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Synthesis of novel 2-aminothieno[3,2-*d*]thiazoles and selenolo[3,2-*d*]thiazoles

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ABSTRACT

In this work, we described the synthesis of 3-isothiocyanatoselenophenes starting from 3-aminoselenophenes (using thiophosgene). Those compounds were then converted to the corresponding thioureas in the presence of ammonium hydroxide. Cyclization in 2-aminoselenolo[3,2-*d*]thiazoles was achieved using DDQ. 2-Aminothieno[3,2-*d*]thiazoles were obtained from 3-isothiocyanatothiophenes using the same pathway.

1. Introduction

Thiazoles are major scaffolds in heterocyclic chemistry, showing various pharmacological activities like antimicrobial[1,2] or anti-inflammatory.[3] Benzothiazoles have also been described for anticancer activity[4] and Riluzole is marketed to treat amyotrophic lateral sclerosis (Fig. 1). Thiazoles condensed with heterocycles present also interesting properties as herbicides,[5] for example, or more recently as selective cardiodepressant products (I).[6] Synthesis of condensed thiazoles with five-membered heterocycles could be achieved by two ways: either by construction of the thiazole ring from the five-membered heterocycle or by creation of the heterocycle from thiazole.[7] Two pathways for the formation of thieno[3,2-*d*]thiazoles have been described, for example, 2-phenylthieno[3,2-*d*]thiazole has been synthesized by condensation of 5-chloro-4-formyl-2-phenylthiazole with thioglycolic acid,[8] whereas 2-mercaptothieno[3,2-*d*]thiazole has been obtained from 2-chlorothiophene by a multi-step synthesis with the intermediate production of chloronitrothiophene.[9] To the best of our knowledge, there is no report on selenolo[3,2-*d*]thiazoles.

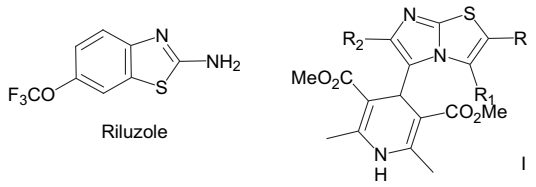

Fig. 1. Examples of thiazole-containing biologically active compounds.

Since many years, our lab is working on the synthesis of heterocyclic compounds with potential biological activity, especially products containing polysubstituted thiophenes.[10] In a previous work, we described the synthesis of 3-aminothiophenes and their use as starting material to obtain isothiocyanates and *N*,*N*′-disubstituted thioureas.[11] Here we extended this methodology to obtain new 3-isothiocyanatoselenophenes. In a second part of this work, we used those scaffolds as well as thienyl isothiocyanates to prepare 2-aminothienothiazoles and 2-aminoselenolothiazoles.

2. Results and discussion

3-Aminoselenophene-2-carboxylates **1** were first saponified by refluxing for 4 h with an aqueous solution of potassium hydroxide to give the corresponding carboxylic acids **2**, which were next decarboxylated by heating with oxalic acid in isopropanol.[12] The obtained aminoselenophenes **3** were finally treated with thiophosgene in presence of sodium hydrogenocarbonate to give the targeted isothiocyanates **4** in moderate to good yields (Scheme 1 and Table 1).

Synthesis of monosubstituted thioureas **5** was performed by stirring the highly reactive isothiocyanates in dichloromethane with a solution of ammonium hydroxide (Scheme 2). The targeted thioureas were obtained in moderate to good yields in both thiophene and selenophene series (Table 2).

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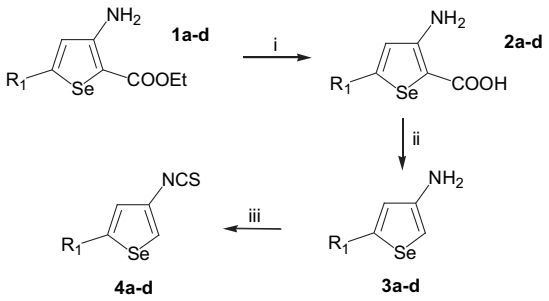
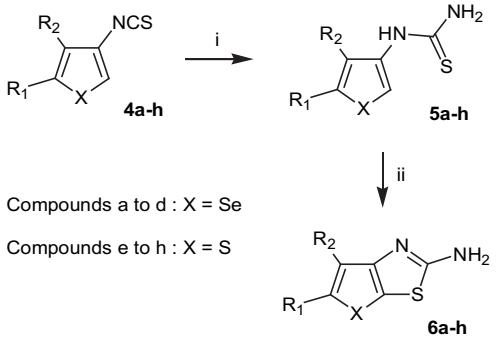


Scheme 1. Synthesis of 3-isothiocyanatoselenophenes. Reagents and conditions: i. KOH/H_2O, EtOH, reflux, 4 h; ii. Oxalic acid, *i*-PrOH, 40 °C; iii. $CSCl_2$, $NaHCO_3$, $CHCl_3$, rt, 2 h.

Table 1
Isothiocyanatoselenophenes prepared[a]

Entry	Product **4**	Yield (%)
1	**4a**	57
2	**4b**	62
3	**4c**	95
4	**4d**	68

[a] 3-Isothiocyanatothiophenes **4e**–**h** were previously synthesized by a similar pathway.[11b]



Scheme 2. Synthesis of selenolo- and thieno[3,2-*d*]thiazoles. Reagents and conditions: i. NH_3/H_2O, CH_2Cl_2, rt, overnight; ii. DDQ, CH_2Cl_2, rt, 4 h.

