# On the stability of 2-aminoselenophene-3-carboxylates: potential dual-acting selenium-containing allosteric enhancers of $A_1$ adenosine receptor binding†

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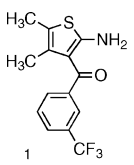
Ethyl-2-amino-4,5,6,7-tetrahydro-1-benzoselenophene-3-carboxylate (**4**), has been prepared as a potential dual-acting selenium-containing allosteric enhancer of adenosine $A_1$A receptor binding utilising a modified Gewald reaction. While preliminary testing indicated that **4** is a superior enhancer of $A_1$AR binding than its thiophene counterpart, its instability under mildly acidic conditions is cause for concern. X-Ray crystallography, together with DFT calculations, provide evidence that the decomposition of **4** involves the ring-opening of selenophenium ion (**12b**) followed by the loss of elemental selenium through a radical chain process.

## Introduction

Adenosine is an important endogenous cardioprotective compound released during ischaemia or hypoxia which interacts with extracellular receptors coupled to secondary messenger systems, including the enzyme adenylate cyclase and potassium and calcium ion channels.[1] Four receptor subtypes ($A_1$, $A_{2A}$, $A_{2B}$ and $A_3$) have been defined based on pharmacological properties and molecular cloning. The first allosteric enhancers acting at the $A_1$ adenosine receptor ($A_1$AR) were identified by Bruns and co-workers in 1990.[2,3] The most effective enhancer in this series was PD81723 (**1**) which proved highly selective for $A_1$ARs, having no major effect on agonist binding at the other adenosine receptor subtypes, $M_2$ muscarinic, $\alpha_2$ adrenergic or γ-opiate receptors. PD81723 has been reported to have a range of cardiovascular effects, including cardioprotective properties *in vivo*.[4] The initial study performed by Parke-Davis established that the amino group and the ketone are necessary for activity[3] and subsequent research has provided detailed information concerning the structure–activity relationships of this class of compound.[5–11] Recently, a number of potent and efficacious $A_1$AR allosteric enhancers possessing ester and amide functionality in the 3-position (*e.g.*, **2**) were identified.[11]



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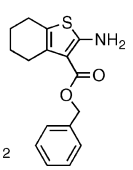

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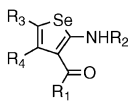

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Selenium is a well-recognized essential trace element in man, with doses of 55–90 μg required to maintain a healthy diet in humans.[12] While selenocysteine is now regarded as the twenty-first essential amino acid,[13] at this point in time there would appear to be no natural biological function of tellurium in mammals.[14] With this in mind, Engman and co-workers demonstrated that various selenium- and tellurium-containing compounds show promising anti-oxidative properties in different model and polymeric systems.[15,16] For example, divalent organoselenides react readily with many types of oxidants, and the resulting tetravalent compounds can be reduced by mild reducing agents. Thus, in the presence of a stoichiometric reductant, these Se-containing materials can act as catalytic antioxidants. Antioxidants have the capacity to protect the heart from reactive oxygen species (ROS) that form in ischaemic tissue and are responsible for the oxidative damage caused during periods of ischaemia and subsequent reperfusion.[17–19]

In a recent review on antioxidant therapy and cardiovascular disorders,[17] it was noted: "that it was doubtful that antioxidants alone could be used for the treatment of cardiovascular disorders. Either the therapeutic agent for a particular condition also possesses antioxidant activity, or a combination of agents is used." With this information in mind, we chose to prepare selenium analogs (*e.g.* **3**) of **1** that act as $A_1$AR allosteric enhancers and also possess antioxidant properties. $A_1$AR enhancers with antioxidant properties will have a dual mechanism of action—they will enhance adenosine's protective effects and limit damage caused by ROS.

## Results and discussion

### Ethyl-2-amino-4,5,6,7-tetrahydro-1-benzoselenophene-3-carboxylate

We began this project by attempting to prepare ethyl 2-amino-4,5,6,7-tetrahydro-1-benzoselenophene-3-carboxylate (**4**) as a representative example of a potential selenium-containing allosteric enhancer. We chose to modify the classic method reported by Gewald[20] for the synthesis of 2-aminothiophenes to the preparation of **4**. An efficient one-pot method for the preparation of a

