Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 473

www.rsc.org/obc

PAPER

Tandem free-radical addition/substitution chemistry and its application to the preparation of novel AT_1 receptor antagonists†‡

Maree K. Staples,[a,b] Rebecca L. Grange,[a,b] James A. Angus,[a,c] James Ziogas,[a,c] Nichole P. H. Tan,[a,b] Michelle K. Taylor[a,b,d] and Carl H. Schiesser*[a,b]

Received 13th August 2010, Accepted 21st September 2010
DOI: 10.1039/c0ob00573h

Benzothiophene and benzoselenophene analogues of the thiophene-containing antihypertensives milfasartan and eprosartan were prepared and tested for AT_1 receptor antagonist properties. While the sulfur-containing systems were prepared following existing methodology, the selenium-containing analogues required the development of novel, tandem free-radical chemistry involving addition of aryl radicals to alkynes, followed by intramolecular homolytic substitution at the higher heteroatom. All four compounds prepared proved to be excellent AT_1 receptor antagonists, with pK_B estimates of 7.2–9.5.

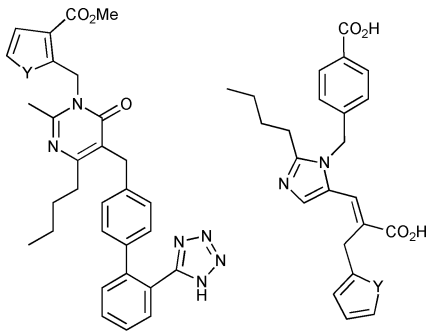
Introduction

Persistently high blood pressure (hypertension) is a major risk factor for many serious illnesses including stroke, myocardial infarction, heart failure and renal failure.[1] Hypertension is now considered to be the world's third leading cause of death.[1] As such, there is some urgency in gaining a further understanding of the causes of, and chemical mechanisms involved in hypertension, as well as the development of new and improved treatments.

Current therapeutic intervention for the treatment of hypertension mostly involves drugs that interact with the *Renin–Angiotensin Cascade*. *Sartans*, for example, are a family of drugs that selectively act on the Angiotensin II, subtype 1 (AT_1) receptor thereby reducing blood pressure.[2]

Milfasartan[3] (**1**; Y = S) and eprosartan[4–7] (**2**; Y = S) are thiophene-containing *sartans*; milfasartan reached Phase I clinical trials, while eprosartan is on the market in many countries.[4,8,9]

We recently reported that the selenium-containing analogues of these compounds (**1**, **2**; Y = Se), as well as *selenofonsartan* analogues, are at least as potent as the parent in their ability to bind to the AT_1 receptor in Chinese Hamster Ovary (CHO) cell assays.[10,11] Given the outcome of our previous work, and as part of an ongoing study, were were curious about the effect that size of the chalcogen-containing heterocyclic unit may have on milfasartan and eprosartan potency.



1 **2**

We now report the preparation and preliminary pharmacological testing of benzothiophene and benzoselenophene analogues (**3**, **4**) of milfasartan and eprosartan.

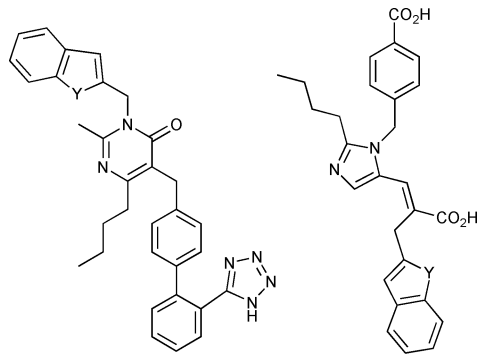
Results and discussion

The milfasartan analogues were prepared by adapting the general protocol decribed by Salimbeni,[3] while the eprosartan analogues were prepared by adapting the general protocol of Keenan.[7] To that end, the sulfur-containing sartans (**3**, **4**; Y = S) required the preparation of the known benzothiophenes (**5**, **6**; Y = S),[12,13] while the selenium-containing sartans required the preparation of the novel benzoselenophenes (**5**, **6**; Y = Se).

[a]*ARC Centre of Excellence for Free Radical Chemistry and Biotechnology, Bio21 Molecular Science and Biotechnology Institute, The University of Melbourne, The University of Melbourne, Victoria, 3010, Australia*
[b]*School of Chemistry, Bio21 Molecular Science and Biotechnology Institute, The University of Melbourne, Victoria, 3010, Australia. E-mail: carlhs@unimelb.edu.au; Fax: +61 3 9347 8189; Tel: +61 3 8344 2432*
[c]*Department of Pharmacology, The University of Melbourne, Victoria, 3010, Australia*
[d]*Current address: Division of Chemistry, School of Science and Technology, The University of New England, Armidale, NSW, 2351, Australia*

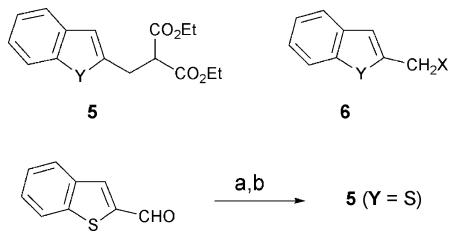
† Dedicated to Professor Athel Beckwith and in recognition of his many contributions to free radical chemistry; he was an exceptional scientist, a gentleman and a scholar. The world has lost a scientific treasure.