Recently, Saeed et al. have described another methodology, which allows obtaining directly phenylthiourea by heating the corresponding aniline with ammonium thiocyanate in presence of hydrochloric acid.[13] We were particularly interested in this procedure as it would be more user-friendly: the reaction occurs in one step and without using thiophosgene. However, when 5-(4-methoxyphenyl)-3-aminothiophene was reacted with ammonium thiocyanate in those conditions, we did not obtain the expected thiourea **5g** as both ^1H and ^{13}C NMR spectra of the two compounds were different. However, HRMS showed that it was an isomer as the two compounds have the same molecular weight. The different data let us to consider that we obtained compound **5′g** (Table 2, entry 9). While the IR spectrum of **5g** showed typical signals from the thioureas (NH_2, NH, and C=S), the spectrum of **5′g** presented neither the characteristic duplet from the NH_2 nor the signal from the C=S, but a strong peak at 1653 cm^{-1}, which may correspond to a C=N group. For compound **5g**, the NH group gave a broad signal at 9.82 ppm, which is not present in ^1H NMR spectrum of compound **5′g**. In the latter, one H-atom appears at 8.23 ppm and a second appears at 10.48 ppm. All the other signals (for aromatic hydrogens and methoxy group) are quite similar. The same observations have been done with the ^{13}C NMR spectra where all signals are identical except one: in compound **5g**, there is a signal at 180.5 ppm (C=S), whereas it is missing in compound **5′g** and replaced by a new one at 159.1 ppm, which may correspond to the C=NH group.

The last step of this work was the intramolecular cyclization of the thioureas into condensed thiazoles. Cyclization of thienylthioamides or thienyl monothiooximes have been achieved by action of potassium ferricyanide $K_3Fe(CN)_6$.[14] Disubstituted thioureas have also been cyclized in presence of bromine as oxidizing agent.[15] Here we decided to use the pathway described by Bose and Idrees[16] for the oxidative cyclization of aryl thioformanilides using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). In this very convenient procedure, thiourea was stirred with DDQ in dichloromethane at rt to give the corresponding thienothiazoles and selenolothiazoles in good yields (49–91%, Table 2). A simple purification by chromatography was required only to remove by-products from the DDQ.

We also tried to perform the cyclization on compound **5′g** under the same conditions as before to check if the isomeric form of the thiourea has an influence on the structure of final compound. One more time, analyses showed some differences with results for compound **6g**. On ^1H NMR, the disappearance of one of the CH signal from thiophene ring proved that the cyclization occurred. However the presence of two NH signals and a missing NH_2 peak revealed that we did not obtain compound **6g** but probably an isomer **6′g**. It was surprising but may be explained via the mechanism of DDQ-induced cyclization proposed by Bose[16] and Wang.[17] In compound **5g** the thiyl radical may be formed after isomerization, whereas it could be produced directly from isothiourea **5′g** that giving two different compounds (Scheme 3).

3. Conclusion

In conclusion, we performed the synthesis of new heterocycle-condensed 2-aminothiazoles in good yields using an easy three-step procedure from the corresponding heteroaryl-amine. These compounds could be considered as interesting analogs of aniline and be used in a lot of various synthetic protocols involving aryl-amine.

4. Experimental section

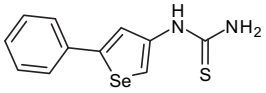
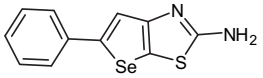
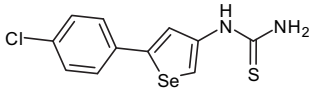
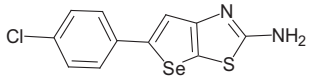
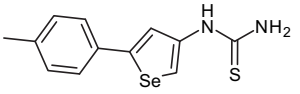
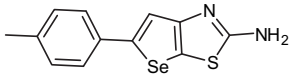
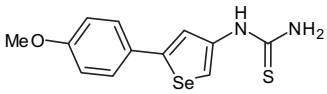
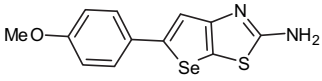
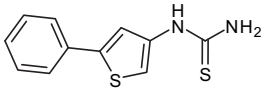
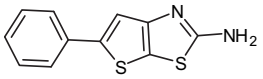
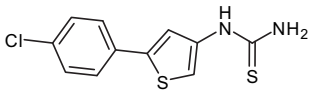
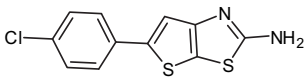
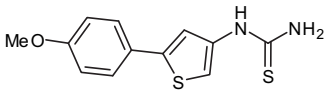
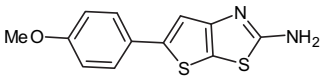
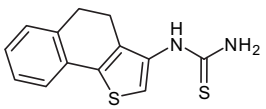
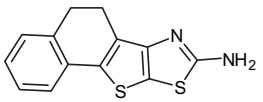
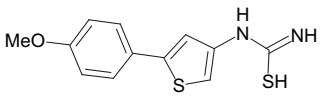
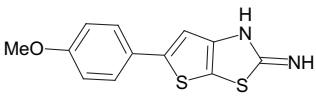
4.1. General

Melting points were determined on a Stuart SMP3 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra (δ in ppm) were recorded on an AC Bruker 250 MHz spectrometer in $CDCl_3$ or DMSO-d_6. MS spectra were recorded with a MicroTof-Q98. IR spectra were recorded with a Perkin–Elmer FTIR Baragon 1000PC instrument equipped with Spectrum (Perkin–Elmer) software version 5.3.1.