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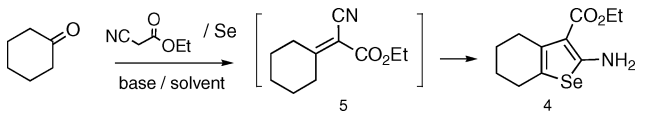
† Electronic supplementary information (ESI) available: B3LYP/6-311G** optimised geometries of **9**, BHandHLYP/6-311G** and BHandHLYP/cc-pVDZ optimised geometries of **12**–**18** as Gaussian archive entries. Table of key bond lengths and Mulliken populations for **9** (Tables S1 and S2). See DOI: 10.1039/b700812k

variety of 2-aminoselenophenes has been reported by Sibor and co-workers.[21] In this "seleno-Gewald" reaction, cyclohexanone, ethyl cyanoacetate and selenium metal are heated in DMF in the presence of triethyl amine. In our hands, under the prescribed conditions,[21] we were unable to isolate any of the expected product (**4**). Variations in reaction time and temperature were also unsuccessful, as was the use of sonication. In all cases, a complex mixture was obtained as evidenced by TLC and $^1$H NMR analysis, or the reaction failed to proceed beyond the intermediate (**5**) produced in the initial Knövenagel condensation step (Scheme 1).‡ We were, after much experimentation, eventually able to isolate **4** in 5% yield as a yellow crystalline solid using DMAP in DMF at 80 °C for 2 hours and employing an aqueous workup that avoided chromatography.




**Scheme 1**

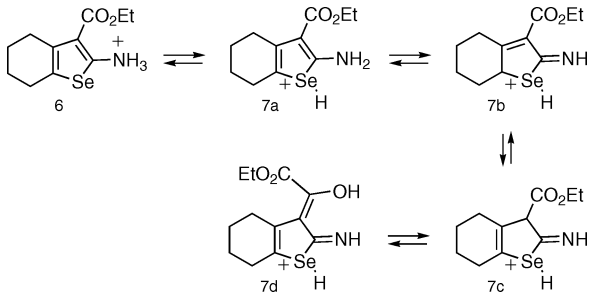
At around this time we became aware of a paper by Adbel-Hafez in which a 2-aminoselenophene was prepared using modified Gewald methodology.[22] Specifically, the use of diethylamine and ethanol appeared to provide good outcomes. When applied to the preparation of **4**, to our delight $^1$H NMR spectroscopy of the crude material suggested a conversion of 20–25%, and **4** could be isolated in 14% yield after recrystallization from ethanol. Nevertheless, despite the apparent low yield, we were rapidly able to prepare multi-gram quantities of **4**.

It quickly became apparent to us that ethyl-2-amino-4,5,6,7-tetrahydro-1-benzoselenophene-3-carboxylate (**4**) was unstable to flash chromatography on silica, and that NMR solutions of **4** in $CDCl_3$ degrade on standing. Indeed, over a period of one week, the complete conversion of **4** to the "intermediate" (**5**) and a black precipitate consistent with elemental selenium, could be observed by $^1$H NMR spectroscopy in $CDCl_3$.§ This degradation could be largely arrested if base-washed $CDCl_3$ was used, suggesting strongly that **4** is sensitive to even trace amounts of acid present in chloroform.

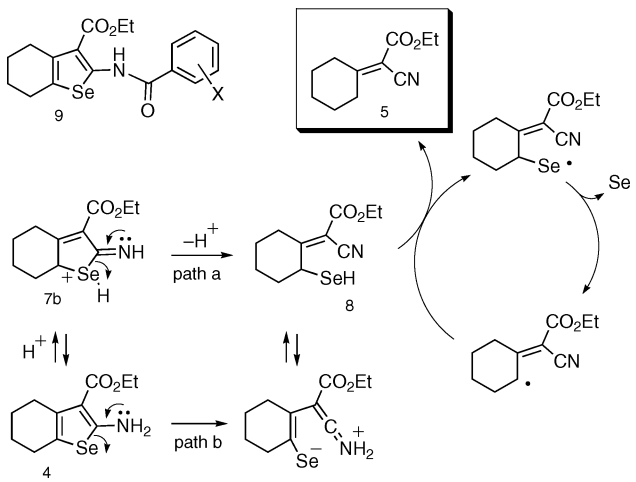
### How do 2-amino-selenophene-3-carboxylates degrade under acidic conditions?

Clearly the instability of selenophene (**4**), and presumably other 2-aminoselenophene-3-carboxylates, under mildly acidic conditions is a cause for concern if these compounds stand any chance of being clinically viable allosteric enhancers of $A_1$ adenosine receptor binding. We therefore set about developing an improved understanding of the stability of **4** with the ultimate aim of fine-tuning the structures of these compounds to meet our requirements.

