81 Å and greater than the C=S double bond value of 1.61 Å. This clearly suggests that the C—S bonds in these thiones have only a partial double bond character. Similarly, the C—Se bond distances in all the selones lie in between single bond and double bond. Significant shortening of the adjacent C—N bond, or lengthening of the olefinic double bond (C=C bond) from the true double bond and as well as significant shortening of the C (ethylenic)−N in the imidazole ring of all thione or selone reported here suggest the formation of a more delocalized structure corresponding to IX (zwitterionic structure).[57] Interestingly, the NBO analysis on compounds **10** and **11** suggest that the selenium atom in **10** carries a positive charge (+0.336), but the selenium atom in **12** carries a negative charge (−0.269) (Figure 9). This indicates that the selenium center is changed from an electrophilic selenium to a nucleophilic selenium upon isomerization.

CONCLUSIONS

The commonly used anti-thyroid agent methimazole (MMI) inhibits the LPO activity with an IC_{50} value of 7.0 ± 1.1 μM, which is much lower than that of the other two anti-thyroid drugs, PTU and MTU. The selenium analogue of methimazole (MSeI) also inhibits the LPO activity with an IC_{50} value of 16.4 ± 1.5 μM, which is about 4–5 times lower than that of PTU and MTU. N,N-disubstituted thiones do not inhibit the LPO activity, whereas the N,N-disubstituted selones completely inhibit LPO-catalyzed oxidation reaction and the activities of these selones are comparable with that of MSeI. In contrast to thiones and selones, the S- and Se-protected compounds do not show any noticeable inhibition under identical experimental conditions. While the inhibition of LPO by MMI cannot be reversed by increasing the hydrogen peroxide concentration, the inhibition by MSeI can be completely reversed by increasing the peroxide concentration.

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