Petroleum ether (PE) used refers to the fraction boiling in the range 35–60 °C.

3-Aminoselenophene-2-carboxylates **1** were synthesized according to Ref. 18.

Table 2
Thioureas and thieno/selenothiazoles prepared

Entry	Thiourea **5**	Yield (%)	Thiazole **6**	Yield (%)
1	 **5a**	47	 **6a**	86
2	 **5b**	61	 **6b**	64
3	 **5c**	62	 **6c**	76
4	 **5d**	81	 **6d**	49
5	 **5e**	86	 **6e**	86
6	 **5f**	77	 **6f**	83
7	 **5g**	64	 **6g**	50
8	 **5h**	87	 **6h**	91
9	 **5'g**	30[a]	 **6'g**	65

[a] Obtained via a different pathway (described in text).

3-Isothiocyanatothiophenes **4e**–**h** were previously synthesized and described in Ref. 11b.

4.2. Aminoselenophene-2-carboxylates 1a–d

*4.2.1. Ethyl 3-amino-5-phenylselenophene-2-carboxylate (**1a**).* Yield: 50%; red solid; mp 87 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=1.24 (t, J=7.1 Hz, 3H, CH_3), 4.16 (q, J=7.1 Hz, 2H, CH_2), 6.73 (s, 2H, NH_2), 7.27 (s, 1H, CH), 7.39–7.42 (m, 3H, 3× CH), 7.55–7.57 (m, 2H, 2× CH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=14.5 (CH_3), 59.4 (CH_2), 96.0 (C), 120.1 (CH), 125.8 (2× CH), 129.2 (2× CH), 134.6 (CH), 138.5 (C), 152.0 (C), 157.1 (C), 164.7 (C=O).

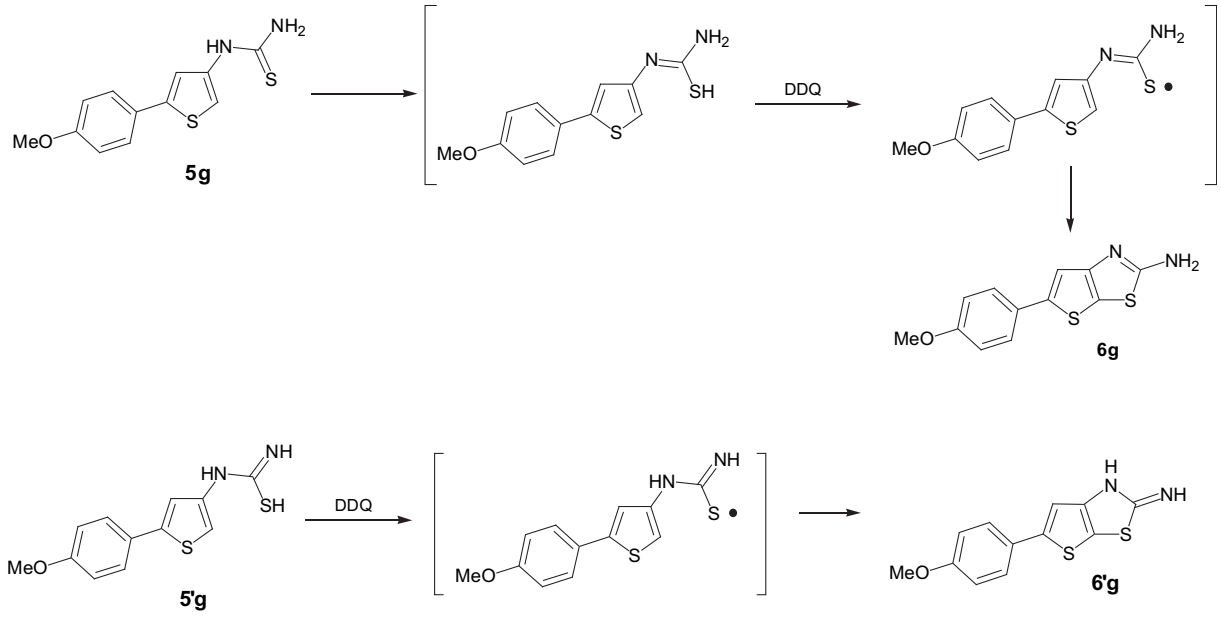
*4.2.2. Ethyl 3-amino-5-(4-chlorophenyl)selenophene-2-carboxylate (**1b**).* Yield: 80%; orange solid; mp 137 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=1.23 (t, J=7.1 Hz, 3H, CH_3), 4.16 (q, J=7.1 Hz, 2H, CH_2), 6.73 (s, 2H, NH_2), 7.28 (s, 1H, CH), 7.47 (d, J=8.75 Hz, 2H, 2× CH), 7.58 (d, J=8.75 Hz, 2H, 2× CH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=14.5 (CH_3), 59.5 (CH_2), 96.5 (C), 120.8 (CH), 127.5 (2× CH), 129.2 (2× CH), 133.5 (C), 133.7 (C), 150.3 (C), 157.0 (C), 164.6 (C=O).