When considering mechanisms for the decomposition of **4** to **5** under acidic conditions, it seems reasonable to propose that the amine (**4**) becomes protonated, and it is the resultant ion (**6**) that further reacts to afford **5** and elemental selenium. However, despite a strong preference for protonation on nitrogen (**6**), for the "retro-seleno-Gewald" process to occur, the nitrogen lone-pair must be available to facilitate ring opening. This, in turn, requires either an effective concentration of selenophenium ion (**7a**) and further reaction of this ion, or one of its tautomers (**7b–d**) (Scheme 2), or direct ring-opening of the unprotonated selenophene (**4**). For example, tautomer (**7b**) could ring-open to afford **8**, and then go on to lose elemental selenium through a radical chain mechanism to afford "intermediate" (**5**) as shown in Scheme 3 (path a). Of course, it is also possible that the unprotonated amine (**4**) reacts directly *via* "path b" to afford **8** through tautomerism mediated by the acidic environment (Scheme 3).




**Scheme 2**




**Scheme 3**

In order to probe the importance of "path b", we chose to examine the effect of substituent (X) on the structure of a series of 2-arylamidoselenophene-3-carboxylates (**9**), prepared by simple treatment of the amine (**4**) with the appropriate acid chloride in dichloromethane in the presence of DMAP and isolated in 91% (X = *p*-$NO_2$), 99% (*p*-Cl), 94% (H), 100% (*m*-Cl) and 86% (*m*-OMe). Despite numerous attempts, we were unable to isolate any ethyl-2-(4-(dimethylamino)benzamido)-4,5,6,7-tetrahydrobenzo-1-selenophene-3-carboxylate (**9**, X = *p*-$NMe_2$) and the complex mixture that resulted was unable to be separated by chromatography.

‡ It should be noted here that, in our hands, the "classic" Gewald reaction involving sulfur provided the expected 2-aminothiophene in quantitative yield under conditions in which the temperature was kept below 100 °C.

§ Over a period of one week, the signals corresponding to the ethyl protons in **4**, at $\delta$ 1.33 and 4.24 are slowly transformed into those corresponding to the equivalent protons in **5**, at $\delta$ 1.23 and 4.15.

Of the five amides (**9**) prepared in good-to-excellent yield, only two (X = H, *p*-$NO_2$) provided crystals suitable for X-ray crystallography and these structures are reproduced in Fig 1.¶

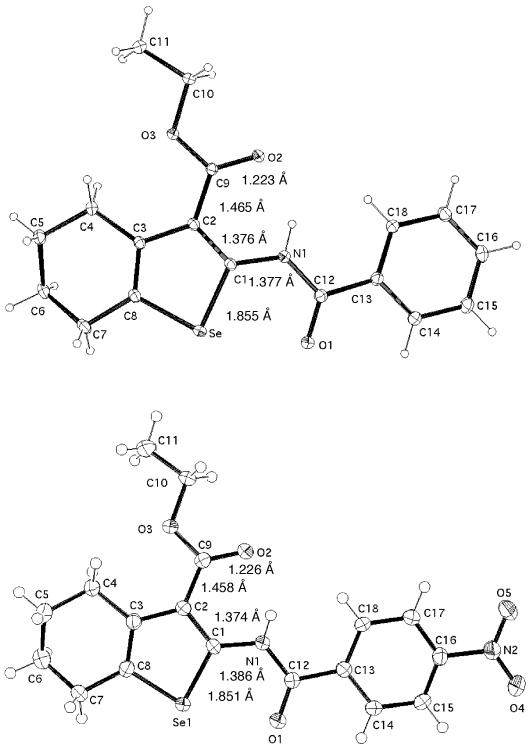



**Fig. 1** Ortep diagrams of the X-ray crystal structures of selenophene-3-carboxylates **9**; X = H (above); X = *p*-$NO_2$ (below) with selected data. The cyclohexene ring of **9**; X = H is disordered with two half chair conformations existing in the crystal, the disordered atoms C5′ and C6′ have been omitted for clarity. Ellipsoids calculated at 20% probability level.

Clearly, there is little difference between the key structural features in the absence of a substituent (X = H) and with the inclusion of a strong withdrawing group (X = *p*-$NO_2$). For example, there is no significant change in the key C–Se (1.85 *vs* 1.86 Å) and C–N (1.38 *vs* 1.39Å) bonds between compounds, however, with the limited X-ray data available, it is hard to draw firm conclusions.