‡ Electronic supplementary information (ESI) available: ^1H and ^{13}C NMR spectra of compounds **3** (Y = Se), **4** (Y = S), **4** (Y = Se), **5** (Y = Se), **9**, **10**, **12** (Y = Se), **13** (Y = Se). See DOI: 10.1039/c0ob00573h



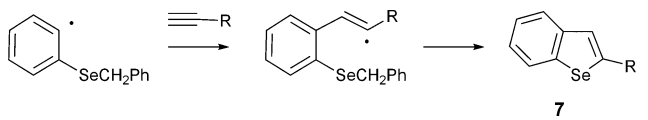
3 4

Malonate (**5**; Y = S) was prepared from benzo[*b*]thiophene-2-carboxaldehyde[14] in 54% yield by condensation with diethyl malonate with subsequent reduction with sodium borohydride (Scheme 1),[7] while 2-(bromomethyl)benzo[b]thiophene (**6**; Y = S, X = Br) was prepared in 91% yield by NBS bromination of commercially-available 2-methylbenzo[b]thiophene.



Scheme 1 *Reagents and conditions:* (a) Diethyl malonate, piperidine, benzoic acid, cyclohexane, reflux; (b) $NaBH_4$, EtOH, r.t., 54% over two steps.

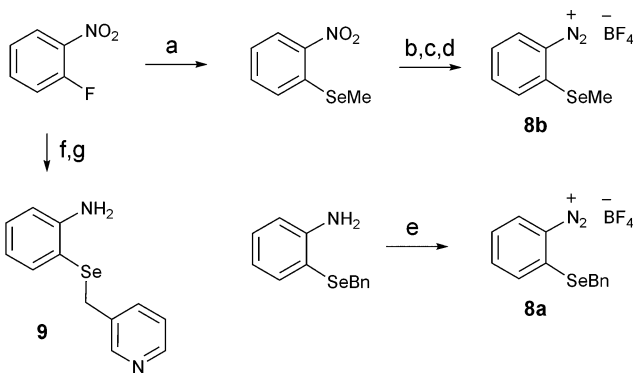
The analogous selenium-containing starting materials (**5**, **6**; Y = Se) required the development of a novel approach for the construction of the core heterocyclic unit and we recognised that ethyl benzo[*b*]selenophene-2-carboxylate (**7**; R = CO_2Et) would be a key intermediate for the construction of both compounds. Ester (**7**; R = CO_2Et) and related compounds have been prepared previously,[15] but the methodology reported is somewhat tedious and was therefore not appealing to us. With our background in free-radical chemistry, especially involving the construction of selenium-containing rings,[16] including tandem addition/substitution sequences,[17,18] we began to explore the tandem addition of aryl radicals to alkynes as synthetically viable methodology for the construction of the required heterocyclic ring system (**7**) (Scheme 2).



Scheme 2

Developing the tandem chemistry

Inspired by the work of Zanardi and coworkers,[19] our attention turned to the use of aryldiazonium tetrafluoroborates such as **8** for the generation of aryl radicals catalysed by iron(II) salts. While our previous work made extensive use of the benzylseleno group for radical ring-closure at selenium, we rapidly discovered that we were unable to prepare 2-(benzylseleno)phenyldiazonium tetrafluoroborate (**8a**) under standard (aqueous) conditions due to solubility problems. We eventually prepared **8a** under anhydrous conditions from 2-(benzylseleno)aniline[20] using *in situ* generated nitrosyl fluoride as described by Doyle and Bryker (Scheme 3),[21] however this tetrafluoroborate salt, when isolated, proved to be unstable, decomposing to a bright red liquid within 5 min at 0 °C. Attempted immediate use of **8a** in any reactions of interest resulted in a red solution and a complex mixture of products as evidenced by TLC.

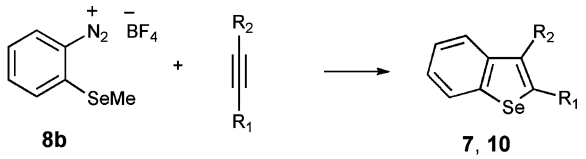


Scheme 3 *Reagents and conditions*: (a) Me_2Se_2, $NaBH_4$, EtOH, r.t., 90%; (b) $Na_2S_2O_3$, $EtOH/H_2O$, reflux, 31%; (c) $NaNO_2$; (d) HBF_4, 10% H_2SO_4, 0 °C, quantitative; (e) *t*-BuONO, $BF_3{\cdot}OEt_2$, −15 to 5 °C (unstable); (f) 3,3′-dipicolyl diselenide, $NaBH_4$, EtOH, r.t., 72%; (g) $Na_2S_2O_4$, EtOH, reflux, 40%.

In order to improve solubility, we also attempted to prepared a pyridyl-substituted salt, however, diazotization of 2-(pyridin-3-ylmethylseleno)aniline **9** under standard conditions did not provide the required diazonium salt as a precipitate, presumably because the salt is too soluble under the acidic reaction conditions.

Given that the key homolytic substitution step (Scheme 2) involves a reactive vinyl radical, we reasoned that while not ideal, the required reaction should proceed even with a methyl radical as leaving group because of the required disparity of reactivities between attacking and leaving radicals in the S_Hi step. To that end, **8b** was prepared by the reaction of 2-fluoronitrobenzene with sodium methylselenoate (formed by the reaction of dimethyl diselenide with sodium borohydride in ethanol) followed by reduction and diazotisation under standard conditions (Scheme 3).