*4.2.3. Ethyl 3-amino-5-(4-methylphenyl)selenophene-2-carboxylate (**1c**).* Yield: 43%; brown solid; mp 111 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=1.23 (t, J=7.1 Hz, 3H, CH_3), 2.30 (s, 1H, CH), 4.16 (q, J=7.1 Hz, 2H, CH_2), 6.70 (s, 2H, NH_2), 7.20 (s, 1H, CH), 7.22 (d, J=8.75 Hz, 2H, 2× CH), 7.44 (d, J=8.75 Hz, 2H, 2× CH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=14.5 (CH_3), 20.8 (CH_3), 59.3 (CH_2), 96.5 (C), 119.5 (CH), 125.7 (2× CH), 129.7 (2× CH), 131.9 (C), 138.9 (C), 152.2 (C), 157.2 (C), 164.7 (C=O).

*4.2.4. Ethyl 3-amino-5-(4-methoxyphenyl)selenophene-2-carboxylate (**1d**).* Yield: 45%; red solid; mp 135 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=1.23 (t, J=7.1 Hz, 3H, CH_3), 3.78 (s, 1H, CH), 4.14 (q, J=7.1 Hz, 2H, CH_2), 6.69 (s, 2H, NH_2), 6.97 (d, J=8.75 Hz, 2H, 2× CH), 7.14 (s, 1H, CH), 7.50 (d, J=8.75 Hz, 2H, 2× CH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=14.5 (CH_3), 55.3 (OCH_3), 59.3 (CH_2), 94.9 (C), 114.5 (2× CH), 118.7 (CH), 127.2 (2× CH), 138.8 (C), 152.1 (C), 157.4 (C), 160.1 (C), 164.7 (C=O).

4.3. Synthesis of aminoselenophenecarboxylic acids 2a–d; general procedure

To a stirred solution of the appropriate selenophene (15 mmol) in EtOH (15 mL) was added a solution of KOH (4 equiv) in H_2O (8 mL). The mixture was heated at reflux for 4 h and then the solvent was evaporated. The residue was poured into H_2O (25 mL) and acidified to neutral pH with *ortho*phosphoric acid. The precipitate



Scheme 3. Proposed mechanism for the DDQ-mediated cyclization of **5g** and **5′g**.

was filtered, washed with H_2O (2×10 mL) and PE (2×10 mL), and dried.

*4.3.1. 3-Amino-5-phenyl-2-selenophenecarboxylic acid (**2a**).* Yield: 88%; pale brown solid; mp 99 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=7.26 (s, 1H, CH), 7.38–7.45 (m, 3H, 3× CH), 7.53–7.61 (m, 2H, 2× CH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=97.6 (C), 120.3 (CH), 125.3 (CH), 125.6 (2× CH), 127.8 (C), 128.9 (2× CH), 135.5 (C), 156.4 (C), 166.6 (C=O).

*4.3.2. 3-Amino-5-(4-chlorophenyl)-2-selenophenecarboxylic acid (**2b**).* Yield: 78%; pale brown solid; mp 114 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=7.26 (s, 1H, CH), 7.46 (d, J=8.0 Hz, 2H, 2× CH), 7.57 (d, J=8.0 Hz, 2H, 2× CH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=98.4 (C), 121.9 (CH), 126.6 (2× CH), 129.1 (2× CH), 131.7 (C), 134.9 (C), 144.6 (C), 149.1 (C), 166.3 (C=O).

*4.3.3. 3-Amino-5-(4-methylphenyl)-2-selenophenecarboxylic acid (**2c**).* Yield: 88%; pale brown solid; mp 161 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=2.27 (s, 3H, CH_3), 7.13–7.19 (m, 3H, 3× CH), 7.34–7.50 (m, 2H, 2× CH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=20.6 (CH_3), 96.1 (C), 125.1 (CH), 129.5 (2× CH), 132.8 (C), 137.2 (2× CH), 146.3 (C), 148.9 (C), 156.2 (C), 166.8 (C=O).

*4.3.4. 3-Amino-5-(4-methoxyphenyl)-2-selenophenecarboxylic acid (**2d**).* Yield: 95%; brown solid; mp 156 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=3.80 (s, 3H, CH_3), 6.96 (d, J=8.0 Hz, 2H, 2× CH), 7.29 (s, 1H, CH), 7.47 (d, J=8.0 Hz, 2H, 2× CH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=55.2 (OCH_3), 96.3 (C), 114.4 (2× CH), 120.1 (CH), 124.1 (2× CH), 126.3 (C), 128.8 (C), 146.1 (C), 148.8 (C), 159.9 (C=O).

4.4. Synthesis of aminoselenophenes 3a–d; general procedure

To a stirred solution of the appropriate aminoselenophenecarboxylic acid (15 mmol) in *i*-PrOH (15 mL) was added anhydrous oxalic acid (1 equiv). The reaction was stirred at 40 °C until CO_2 evolution ceased. The mixture was cooled to rt and Et_2O (25 mL) was added. The precipitate was filtered, washed with PE (2×10 mL), and dried.