In order to provide further structural data, we turned to density functional (DFT) calculations. After some exploration involving basis set alteration, we eventually chose to use the B3LYP/6–311G** method because it provided close agreement between calculated and computational data for the two compounds that we had X-ray data for.

Key computational data are summarized in Fig 2, while full data that include optimized geometries and energies are provided in the ESI.† The salient feature of these calculations is that there is no apparent effect or trend on either key C–Se or C–N bond lengths or bond populations. For example, when substituted with a *p*-$NO_2$ group, these distances are calculated to be 1.877 and 1.376 Å, respectively, in good agreement with the experimentally determined numbers. Bond populations of 0.344 (C–Se) and 0.365

¶ CCDC reference numbers 633017 and 633018. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b700812k

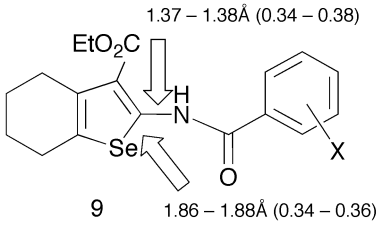
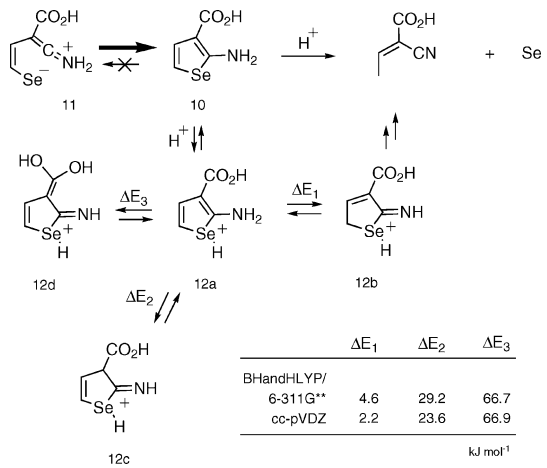



**Fig. 2** Key B3LYP/6-311G** calculated structural parameters for substituted amides (**9**). Mulliken population data in parentheses.

(C–N) were also determined. At the other extreme, the *p*-($NMe_2$) substituted system was calculated to have values of 1.880 and 1.370 Å for these same two parameters, and bond populations of 0.345 (C–Se) and 0.375 (C–N).

### Modelling the acid-catalysed "retro-seleno-Gewald" reaction

In order to provide a clear mechanistic picture for the chemistry involved in the "retro-seleno-Gewald" reaction, we next turned to modelling the reaction profiles of both pathways depicted in Scheme 3 using molecular orbital techniques. With the aim of achieving a good qualitative understanding of this chemistry in general, we chose to examine the ring-opening of the simplified model system 2-aminoselenophene-3-carboxylic acid (**10**) (Scheme 4).




| | ΔE1 | ΔE2 | ΔE3 |
|---|---|---|---|
| BHandHLYP/ | | | |
| 6-311G** | 4.6 | 29.2 | 66.7 |
| cc-pVDZ | 2.2 | 23.6 | 66.9 |

kJ mol$^{-1}$

**Scheme 4**

Work within our group[23] and others[24,25] has shown that the B3LYP method can be unreliable when dealing with the electronic structures and energies of open-shell systems, while BHandHLYP performs considerably better.[25] With this in mind, and with past experience,[23] we settled on BHandHLYP/6-311G** and BHandHLYP/cc-pVDZ as the methods of choice in this study.†

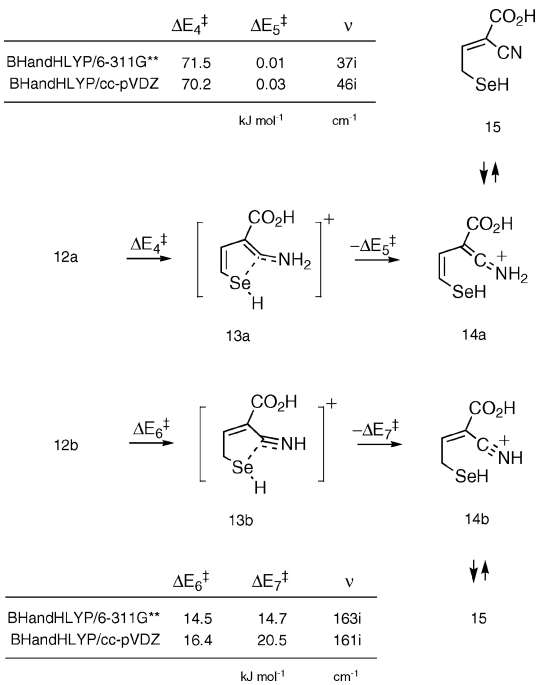
At all levels of theory, extensive searching of the $C_5H_5NO_2Se$ potential energy surface failed to locate the ring-opened structure (**11**). Indeed, all attempts to locate this stationary point resulted in spontaneous ring-closure to afford selenophene (**10**) suggesting, that at least in the gas phase, "path b" in Scheme 3 is unlikely to be important. This outcome is also consistent with the X-ray and computed structural data for amides (**9**) that suggest the selenium atom is insensitive to changes in the electron density on nitrogen