With diazonium salt **8b** in hand, reactions with alkynes of varying electronic demand were attempted. To our delight, alkynes bearing electron-withdrawing groups provided benzo[*b*]selenophenes (**7**, **10**) in 19–50% conversion (Scheme 4). In the absence of electron-withdrawing substituents on the alkyne, only poor yields were obtained (entries 3, 4), while the more sterically demanding TMS group resulted in an absence of reaction (entry 5). The "one-pot" tandem sequence described herein represents a significant improvement over previous methods for the preparation of benzo[*b*]selenophenes bearing electron-withdrawing groups at positions 2 and 3, especially for the preparation of the required ester (**7**; R = CO_2Et).



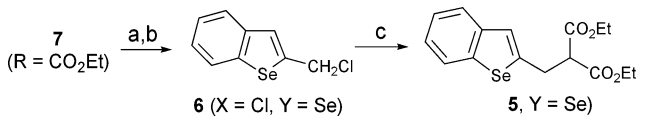
Entry	Product	R_1	R_2	Conversion[a,b] (%)
1	**7**	Ph	H	33 (30)
2	**7**	CO_2Et	H	50 (29)
3	**7**	CH_2OH	H	9
4	**7**	CH_2NH_2	H	7
5	**7**	TMS	H	0
6	**10**	CO_2Et	CO_2Et	19 (15)

[a]Conversions determined from ^{1}H NMR spectra of crude reaction mixtures. [b]Isolated yields in parentheses.

Scheme 4 *Reagents and conditions*: $FeSO_4$, $DMSO/H_2O$, 15 min., r.t.

It should be noted that in our hands yields were not improved through the use of additional $FeSO_4$ or copper powder in acetone,[19] and increasing the amount of diazonium salt led to more complex reaction mixtures.

With convenient access to selenophene (**7**; R = CO_2Et), it was then reduced by the action of DiBALH and the resultant alcohol converted to the corresponding chloride (**6**; X = Cl, Y = Se) by reaction with thionyl chloride (Scheme 5). Subsequent treatment with diethyl malonate as described by Kaiser afforded **5** (Y = Se) in 32% yield.[12]



Scheme 5 *Reagents and conditions*: (a) DiBALH, Et_2O, –78 °C, 75%; (b) $SOCl_2$, dioxane, reflux, 68%; (c) Diethyl malonate, NaH, DMF, 32%.

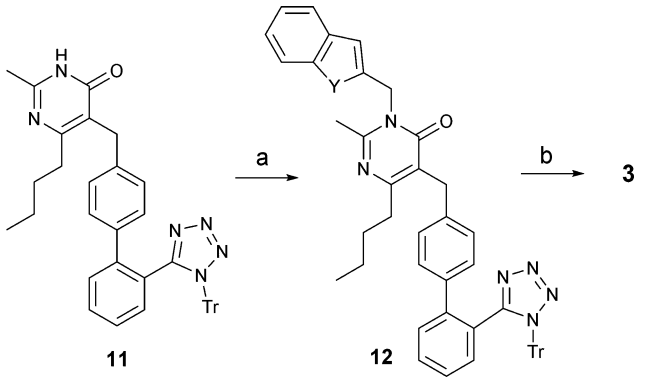
Synthesis of the novel sartan analogues

With key materials (**5**, **6**) in hand, the route to the milfasartan analogues (**3**) involved coupling of **6** to the common trityl-protected biphenyl "scaffold" (**11**) following the procedure of Salimbeni;[3] subsequent deprotection afforded sartans **3** in acceptable yield (Scheme 6).

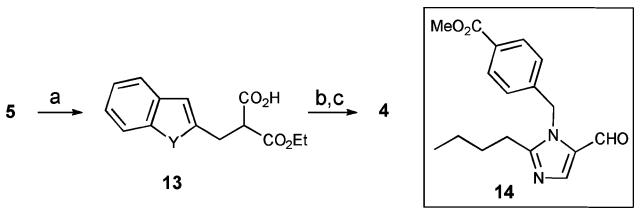
The eprosartan analogues were prepared by conversion of the diesters (**5**) to the corresponding half-acids (**13**). Condensation with the formylimidazole (**14**)[6] followed by saponification afforded the target compounds (**4**) in 29–51% yield (Scheme 7).

Preliminary pharmacology

Chinese hamster ovary cells stably expressing the rat AT_{1a} receptor were used to assess the receptor antagonist properties of the sartan analogues prepared in this study.[22] In initial experiments, the ability of 30 nM of compounds **3** and **4** to inhibit angiotensin II mediated increases in intracellular calcium was compared to the parent sartans **1**, **2** (Y = S). Fig. 1 shows the right-ward shift of the angiotensin concentration response curve for milfasartan derivative **3** (Se) from a which a pK_B estimate of 9.5 was obtained.



Scheme 6 *Reagents and conditions*: (a) 6, NaH, LiBr, DMF, 0 °C r.t., 57–72%; (b) MeOH, reflux, 89–96%.



Scheme 7 *Reagents and conditions*: (a) KOH, EtOH, r.t. 65–88%; (b) **14**, piperidine, benzoic acid, cyclohexane/toluene, reflux; (c) NaOH, EtOH, H_2O, r.t. 29–51% (2 steps).