*4.4.1. 5-Phenyl-3-selenophenamine (**3a**).* Yield: 71%; pale brown solid; mp 153 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=6.49 (s, 1H, CH), 7.25–7.29 (m, 2H, 2× CH), 7.35 (t, J=7.0 Hz, 2H, 2× CH), 7.48 (d, J=7.0 Hz, 2H, 2× CH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=101.3 (CH), 121.3 (CH), 125.1 (2× CH), 127.8 (CH), 129.3 (2× CH), 135.5 (C), 143.9 (C), 146.4 (C).

*4.4.2. 5-(4-Chlorophenyl)-3-selenophenamine (**3b**).* Yield: 91%; yellow solid; mp 177 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=6.44 (s, 1H, CH), 7.24 (s, 1H, CH), 7.40 (d, J=8.25 Hz, 2H, 2× CH), 7.49 (d, J=8.25 Hz, 2H, 2× CH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=99.3 (CH), 121.9 (CH), 126.7 (2× CH), 129.1 (2× CH), 131.7 (C), 134.8 (C), 144.8 (C), 162.8 (C).

*4.4.3. 5-(4-Methylphenyl)-2-selenophenamine (**3c**).* Yield: 92%; green solid; mp 220 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=2.29 (s, 3H, CH_3), 6.48 (s, 1H, CH), 7.18 (d, J=8.0 Hz, 2H, 2× CH), 7.24 (s, 1H, CH), 7.40 (d, J=8.0 Hz, 2H, 2× CH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=20.8 (CH_3), 100.5 (CH), 120.6 (CH), 124.9 (2× CH), 129.6 (2× CH), 132.8 (C), 137.2 (C), 143.8 (C), 146.4 (C).

*4.4.4. 5-(4-Methoxyphenyl)-2-selenophenamine (**3d**).* Yield: 81%; yellow solid; mp 176 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=3.76 (s, 3H, CH_3), 6.44 (s, 1H, CH), 6.92 (d, J=8.0 Hz, 2H, 2× CH), 7.12 (s, 1H, CH), 7.42 (d, J=8.0 Hz, 2H, 2× CH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=55.2 (OCH_3), 99.9 (CH), 114.4 (2× CH), 120.1 (CH), 126.4 (2× CH), 128.3 (C), 143.8 (C), 146.2 (C), 159.0 (C).

4.5. Synthesis of isothiocyanatoselenophenes 4a–d; general procedure

To a stirred mixture of $NaHCO_3$ (10 mmol) in $CHCl_3/H_2O$ (8:6 mL) was added $CSCl_2$ (575 mg, 5 mmol), followed by dropwise addition of a solution of the corresponding aminoselenophene (5 mmol) in $CHCl_3$ (15 mL). The mixture was stirred at rt for 2 h. The layers were separated and the organic layer was washed with H_2O (15 mL), dried ($MgSO_4$), and evaporated. The residue was poured into PE (15 mL), filtered, and evaporated.

*4.5.1. 3-Isothiocyanato-5-phenylselenophene (**4a**).* Yield: 57%; brown oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.25 (d, J=1.5 Hz, 1H, CH),

7.35–7.42 (m, 3H, 3× CH), 7.49–7.53 (m, 2H, 2× CH), 7.69 (d, J=1.5 Hz, 1H, CH). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=122.4 (CH), 123.8 (CH), 126.0 (2× CH), 126.2 (C), 128.6 (CH), 129.1 (2× CH), 129.3 (C), 134.9 (C), 150.2 (C).

*4.5.2. 3-Isothiocyanato-5-(4-chlorophenyl)selenophene (**4b**).* Yield: 62%; dark red oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ=7.26 (d, J=1.5 Hz, 1H, CH), 7.28 (d, J=9.0 Hz, 2H, 2× CH), 7.37 (d, J=9.0 Hz, 2H, 2× CH), 7.61 (d, J=1.5 Hz, 1H, CH). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=122.8 (CH), 124.1 (CH), 127.1 (2× CH), 127.3 (C), 129.3 (2× CH), 129.9 (C), 134.5 (C), 135.7 (C), 148.7 (C).

*4.5.3. 3-Isothiocyanato-5-(4-methylphenyl)selenophene (**4c**).* Yield: 95%; dark red oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.40 (s, 3H, CH_3), 7.20 (d, J=8.0 Hz, 2H, 2× CH), 7.24 (d, J=1.5 Hz, 1H, CH), 7.32 (d, J=8.0 Hz, 2H, 2× CH), 7.57 (d, J=1.5 Hz, 1H, CH). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=21.2 (CH_3), 121.8 (CH), 123.2 (CH), 125.8 (2× CH), 126.0 (C), 129.1 (2× CH), 129.9 (C), 132.2 (C), 138.7 (C), 150.4 (C).

*4.5.4. 3-Isothiocyanato-5-(4-methoxyphenyl)selenophene (**4d**).* Yield: 68%; brown oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.78 (s, 3H, CH_3), 6.84 (d, J=9.0 Hz, 2H, 2× CH), 7.18 (d, J=1.5 Hz, 1H, CH), 7.36 (d, J=9.0 Hz, 2H, 2× CH), 7.54 (d, J=1.5 Hz, 1H, CH). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=55.4 (OCH_3), 114.4 (2× CH), 114.6 (C), 121.2 (CH), 122.7 (CH), 127.3 (2× CH), 127.5 (C), 127.8 (C), 150.1 (C), 160.0 (C).