in the neutral molecule and is therefore unlikely to act readily as a leaving group.

As already alluded to, there are four possibly important tautomeric forms of the selenophenium ion (**12**). Not unexpectedly, the aromatic system (**12a**) is calculated to be the most favourable. However, these calculations also suggest that **12b** is only 2–5 kJ mol$^{-1}$ less favourable than **12a**, with the remaining ions (**12c**–**d**) of significantly higher energy (Scheme 4).†

Searching of the potential energy surface located transition states (**13a**, **13b**) for the ring opening of selenophenium ions (**12a**, **12b**) to afford selenols (**14a**, **14b**) (Scheme 5). It is interesting to note that while **13b** was found to lie about 15 kJ mol$^{-1}$ above the reactant (**12b**) and about 15–20 kJ mol$^{-1}$ above the product (**14b**), depending on the basis set used, **13a** was found to lie about 70 kJ mol$^{-1}$ above the reactants and less than 0.05 kJ mol$^{-1}$ above selenol (**14a**) suggesting that, similar to **10**, ion (**14a**) (almost) spontaneously ring closes to afford aromatic structure (**12a**).




**Scheme 5**

The calculated transition states (**13a**, **13b**) are displayed in Fig 3.† Consistent with the thermodynamic data, **13b** is calculated to be significantly "earlier" (in the direction of ring-opening) than **13a**, with BHandHLYP/6-311G** calculated C–Se separations of 2.534 and 2.948 Å, respectively, and small imaginary frequencies (37i, 46i) corresponding to the transition state vector. Indeed, the 2.948Å C–Se separation in **13a** is only marginally smaller than the value of 2.999 Å for the analogous distance in the product (**14a**). It is, therefore, very unlikely that tautomer (**12a**) is of direct importance in the overall ring-opening chemistry, and that the most likely pathway involves ion (**12b**). In addition, with similar calculated energy barriers for the forward and reverse reactions, it is very likely that the ring-opening of **12b** is an equilibrium process, with rapid deprotonation affording the selenol (**15**).

Selenols (*e.g.* **8**, **15**) are excellent hydrogen atom donors in free radical chemistry, reacting with near diffusion-controlled rate

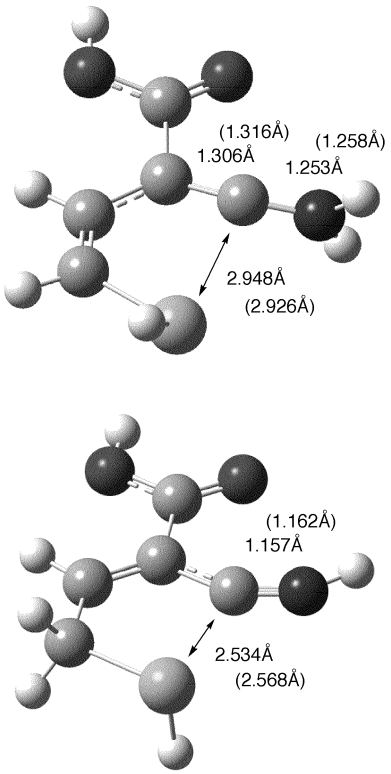
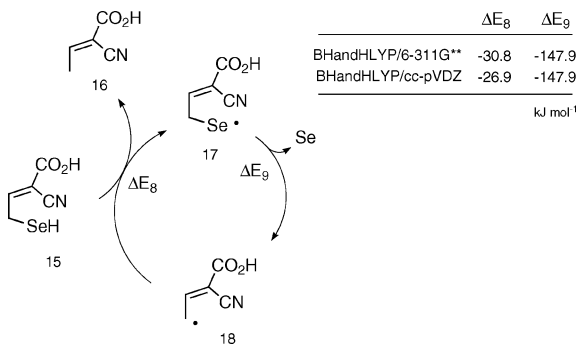