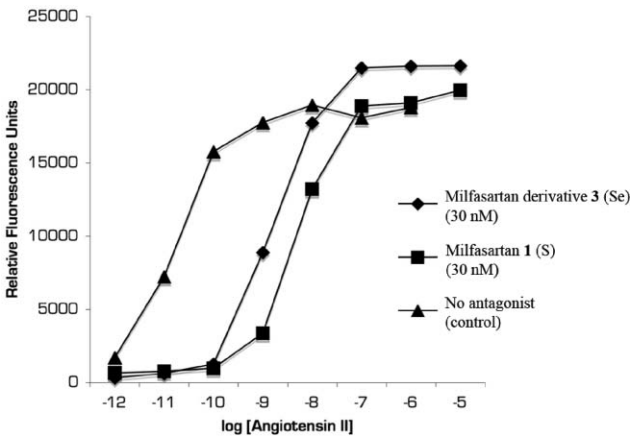


Fig. 1 Inhibition of angiotensin II-evoked increases in intracellular calcium in CHO cells stably expressing the AT_{1a} receptor by milfasasrtan derivation (Se) against the parent milfasartan **1** (S).

Similar data were obtained for the other sartans in this study and the pK_B estimates are summarized in Table 1.

Inspection of Table 1 reveals that in each series of sartans, increasing the size of the heterocyclic unit serves to lower the ability of the compound to bind to the AT_1 receptor (entries 1 *versus* 2 and 4 *versus* 5). However, in moving from sulfur to selenium (entries 3 and 6), binding affinity appears to be somewhat restored. While the origins of this phenomenon are not clear at this point, it would appear that, at least for benzothiophene and benzoselenophene analogues of milfasartan and eprosartan, incorporation of selenium into the heterocyclic unit appears to engender an increased receptor binding affinity over the sulfur–containing analogue.

Table 1 pKB Estimates of the sartans (**3**, **4**) prepared in this study as compared with the parent compounds milfasartan and eprosartan

Entry	Sartan	pK_B estimate[a]
1	Milfasartan (**1**, Y = S)	9.5
2	**3** (Y = S)	7.9
3	**3** (Y = Se)	9.5
4	Eprosartan (**2**, Y = S)	8.4
5	**4** (Y = S)	7.2
6	**4** (Y = Se)	8.1

[a] See text.

Conclusions

Benzothiophene and benzoselenophene derivatives (**3**, **4**) of milfasartan and eprosartan were prepared and assessed for their AT_1 receptor antagonist properties. The selenium–containing analogues required the development of novel, tandem, homolytic addition/substitution chemistry for construction of the benzoselenophene moiety and this was achieved through the use of diazonium salt chemistry. All sartan derivatives prepared proved to be excellent AT_1 receptor antagonists, with pK_B estimates of 7.2–9.5. While the benzothiophene analogues showed reduced sartan activity when compared with the parent compounds, incorporation of selenium into these molecules appears to restore AT_1 receptor binding ability.

Experimental‡

2-(Methylseleno)phenyldiazonium tetrafluoroborate (8b)

2-(Methylseleno)aniline was dissolved in 10% sulfuric acid (0.73 mmol of aniline per mL) and the solution chilled to 0 °C. A chilled solution of sodium nitrite (1.05 equivalents) in water (20% of the volume of the acid) was added dropwise to the aniline solution followed by stirring for 30 min. at 0 °C. Cold tetrafluoroboric acid (43% solution in water, 2.4 equivalents) was added dropwise to form a precipitate, which was filtered through a chilled sintered glass funnel and washed with cold water (2 × 3 mL), cold ether (3 × 5 mL) and dried under vacuum at 0 °C. The diazonium salt was used immediately and without further purification.

2-(Pyridin-3-ylmethylseleno)nitrobenzene

3,3′-Dipicolyl diselenide[23] (0.22 g, 0.64 mmol) was dissolved in ethanol (20 mL) and excess sodium borohydride (48 mg, 0.13 mmol) added until the solution became a pale orange colour. 2-Fluoronitrobenzene was added and the reaction stirred overnight. The ethanol was removed *in vacuo* and the product extracted into diethyl ether (70 mL), washed with water (2 × 70 mL), dried (MgSO4) and the solvent removed. The product was purified by flash chromatography (2% methanol–dichloromethane) to give the title compound (0.26 g, 72%). Mp 90–91 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.52 (d, J = 3.3, 1H), 8.31 (dd, J = 1.0, 8.3, 1H), 7.75 (d, J = 7.9, 1H), 7.61 – 7.50 (m, 2H), 7.36 (ddd, J = 1.7, 6.8, 8.3, 1H), 7.27 (q, J = 4.6, 1H), 4.16 (s, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 150.2, 148.8, 146.4, 136.7, 133.9, 133.5, 131.8, 129.1, 126.5, 126.0, 123.6, 27.7; ^{77}Se NMR (95.4 MHz, $CDCl_3$) δ 400.0; MS (EI) m/z (relative intensity) 294.1 (10) 186 (31) 92.1 (100) 65.1 (33); (Found: C, 49.1; H, 3.5. $C_{12}H_{10}N_2O_2Se$ requires C, 49.2; H, 3.4%).