4.6. Synthesis of thioureas 5a–h; general procedure

To a stirred solution of the corresponding isothiocyanate (3 mmol) in CH_2Cl_2 (10 mL) was added ammonia (25% in H_2O, 0.5 mL). The mixture was stirred at rt overnight. PE (20 mL) was added and then the precipitate was filtered, washed with Et_2O (10 mL), and dried.

*4.6.1. N-(5-Phenyl-3-selenophenyl)thiourea (**5a**).* Yield: 47%; brown solid; mp 180 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=7.30 (t, J=7.5 Hz, 1H, CH), 7.39 (t, J=7.5 Hz, 2H, 2× CH), 7.55 (d, J=7.5 Hz, 2H, 2× CH), 7.62 (s, 1H, CH), 8.02 (s, 1H, CH), 9.88 (s, 1H, NH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=122.9 (CH), 125.4 (2× CH), 127.8 (CH), 129.1 (2× CH), 135.4 (CH), 139.2 (C), 144.1 (C), 165.2 (C), 180.7 (C=S). HRMS (ESI): m/z calcd for $[C_{11}H_{10}N_2SSe+H]^+$: 282.9802; found: 282.9754.

*4.6.2. N-(5-(4-Chlorophenyl)-3-selenophenyl)thiourea (**5b**).* Yield: 61%; brown solid; mp 172 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=7.43 (d, J=8.75 Hz, 2H, 2× CH), 7.57 (d, J=8.75 Hz, 2H, 2× CH), 7.64 (s, 1H, CH), 8.01 (s, 1H, CH), 9.81 (s, 1H, NH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=117.6 (C), 123.6 (CH), 127.0 (2× CH), 129.0 (2× CH), 132.3 (CH), 134.3 (C), 139.2 (C), 145.2 (C), 180.7 (C=S). HRMS (ESI): m/z calcd for $[C_{11}H_9ClN_2SSe+H]^+$: 316.9410; found: 316.9345.

*4.6.3. N-(5-(4-Methylphenyl)-3-selenophenyl)thiourea (**5c**).* Yield: 62%; yellow solid; mp 183 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=2.29 (s, 3H, CH_3), 7.20 (d, J=7.75 Hz, 2H, 2× CH), 7.43 (d, J=7.75 Hz, 2H, 2× CH), 7.54 (s, 1H, CH), 7.94 (s, 1H, CH), 9.80 (s, 1H, NH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=20.7 (CH_3), 116.1 (C), 122.2 (CH), 125.3 (2× CH), 129.6 (2× CH), 132.7 (CH), 137.4 (C), 139.0 (C), 146.9 (C), 180.6 (C=S). HRMS (ESI): m/z calcd for $[C_{12}H_{12}N_2SSe+H]^+$: 296.9959; found: 296.9912.

*4.6.4. N-(5-(4-Methoxyphenyl)-3-selenophenyl)thiourea (**5d**).* Yield: 81%; brown solid; mp 185 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=3.77 (s, 3H, CH_3), 6.95 (d, J=8.75 Hz, 2H, 2× CH), 7.45 (s, 1H, CH), 7.48 (d, J=8.75 Hz, 2H, 2× CH), 7.91 (s, 1H, CH), 9.85 (s, 1H, NH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=55.3 (OCH_3), 114.5 (2× CH), 114.8 (C), 121.5 (CH), 126.7 (2× CH), 127.7 (C), 128.1 (CH), 139.0 (C), 159.1 (C), 180.6 (C=S). HRMS (ESI): m/z calcd for $[C_{12}H_{12}N_2OSSe+H]^+$: 312.9908; found: 312.9823.

*4.6.5. N-(5-Phenyl-3-thienyl)thiourea (**5e**).* Yield: 86%; orange solid; mp 198 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=7.31 (t, J=7.25 Hz, 1H, CH), 7.38–7.44 (m, 3H, 3× CH), 7.52 (s, 1H, CH), 7.59 (d, J=7.25 Hz, 2H, 2× CH), 9.89 (s, 1H, NH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=119.9 (CH), 125.0 (2× CH), 127.8 (CH), 129.1 (2× CH), 133.4 (CH), 137.9 (C), 140.9 (C), 141.3 (C), 180.7 (C=S). HRMS (ESI): m/z calcd for $[C_{11}H_{10}N_2S_2+H]^+$: 235.0358; found: 235.0360.

*4.6.6. N-(5-(4-Chlorophenyl)-3-thienyl)thiourea (**5f**).* Yield: 77%; pale brown solid; mp 164 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=7.44 (s, 1H, CH), 7.46 (d, J=8.5 Hz, 2H, 2× CH), 7.53 (s, 1H, CH), 7.62 (d, J=8.5 Hz, 2H, 2× CH), 9.88 (s, 1H, NH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=120.6 (CH), 126.7 (2× CH), 129.1 (2× CH), 132.2 (CH), 135.4 (C), 138.1 (C), 139.8 (C), 140.9 (C), 180.7 (C=S). HRMS (ESI): m/z calcd for $[C_{11}H_9ClN_2S_2+H]^+$: 268.9968; found: 268.9931.