**Fig. 3** BHandHLYP/6-311G** structures of transition states **13a** (above) and **13b** (below). (BHandHLYP/cc-pVDZ data in parentheses).

constants.[26] When activated, selanyl radicals (RSe·) are able to afford alkyl radicals (R·) and elemental selenium, as suggested in Scheme 3 and Scheme 6. However, for this chain process to be viable, the participating steps must be energetically favourable. We were pleased to discover that BHandHLYP/6-311G** calculations predict that the hydrogen transfer process from **15** to afford the "Knövenagel intermediate" (**16**) is exothermic ($\Delta E_8$) by about 30 kJ mol$^{-1}$, while the loss of selenium from the intermediate selanyl radical (**17**) is exothermic ($\Delta E_9$) to the tune of some 150 kJ mol$^{-1}$. Similar predictions are made using cc-pVDZ.




**Scheme 6**

## Conclusions

We have prepared ethyl-2-amino-4,5,6,7-tetrahydro-1-benzoselenophene-3-carboxylate (**4**) as a representative example of a

selenium-containing allosteric enhancer of adenosine $A_1$AR. Unfortunately, this compound proved to be unstable in mildly acid media. X-Ray structural data and DFT calculations provide strong evidence that the decomposition mechanism involves the selenophenium tautomer (**12b**) which undergoes ring-opening followed by loss of elemental selenium through a radical chain mechanism.

Finally, it is worth noting that, in preliminary screening, **4**, with an allosteric enhancement (AE) score[27] of 64% is significantly more potent allosteric enhancer of $A_1$AR than its thiophene counterpart (3.5%),[27] and additionally provides antioxidant protection against peroxyl radicals in cell lysis assays.[28]

## Experimental

Melting points are uncorrected. Unless otherwise stated, $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded in $CDCl_3$ on a Varian unity 400 spectrometer. For proton spectra, the residual peak of $CHCl_3$ was used as the internal reference (7.26 ppm) while the central peak of $CDCl_3$ (77.0 ppm) was used as the reference for carbon spectra. $^{77}$Se NMR chemical shifts are given in ppm relative to externally-referenced diphenyl diselenide ($\delta$ 464). EI mass spectra were recorded at 70 eV. $M^+$ Ions are given for $^{80}$Se. Tetrahydrofuran and diethyl ether were distilled under nitrogen from sodium/benzophenone. Elemental analyses were performed by Chemical and Micro Analytical services Pty. Ltd, Geelong, Victoria, Australia.

### Ethyl-2-amino-4,5,6,7-tetrahydro-1-benzoselenophene-3-carboxylate (4)[21]

Diethylamine (100 mL, 960 mmol) was added to a stirring suspension of cyclohexanone (20 mL, 193 mmol), ethyl cyanoacetate (20.5 mL, 192 mmol) and selenium powder (15.2 g, 193 mmol) in ethanol (100 mL). The suspension was stirred at reflux overnight, filtered through a plug of celite to remove unreacted selenium then tipped onto crushed ice. After 3 days, some of the oily emulsion had crystallized. The yellow needles were collected *via* filtration and washed with ethyl acetate to afford the title compound (7.56 g, 16 mmol, 14%): mp 141.2–141.3 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.33, (t, $J$ = 7 Hz, 3 H), 1.76 (m, 4 H), 2.59 (m, 2 H), 2.69 (m, 2 H), 4.24 (q, $J$ = 7 Hz, 2 H), 6.40 (bs, 2 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.4, 22.8, 23.6, 26.9, 28.7, 59.3, 107.2, 121.5, 134.1, 166.6, 166.8; $^{77}$Se NMR ($CDCl_3$) $\delta$ 544.5; IR: $\upsilon$ = 3392, 3289, 1633, 1579, 1475, 1399, 1376, 1289, 1260 cm$^{-1}$; MS $m/z$ $(M + H)^+$ 274.0; HRMS calcd for $C_{11}H_{15}NO_2Se$ $[M + Na]^+$ 296.0168, found 296.0168; anal. calcd for $C_{11}H_{15}NO_2Se$: C, 48.5; H 5.6; N, 5.2%. Found C, 48.6; H, 5.5; N, 5.2%.