2-(Pyridin-3-ylmethylseleno)aniline (9)

2-(Pyridin-3-ylmethylseleno)nitrobenzene (0.1 g, 0.36 mmol) was dissolved in ethanol (5 mL) and water (2 mL). Sodium dithionite (0.37 g, 2.15 mmol) was added and the mixture heated at reflux for 3 h. The solution was made basic with ammonia solution and the product extracted into chloroform (3 × 50 mL) and the solvent removed *in vacuo*. The product was purified by flash chromatography (2% methanol–dichloromethane) to give the title aniline (36 mg, 40%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (dd, J = 1.6, 4.8, 1H), 8.30 (d, J = 2.1, 1H), 7.33 – 7.28 (m, 1H), 7.24 (dd, J = 8.4, 10.0, 1H), 7.11 (m, 2H), 6.71 (dd, J = 6.7, 1.3, 1H), 6.56 (td, J = 6.0, 1.3, 1H), 4.25 (s, 2H), 3.89 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.8, 148.8, 147.9, 138.5, 136.0, 135.1, 130.8, 123.0, 118.6, 114.6, 112.8, 27.6; ^{77}Se NMR (95.4 MHz, $CDCl_3$) δ 289.8; HRMS calcd for $C_{12}H_{13}N_2Se$ [M+H]+ 265.02385, found 265.02387.

General procedure for the reaction of 2-(methylseleno)-phenyldiazonium tetrafluoroborate (8b) with alkynes

DMSO (1.1 mL) was degassed with argon for 10 min. Iron(II) sulfate heptahydrate (0.22 g, 1.35 mmol, 1.5 eq) and water (0.2 mL) and the alkyne (2.6 eq) were added and the solution degassed for a further 20 min. 2-(Methylseleno)phenyldiazonium tetrafluoroborate (**8b**) (5.21 mmol) was added and the reaction stirred for 15 min. Significant evolution of gas was observed in the initial stages of the reaction. The reaction was diluted with water (25 mL) and extracted into diethyl ether (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed. The product was purified and characterized as detailed below.

2-Phenylbenzo[*b*]selenophene (7, R = Ph)[24]. was purified by flash chromatography (2% ethyl acetate/petroleum spirits) to give the product as a red solid (30%). Mp 154–156 °C (Lit.[24] mp 160 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (dd, J = 1.1, 8.0, 1H), 7.77 (d, J = 8.0, 1H), 7.71 (s, 1H), 7.67 – 7.62 (m, 2H), 7.45 – 7.38 (m, 2H), 7.37 – 7.31 (m, 2H), 7.28 – 7.22 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.69, 143.26, 140.94, 136.20, 128.94, 128.25, 126.87, 125.40, 125.37, 124.84, 124.50, 123.04; ^{77}Se NMR (95.4 MHz, $CDCl_3$) δ 515.57; MS (EI) m/z (relative intensity) 258.1 (100), 178.1 (58).

Ethyl benzo[*b*]selenophene-2-carboxylate (7, R = CO_2Et)[15]. was purified by flash chromatography (10% ethyl acetate/petroleum spirits) to give the product as a yellow oil (29%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.88 (dd, J = 6.7, 1.9, 2H), 7.38 (dq, J = 5.6, 1.6, 2H), 4.37 (q, J = 7.1, 2H), 1.39 (t, J = 7.1, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.0, 144.1, 141.3, 136.5, 134.3, 127.5, 126.9, 125.9, 125.1, 61.7, 14.4; ^{77}Se NMR (95.4 MHz, $CDCl_3$) δ 540.1; IR (neat): 1699 cm^{-1}; MS (EI) m/z (relative intensity) 254 (68), 226 (26), 209 (100), 181 (28), 89.1 (42).

Diethyl benzo[*b*]selenophene-2,3-dicarboxylate (10, R_1 = R_2 = CO_2Et). was purified by flash chromatography (5% ethyl acetate/petroleum spirits) to give the product (15%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 – 7.83 (m, 2H), 7.49 – 7.39 (m, 2H), 4.50

(q, J = 7.1, 2H), 4.38 (q, J = 7.1, 2H), 1.47 – 1.36 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.97, 163.04, 142.85, 139.37, 137.82, 135.83, 127.58, 126.48, 125.86, 125.82, 62.35, 62.28, 14.41, 14.38; ^{77}Se NMR (95.4 MHz, $CDCl_3$) δ 551.0; IR (neat): 1718 cm^{-1}; MS (EI) m/z (relative intensity) 326.1 (52), 281 (15), 253 (100), 209 (14), 169 (18), 89.1 (20); HRMS calcd. for $C_{14}H_{15}O_4Se$ $[M+H]^+$ 327.01301, found 327.01297.

Diethyl ((benzo[*b*]thiophen-2-yl)methyl)malonate (5, Y = S).[12]