*4.6.7. N-(5-(4-Methoxyphenyl)-3-thienyl)thiourea (**5g**).* Yield: 64%; pale orange solid; mp 208 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=3.76 (s, 3H, CH_3), 6.97 (d, J=8.5 Hz, 2H, 2× CH), 7.26 (s, 1H, CH), 7.41 (s, 1H, CH), 7.52 (d, J=8.5 Hz, 2H, 2× CH), 9.82 (s, 1H, NH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=55.2 (OCH_3), 110.8 (C), 114.5 (2× CH), 118.8 (CH), 126.1 (CH), 126.4 (2× CH), 137.7 (C), 141.4 (C), 159.0 (C), 180.5 (C=S). HRMS (ESI): m/z calcd for $[C_{12}H_{12}N_2OS_2+H]^+$: 265.0464; found: 265.0474. IR (KBr): 3360, 3259 (NH_2), 3142 (NH), 1250 (C=S) cm^{-1}.

*4.6.8. N-(4,5-Dihydronaphto[1,2-b]-3-thienyl)thiourea (**5h**).* Yield: 87%; brown solid; mp 215 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=2.61 (t, J=8.0 Hz, 2H, CH_2), 2.88 (t, J=8.0 Hz, 2H, CH_2), 7.15–7.31 (m, 4H, 4× CH), 7.51 (s, 1H, CH), 9.30 (s, 1H, NH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=21.7 (CH_2), 27.8 (CH_2), 115.2 (C), 121.9 (CH), 127.0 (CH), 127.1 (C), 128.1 (CH), 130.8 (CH), 133.3 (C), 133.9 (C), 134.3 (CH), 135.6 (C), 181.6 (C=S). HRMS (ESI): m/z calcd for $[C_{13}H_{12}N_2S_2+H]^+$: 261.0515; found: 261.0534.

4.7. One-step synthesis of thiourea; synthesis of *N*-[5-(4-methoxyphenyl)-3-thienyl]carbamimidothioic acid (5′g)

To a stirred solution of the corresponding thiophenamine (1 mmol) in DMF (5 mL) were added concd HCl (1 mL) and ammonium thiocyanate (1.5 mmol). The mixture was stirred at 80 °C for 3 h. After cooling to rt, the mixture was poured into water (30 mL) and the precipitate formed was filtered, washed with water (2×10 mL), and dried to afford the crude product, which was purified by chromatography on silica gel (cyclohexane/EtOAc, 1:1).

Yield: 30%; yellow solid; mp 78 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=3.77 (s, 3H, CH_3), 6.97 (d, J=8.5 Hz, 2H, 2× CH), 7.26 (s, 1H, CH), 7.42 (s, 1H, CH), 7.51 (d, J=8.5 Hz, 2H, 2× CH), 8.23 (s, 1H, NH), 10.48 (s, 1H, NH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=55.2 (OCH_3), 108.1 (CH), 114.5 (2× CH), 116.2 (CH), 126.0 (C), 126.5 (2× CH), 136.1 (C), 141.7 (C), 158.8 (C), 159.1 (C). HRMS (ESI): m/z calcd for $[C_{12}H_{12}N_2OS_2-H]^+$: 263.0307; found: 263.0305. IR (KBr): 3269 (NH), 1653 (C=N) cm^{-1}.

4.8. Synthesis of thiazoles 6a–h; general procedure

To a stirred solution of the corresponding thiourea (1 mmol) in CH_2Cl_2 (10 mL) was added DDQ (1 equiv). The mixture was stirred at rt for 4 h. The layer was washed with a 2 M aqueous solution of NaOH (2×10 mL), dried ($MgSO_4$), and evaporated to afford the crude product, which was purified by chromatography on silica gel (cyclohexane/EtOAc, 1:1).

*4.8.1. 5-Phenylselenolo[3,2-d][1,3]thiazol-2-amine (**6a**).* Yield: 86%; green solid; mp 149 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=7.13 (s, 2H, NH_2), 7.26 (t, J=7.5 Hz, 1H, CH), 7.37 (t, J=7.5 Hz, 2H, 2× CH), 7.57 (d, J=7.5 Hz, 2H, 2× CH), 7.68 (s, 1H, CH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=116.5 (C), 116.9 (CH), 124.9 (2× CH), 127.4 (C), 129.1(2× CH), 136.1 (C), 147.7 (C), 158.2 (C), 171.0 (C). HRMS (ESI): m/z calcd for $[C_{11}H_8N_2SSe+H]^+$: 280.9646; found: 280.9641.

*4.8.2. 5-(4-Chlorophenyl)selenolo[3,2-d][1,3]thiazol-2-amine (**6b**).* Yield: 64%; green solid; mp 186 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=7.15 (s, 2H, NH_2), 7.40 (d, J=8.5 Hz, 2H, 2× CH), 7.60 (d, J=8.5 Hz, 2H, 2× CH), 7.72 (s, 1H, CH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=117.4 (C), 117.6 (CH), 126.5 (2× CH), 128.9 (2× CH), 131.6 (C), 135.1 (C), 146.0 (C), 158.2 (C), 171.1 (C). HRMS (ESI): m/z calcd for $[C_{11}H_7ClN_2SSe+H]^+$: 314.9253; found: 314.9253.