### General procedure for the synthesis of ethyl-2-arylamido-4,5,6,7-tetrahydrobenzo-1-selenophene-3-carboxylates (9)

DMAP (0.330 g, 2.6 mmol) was added to a solution of crude ethyl-2-amino-4,5,6,7-tetrahydro-1-benzoselenophene-3-carboxylate (0.512 g, 2.2 mmol) and the appropriate acid chloride (2.4 mmol) in dichloromethane (20 mL) and the solution stirred overnight. Water (20 mL) was added and the aqueous phase extracted with dichloromethane (3 × 30 mL). The combined organic phases were washed with 10% HCl (30 mL), water (30 mL) and sat. $NaHCO_3$ (30 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to afford the crude title compound as a solid. Recrystallization from EtOAc afforded the pure amide.

**Ethyl-2-[(4-nitrobenzoyl)amino]-4,5,6,7-tetrahydro-1-benzoselenophene-3-carboxylate (9, X = *p*-NO$_2$).** Product isolated in 91% yield. Mp 192–193 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.42 (t, $J$ = 6 Hz, 3 H), 1.82 (m, 4 H), 2.80 (m, 4 H), 4.38 (q, $J$ = 6 Hz, 2 H), 8.18 (d, $J$ = 6 Hz, 2 H), 8.37 (d, $J$ = 6 Hz, 2 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.2, 22.8, 23.1, 26.6, 28.0, 60.9, 115.0, 124.0, 128.5, 132.5, 133.6, 137.8, 150.0, 151.0, 161.2, 167.7; $^{77}$Se NMR ($CDCl_3$) $\delta$ 619.1; IR: $\upsilon$ = 3238, 1690, 1657, 1560, 1538, 1343, 1265, 1208 cm$^{-1}$; $m/z$ $(M + H)^+$ 423.1; HRMS expected $m/z$ $[M + Na]^+$ 445.0279, found $m/z$ $[M + Na]^+$ 445.0288.

**Ethyl-2-[(4-chlorobenzoyl)amino]-4,5,6,7-tetrahydro-1-benzoselenophene-3-carboxylate (9, X = *p*-Cl).** Product isolated in 99% yield. Mp 170–172.5 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.41 (t, $J$ = 7 Hz, 3 H), 1.81 (m, 4 H), 2.80 (m, 4 H), 4.37 (q, $J$ = 7 Hz, 2 H), 7.51 (dd, $J$ = 8.4 Hz, 2.8 Hz 2 H), 7.97 (dd, $J$ = 8.4 Hz, 2.8 Hz, 2 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.3, 22.9, 23.2, 26.5, 28.0, 60.9, 114.2, 127.0, 130.8, 132.3, 132.3, 132.8, 138.8, 151.6, 162.5, 167.6;$^{77}$Se NMR ($CDCl_3$) $\delta$ 616.1; IR: $\upsilon$ = 2939, 1790, 1722, 1647, 1534, 1374, 1216 cm$^{-1}$; $m/z$ $(M + H)^+$ 423.1; $m/z$ $(M + H)^+$ 412.2; HRMS expected $m/z$ $[M + Na]^+$ 434.0038, found $m/z$ $[M + Na]^+$ 434.0019.

**Ethyl-2-(benzoylamino)-4,5,6,7-tetrahydro-1-benzoselenophene-3-carboxylate (9, X = H).** Product isolated in 94% yield. Mp 176.7–176.8 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.41 (t, $J$ = 8 Hz, 3H), 1.80 (m, 4 H), 2.82 (m, 4 H), 4.37 (q, $J$ = 8 Hz, 2 H), 7.52 (m, 3 H), 8.02 (d, $J$ = 8 Hz, 2 H), 12.81 (bs, 1 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.3, 22.9, 25.2, 26.5, 28.1, 60.6, 114.0, 127.4, 128.9, 132.3, 132.4, 132.4, 132.5, 151.9, 163.6, 167.5; $^{77}$Se NMR ($CDCl_3$) $\delta$ 615.4; IR: $\upsilon$ = 2972, 1739, 1535, 1366, 1217 cm$^{-1}$; $m/z$ $(M + H)^+$ 423.1; $m/z$ $(M + H)^+$ 378.3. Anal. calcd for $C_{18}H_{19}NO_3Se$: C, 57.5; H 5.1; N, 3.7%. Found C, 57.7; H, 5.3; N, 4.0%.