Piperidine (92 μL, 0.87 mmol) and benzoic acid (28.9 mg, 0.237 mmol) were added to a solution of 2-benzo[*b*]thiophene-2-carboxaldehyde[14] (1.10 g, 6.81 mmol) and diethyl malonate (1.0 mL, 6.59 mmol) in cyclohexane (36 mL) and the mixture was refluxed overnight with azeotropic removal of water. The solvent was removed *in vacuo* and the residue was dissolved in diethyl ether. The solution was washed with 10% aqueous hydrochloric acid (3×), sat. sodium bicarbonate (3×) and brine (1×). Drying (magnesium sulfate) followed by concentration *in vacuo* afforded a crude mixture of diethyl 2-benzo[*b*]thiophenylidenemalonate and diethyl malonate which was used without further purification. Sodium borohydride (19.2 mg, 51 mmol) was added to a solution of the crude diethyl 2-benzo[*b*]thiophenylidenemalonate (260 mg) in dry EtOH (2.5 mL) at 0 °C and the mixture was stirred at 0 °C for 30 min. The pH was adjusted to 6 with 5% aqueous acetic acid and the solids were removed by filtration. The ethanol was removed *in vacuo* and the product was extracted into diethyl ether. The organic layer was washed with water (2×) and brine. Drying (sodium sulfate) followed by concentration *in vacuo* provided the crude product and flash chromatography (hexane: ethyl acetate 80 : 20) furnished the title compound as a yellow oil (170 mg, 54%). ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J = 7.0 Hz, 6H), 3.51 (d, J = 7.5 Hz, 2H), 3.76 (t, J = 7.5 Hz, 1H), 4.20 (q, J = 7.0 Hz, 4H), 7.08 (s, 1H), 7.26 – 7.33 (m, 2H), 7.67 (d, J = 7.4 Hz, 1H), 7.75 (d, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 30.0, 53.5, 61.7, 122.0, 122.5, 123.0, 123.8, 124.1, 139.5, 139.7, 141.0, 168.3; Mass spectrum (ESI) 329 ($[M + H]^+$).

Diethyl ((benzo[*b*]selenophen-2-yl)methyl)malonate (5, Y = Se)

Sodium hydride (60% dispersion in mineral oil) (37.0 mg, 0.925 mmol) was added to anhydrous DMF (5 mL) and was stirred vigorously for 30 min under argon at room temperature. Diethyl malonate (140 μL, 0.922 mmol) was added to the suspension and the mixture was stirred for 30 min. 2-(Chloromethyl)benzo[*b*]selenophene (**6**, X = Cl, Y = Se) (205 mg, 0.892 mmol) was added, after which the mixture was stirred at r.t. for 3 h and for another 4 h at 60 °C. After cooling, the reaction mixture was poured into a water–ice mixture and the product was extracted into ethyl acetate. Drying (sodium sulfate), followed by concentration *in vacuo* provided a crude product. Excess diethyl malonate was removed using **Kügel**rohr distillation. Further purification by flash chromatography (Petroleum spirit: dichloromethane 1 : 1) furnished the title compound as pale yellow oil (100 mg, 32%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, J = 7 Hz, 3H), 3.56 (dd, J = 7.5, 1.0 Hz, 2H), 3.74 (t, J = 7.5 Hz, 1H), 4.22 (m, 4H), 7.21 (dd, J = 7.2, 1.2 Hz, 1H), 7.27 (s, 1H), 7.32 (dd, J = 7.5, 1.2 Hz, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.81 (dd, J = 8.0, 1.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.0, 32.3, 54.0, 61.8, 124.2, 124.6, 124.8, 125.4, 126.5, 141.4, 142.1, 144.9, 168.4; ^{77}Se NMR (95.4 MHz, $CDCl_3$) δ 534.83; HRMS calcd. for $C_{16}H_{19}O_4Se$ [M+H]+ 355.0443, found 355.0444.

2-(Bromomethyl)benzo[*b*]thiophene (6, X = Br, Y = S).[13]

N-Bromosuccinimide (107 mg, 0.600 mmol) and AIBN (9 mg, 0.054 mmol) were added to a solution of 2-methylbenzo[*b*]thiophene (95 mg, 0.63 mmol) in α,α,α-trifluorotoluene (5 mL). The mixture was refluxed for 1.5 h, cooled and filtered to remove solids. The filtrate was concentrated *in vacuo* to afford the crude product, which was used without further purification (125 mg, 91%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.83 (s, 2H), 7.32–7.36 (m, 3H), 7.72–7.30 (m, 1H), 7.78–7.80 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.2, 122.5, 123.8, 124.5, 124.6, 125.0, 139.2, 140.6, 141.1. mp 46.5 – 47.1 °C. MS (ESI) m/z 226, ($[M(^{79}Br)]^+$), 228 ($[M(^{81}Br)]^+$).

2-(Hydroxymethyl)benzo[*b*]selenophene (6, X = OH, Y = Se).[25]

Ethyl benzo[*b*]selenophene-2-carboxylate (**7**, R = CO_2Et) (88 mg, 0.35 mmol) was dissolved in dry diethyl ether (6 mL) and chilled to −78 °C. DiBALH (1 M in hexane, 0.87 mL, 0.87 mmol) was added dropwise and the reaction stirred for 17 h, returning to room temperature. Water (35 μL), 15% aqueous sodium hydroxide (35 μL) and water (87 μL) were added sequentially at 0 °C and the resultant solution stirred for a further 20 min. Magnesium sulfate was added and the mixture was filtered through celite, solids were washed with diethyl ether and the filtrate was dried *in vacuo* to afford the desired product, which was used without further purification (55 mg, 75%). Mp 104–105 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 8.0, 1H), 7.74 (d, J = 7.9, 1H), 7.41 – 7.33 (m, 2H), 7.29 – 7.24 (m, 1H), 4.96 (dd, J = 1.0, 6.0, 2H), 2.06 (t, J = 6.1, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 149.2, 141.8, 141.2, 125.6, 125.2, 124.6, 124.3, 124.3, 62.8; ^{77}Se NMR ($CDCl_3$) δ 520.64; IR: 3260, 1454, 1437 cm^{-1}; MS (EI) m/z 212 ($[M+H]^+$); HRMS calcd. for C_9H_8OSe ($[M+Ag]^+$) 318.87858, found 318.87867.