*4.8.3. 5-(4-Methylphenyl)selenolo[3,2-d][1,3]thiazol-2-amine (**6c**).* Yield: 76%; green solid; mp 135 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=2.33 (s, 3H, CH_3), 7.12 (s, 2H, NH_2), 7.17 (d, J=8.0 Hz, 2H, 2× CH), 7.45 (d, J=8.0 Hz, 2H, 2× CH), 7.61 (s, 1H, CH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=20.7 (CH_3), 115.8 (C), 116.3 (CH), 124.8 (2× CH), 129.6 (2× CH), 133.4 (C), 136.8 (C), 147.9 (C), 158.2 (C), 170.9 (C). HRMS (ESI): m/z calcd for $[C_{12}H_{10}N_2SSe+H]^+$: 294.9802; found: 294.9796.

*4.8.4. 5-(4-Methoxyphenyl)selenolo[3,2-d][1,3]thiazol-2-amine (**6d**).* Yield: 49%; brown solid; mp 201 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=3.76 (s, 3H, CH_3), 6.92 (d, J=9.0 Hz, 2H, 2× CH), 7.10 (s, 2H, NH_2), 7.49 (d, J=9.0 Hz, 2H, 2× CH), 7.53 (s, 1H, CH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=55.2 (OCH_3), 114.4 (2× CH), 115.7 (CH), 126.3 (2× CH), 128.9 (C), 147.7 (C), 154.2 (C), 158.2 (C), 158.8 (C), 170.9 (C). HRMS (ESI): m/z calcd for $[C_{12}H_{10}N_2OSSe+H]^+$: 310.9751; found: 310.9756.

*4.8.5. 5-Phenylthieno[3,2-d][1,3]thiazol-2-amine (**6e**).* Yield: 86%; green solid; mp 186 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=7.25 (s, 2H, NH_2), 7.27 (t, J=7.25 Hz, 1H, CH), 7.39 (t, J=7.25 Hz, 2H, 2× CH), 7.50 (s, 1H, CH), 7.62 (d, J=7.25 Hz, 2H, 2× CH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=114.1 (CH), 117.9 (C), 124.6 (2× CH), 127.3 (CH), 129.1 (2× CH), 134.4 (C), 143.0 (C), 157.4 (C), 170.7 (C). HRMS (ESI): m/z calcd for $[C_{11}H_8N_2S_2+H]^+$: 233.0202; found: 233.0202.

*4.8.6. 5-(4-Chlorophenyl)thieno[3,2-d][1,3]thiazol-2-amine (**6f**).* Yield: 83%; green solid; mp 202 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=7.25 (s, 2H, NH_2), 7.43 (d, J=8.75 Hz, 2H, 2× CH), 7.53 (s, 1H, CH), 7.64 (d, J=8.75 Hz, 2H, 2× CH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=114.7 (CH), 118.5 (C), 126.2 (2× CH), 128.9 (2× CH), 131.6 (C), 133.3 (C), 141.5 (C), 157.4 (C), 170.8 (C). HRMS (ESI): m/z calcd for $[C_{11}H_7ClN_2S_2+H]^+$: 266.9812; found: 266.9810.

*4.8.7. 5-(4-Methoxyphenyl)thieno[3,2-d][1,3]thiazol-2-amine (**6g**).* Yield: 50%; yellow solid; mp 232 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=3.76 (s, 3H, CH_3), 6.95 (d, J=8.75 Hz, 2H, 2× CH), 7.35 (s, 1H, CH), 7.37 (s, 2H, NH_2), 7.54 (d, J=8.75 Hz, 2H, 2× CH). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=55.2 (OCH_3), 112.9 (CH), 114.4 (2× CH), 116.5 (C), 126.1 (2× CH), 127.1 (C), 143.2 (C), 157.3 (C), 158.7 (C), 170.6 (C). HRMS (ESI): m/z calcd for $[C_{12}H_{10}N_2OS_2+H]^+$: 263.0307; found: 263.0299.

*4.8.8. 4,5-Dihydronaphto[1,2-b]thieno[3,2-d][1,3]thiazol-2-amine (**6h**).* Yield: 91%; yellow solid; mp 233 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=2.79 (t, J=7.0 Hz, 2H, CH_2), 2.91 (t, J=7.0 Hz, 2H, CH_2), 7.10–7.29 (m, 4H, 4× CH), 7.30 (s, 2H, NH_2). ^{13}C NMR (62.5 MHz, DMSO-d_6): δ=22.2 (CH_2), 27.9 (CH_2), 116.5 (C), 121.3 (CH), 126.5 (C), 126.8 (CH), 127.0 (C), 128.1 (CH), 131.6 (C), 133.9 (CH), 135.1 (C), 155.6 (C), 170.9 (C). HRMS (ESI): m/z calcd for $[C_{13}H_{10}N_2S_2+H]^+$: 259.0358; found: 259.0354.

*4.8.9. 5-(4-Methoxyphenyl)thieno[3,2-d][1,3]thiazol-2(1H)imine (**6′g**).* Yield: 65%; orange solid; mp 259 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ=3.60 (s, 3H, CH_3), 6.91 (d, J=8.75 Hz, 2H, 2× CH), 7.42 (d, J=8.75 Hz, 2H, 2× CH), 7.68 (s, 1H, CH), 8.19 (s, 1H, NH), 10.18 (s, 1H, NH). IR (KBr): 3369 (NH), 2921 (NH), 1687 (C=N) cm^{-1}.

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