**Ethyl-2-[(3-chlorobenzoyl)amino]-4,5,6,7-tetrahydro-1-benzoselenophene-3-carboxylate (9, X = *m*-Cl).** Product isolated in 100% yield. Mp 173–175 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.41 (t, $J$ = 7.2 Hz, 3 H), 1.80 (m, 4 H), 2.79 (m, 4 H), 4.37 (q, $J$ = 72 Hz, 2 H), 7.45 (dd, $J$ = 7.6 Hz, 1 H), 7.54 (dd, $J$ = 8.4 Hz, 2 Hz, 1 H), 7.86 (d, $J$ = 8 Hz, 1 H), 8.02 (dd, $J$ = 2 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.5, 23.1, 23.5, 26.8, 28.3, 61.0, 114.7, 125.3, 128.2, 130.4, 132.6, 132.7, 133.2, 134.5, 135.5, 151.7, 162.5, 167.8; $^{77}$Se NMR ($CDCl_3$) $\delta$ 622.7; IR: $\nu$ = 3226, 2940, 1650, 1561, 1531, 1412, 1247, 1211 cm$^{-1}$; $m/z$ $(M + H)^+$ 412.3; HRMS expected $m/z$ $[M + Na]^+$ 434.0038, found $m/z$ $[M + Na]^+$ 434.0051.

**Ethyl 2-[(3-methoxybenzoyl)amino]-4,5,6,7-tetrahydro-1-benzoselenophene-3-carboxylate (9, X = *m*-OMe).** Product isolated in 86% yield. Mp 166–168 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.38 (t, $J$ = 7.2 Hz, 3 H), 1.79 (m, 4 H), 2.77 (m, 4 H), 3.89 (s, 3 H), 4.34 (q, $J$ = 7.2 Hz, 2 H), 7.09 (dd, $J$ = 8 Hz, 2.8 Hz, 1 H), 7.40 (dd, $J$ = 8 Hz, 8 Hz, 1 H), 7.53 (d, $J$ = 8 Hz, 1 H), 7.59 (dd, $J$ = 2.8 Hz, 2.8 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.2, 22.8, 23.2, 26.5, 28.0, 55.3, 60.5, 112.5, 114.0, 118.8, 118.9, 129.8, 132.2, 132.5, 133.7, 151.7, 159.9, 163.3, 167.3; $^{77}$Se NMR ($CDCl_3$) $\delta$ 615.1; IR: $\nu$ = 3231, 2932, 1648, 1528, 1275, 1231, 1201 cm$^{-1}$; $m/z$ $(M + H)^+$ 408.3; HRMS expected $m/z$ $[M + Na]^+$ 430.0533, found $m/z$ $[M + Na]^+$ 430.0512.

### Crystallography¶

Intensity data were collected with a Bruker SMART Apex CCD detector using Mo Kα radiation (graphite crystal monochromator $\lambda = 0.71073$). Data were reduced using the program SAINT.[29] The structure was solved by direct methods and difference Fourier synthesis using the SHELX suite of programs[30] as implemented with the WINGX software.[31]

Crystal data for **9** (X = H). $C_{18}H_{19}NO_3Se$, $M = 376.30$, $T = 130.0(2)$ K, $\lambda = 0.71069$, monoclinic, space group $P2(1)/c$, $a = 8.0161(9)$, $b = 10.634(1)$, $c = 18.746(2)$, Å, $V = 1594.9(3)$ Å$^3$, $Z = 4$, $D_c = 1.506$ mg M$^{-3}$ $\mu$(Mo Kα) = 2.276 mm$^{-1}$, $F(000) = 768$, crystal size 0.50 × 0.50 × 0.50 mm. 9581 reflections measured, 3629 independent reflections ($R_{int} = 0.028$) the final $R$ was 0.0304 [$I > 2\sigma(I)$] and $wR(F^2)$ was 0.0831 (all data).

Crystal data for **9** (X = *p*-$NO_2$). $C_{18}H_{18}N_2O_5Se$, $M = 421.30$, $T = 130(2)$ K, $\lambda = 0.71069$, triclinic, space group $P$-1, $a = 9.6394(10)$, $b = 10.0481(11)$, $c = 10.1555(11)$, Å, $V = 840.57(16)$ Å$^3$, $Z = 2$, $D_c = 1.665$ mg M$^{-3}$ $\mu$(Mo Kα) 2.267 mm$^{-1}$, $F(000) = 428$, crystal size 0.40 × 0.30 × 0.20 mm. 5132 reflections measured, 3646 independent reflections ($R_{int} = 0.0178$) the final $R$ was 0.0342 [$I > 2\sigma(I)$] and $wR(F^2)$ was 0.0897 (all data).

### Computational chemistry

Molecular orbital calculations were carried out using the Gaussian 03 program.[32] Geometry optimisations were performed using standard gradient techniques at the levels of theory discussed in the text. Optimised geometries are summarised in the ESI.†

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