2-(Chloromethyl)benzo[*b*]selenophene (6, X = Cl, Y = Se).[26]

2-(Hydroxymethyl)benzo[*b*]selenophene (53 mg, 0.25 mmol) and thionyl chloride (0.29 mL, 4 mmol) were refluxed for 2 h in anhydrous dioxane (4 mL). The solvent was removed *in vacuo* and the crude residue purified by flash column chromatography (petroleum spirits) to give the product as a white solid (55 mg, 68%); mp 67 °C (sharp). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (dd, J = 0.8, 7.8, 1H), 7.73 (d, J = 7.7, 1H), 7.36 (ddd, J = 1.1, 7.2, 8.2, 1H), 7.27 (ddd, J = 1.3, 4.6, 7.2, 2H), 4.92 – 4.87 (m, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 144.7, 142.1, 141.4, 127.5, 125.6, 125.6, 125.1, 124.9, 43.6; ^{77}Se NMR ($CDCl_3$) δ 533.02; IR: 1454, 1255 cm^{-1}; MS (EI) m/z 230 ($[M+H]^+$).

Methyl 2-[[4-butyl-2-methyl-6-oxo-5-[[2′-[1-(triphenylmethyl)-1*H*-tetrazol-5-yl][1,1′-biphenyl]-4-yl]methyl]-1(6H)pyrimidinyl]-methyl]-3-benzo[*b*]selenophene (12, Y = Se)

Following the procedure of Salimbeni,[3] a solution of 6-butyl - 2 - methyl - 5 - [[2′ - [1 - (triphenylmethyl) - 1*H* - tetrazol - 5 - yl][1,1′-biphenyl]-4-yl]methyl]pyrimidin-4(1*H*)-one (140 mg, 0.218 mmol) (**10**) in DMF (1 mL) was added to a suspension of NaH (60%

dispersion in mineral oil, 14 mg, 0.35 mmol)) in anhydrous DMF (0.5 mL) at 0 °C. The mixture was stirred at 0 °C for 10 mins, followed by addition of lithium bromide (57 mg, 0.65 mmol) in DMF (1 mL). After stirring for a further 10 min. at 0 °C a solution of 2-(chloromethyl)benzo[*b*]selenophene (**6**, X = Cl, Y = Se) (55 mg, 0.24 mmol) in DMF (0.5 mL) was added. The mixture was allowed to warm to ambient temperature. After stirring for 2 h the solution was poured carefully into ice water (30 mL) and acidified to pH 5 with 10% aqueous acetic acid. The resulting precipitate was collected *via* filtration, washed with water and dried under vacuum. Purification by flash column chromatography (gradient elution: 15 : 85 to 30 : 70 ethyl acetate : petroleum spirit) afforded the title compound as a white solid (104 mg, 57%.) Mp 92–96 °C (dec.). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 – 7.83 (m, 1H), 7.79 (d, J = 7.5, 1H), 7.69 (d, J = 8.0, 1H), 7.43 (ddd, J = 1.6, 6.0, 12.5, 3H), 7.37 – 7.20 (m, 12H), 7.05 (q (apparent), J = 8.2, 4H), 6.95 – 6.88 (m, 6H), 5.40 (s, 2H), 3.87 (s, 2H), 2.61 (s, 3H), 2.49 – 2.40 (m, 2H), 1.48 (m, 2H), 1.29 (dd, J = 10.7, 18.3, 2H), 0.85 (t, J = 7.3, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 164.1, 163.0, 162.9, 155.5, 142.3, 142.3, 142.0, 141.3, 141.0, 138.8, 138.5, 130.8, 130.3, 130.2, 129.8, 129.3, 128.2, 127.9, 127.6, 127.3, 127.2, 126.4, 125.5, 125.2, 124.9, 124.7, 120.9, 46.4, 34.6, 31.1, 30.5, 29.7, 22.8, 22.7, 14.0; ^{77}Se NMR ($CDCl_3$) δ 545.8; IR: 1649 cm^{-1}; HRMS calcd. for $C_{51}H_{44}N_6OSe$ [M+Ag] 943.17873, found 943.17878.

Methyl 2-[[4-butyl-2-methyl-6-oxo-5-[[2′-[1-(triphenylmethyl)-1*H*-tetrazol-5-yl][1,1′-biphenyl]-4-yl]methyl]-1(6H)pyrimidinyl]-methyl]-3-benzo[*b*]thiophene (12, Y = S). was prepared in analogous fashion to **12** (Y = Se) from 2-(bromomethyl)-benzo[*b*]thiophene (**6**, X = Br, Y = S) (65 mg, 0.28 mmol), 6-butyl - 2 - methyl - 5 - [[2′ - [1 - (triphenylmethyl) - 1*H* - tetrazol - 5 - yl][1, 1′-biphenyl]-4-yl]methyl]pyrimidin-4(1*H*)-one (10) (122 mg, 0.19 mmol), sodium hydride (15 mg, 0.38 mmol) and lithium bromide (57 mg, 0.65 mmol). Purification by flash column chromatography (2 : 1.5 petroleum spirit : ethyl acetate) yielded the title compound as a white solid (107 mg, 72%). Mp 79–83 °C (dec.). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (ddd, J = 0.5, 1.5, 7.5 Hz, 1H), 7.75 – 7.75 (m, 1H), 7.71 – 7.69 (m, 1H), 7.47 (ddd, J = 1.5, 7.5, 7.5, 1H), 7.42 (ddd, J = 1.5, 7.5, 7.5, 1H), 7.37 – 7.23 (m, 13H), 7.08 (d, J = 8.5 Hz, 2H), 7.05(d, J = 8.5 Hz, 2H), 6.95 – 6.92 (m, 6H), 5.42 (s, 2H), 3.87 (s, 2H), 2.61 (s, 3H), 2.49 – 2.47 (m, 2H), 1.54 – 1.48 (m, 2H), 1.36 – 1.27 (sextet, J = 7.5 Hz, 2H), 0.88 (t, J = 7.5, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 164.1, 162.9, 155.5, 149.6, 142.2, 141.3, 140.0, 139.1, 138.8, 138.5, 130.8, 130.3, 130.2, 129.8, 129.3, 128.2, 127.9, 127.6, 127.2, 126.4, 124.7, 124.5, 123.5, 123.4, 122.3, 120.8, 82.8, 43.8, 34.7, 31.2, 30.5, 22.8, 17.6, 14.0; IR: 1651 cm^{-1}. HRMS calcd. for $C_{51}H_{44}N_6OS$ [M+H]$^+$ 789.33701, found 789.33744. (Found: C, 77.6; H, 5.5; N, 10.6. $C_{51}H_{44}N_6OS$ requires C, 77.6; H, 5.6; N, 10.7%).

2-Carboethoxy-3-(benzo[*b*]thiophen-2-yl)propanoic acid (13, Y = S)

Potassium hydroxide (29.6 mg, 0.527 mmol) in ethanol (0.5 mL) was added to a solution of diethyl ((benzo[*b*]thiophen-2-yl)methyl)malonate (**5**, Y = S) (0.162 g, 0.530 mmol) in ethanol (84 mL). The mixture was stirred for 48 h at r.t. after which the solvent was removed *in vacuo*. The residue was taken up in sat. sodium bicarbonate and the solution was washed with diethyl ether. The aqueous layer was acidified to pH 0 with 5% aqueous sulfuric acid and the product was extracted into diethyl ether (2×). The combined organic layers were dried (sodium sulfate) and concentrated *in vacuo* to provide the title compound as an orange oil (0.130 g, 88%). ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 3H), 3.54 (t, J = 7.5 Hz, 2H), 3.82 (t, J = 7.5 Hz, 1H), 4.23 (q, J = 7.0 Hz, 2H), 7.09 (s, 1H), 7.26 – 7.33 (m, 2H), 7.67 (d, J = 7.6 Hz, 1H), 7.75 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.8, 29.6, 53.2, 62.1, 122,0, 122.6, 123.0, 123.9, 124.2, 139.5, 139.7, 140.5, 168.1, 173.7; IR: 1732, 1713 cm^{-1}; Mass spectrum (EI) 278 (M$^{+\cdot}$, 35), 234 (31), 147 (100). (Found: C, 60.5; H, 5.0. $C_{14}H_{14}O_4S$ requires C, 60.4; H, 5.1%).

2-Carboethoxy-3-(benzo[*b*]selenophen-2-yl)propanoic acid (13, Y = Se). was prepared in analogous fashion to **13** (Y = S) using potassium hydroxide (12.7 mg, 0.226 mmol) and diethyl ((benzo[*b*]selenophen-2-yl)methyl)malonate (**5**, X = Se) (80.0 mg, 0.226 mmol) and isolated as a red oil (36 mg, 65% brsm). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, J = 7 Hz), 3.57 (m, 2H), 3.80 (t, J = 7 Hz, 1H), 4.23 (q, J = 7 Hz, 2H), 7.22 (m, 1H), 7.28 (s, 1H), 7.32 (td, J = 7.5, 1 Hz 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.80 (dd, J = 0.5, 8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.0, 32.2, 53.7, 62.2,124.3, 124.6, 124.9, 125.4, 126.7, 141.4, 142.0, 144.1, 168.2; ^{77}Se NMR (95.4 MHz, $CDCl_3$) δ 534.85; HRMS calcd. for $C_{14}H_{14}O_4Se$ [M – H]- 324.9985, found 324.9980.

Methyl 2-[[4-butyl-2-methyl-6-oxo-5-[[2′-(1*H*-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl]methyl]-1(6*H*)pyrimidinyl]methyl-2-benzo[*b*]thiophene (3, Y = S)

The trityl protected sartan (**12**, Y = S) (107 mg, 0.136 mmol) was refluxed in methanol (10 mL) for 17 h. Cooling, followed by concentration *in vacuo* afforded the crude product. Purification by flash column chromatography (Gradient elution: 0 – 5% methanol–dichloromethane) afforded the title compound as a white solid (71 mg, 96%). Mp 106–108 °C (dec.). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17–8.19 (m, 1H), 7.81–7.83 (m, 1H), 7.71–7.73 (m, 1H), 7.51–7.57 (m, 2H), 7.41 (dd, 1H), 7.31–7.37 (m, 2H), 7.25–7.28 (m), 7.12–7.13 (m, 2H), 5.46 (s, 2H), 3.97 (s, 2H), 2.69 (s, 3H), 2.62 (t, 2H), 1.59–1.63 (m, 2H), 1.36–1.41 (m, 2H), 0.90–0.93 (t, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.6, 162.9, 156.4, 155.0, 141.2, 140.1, 139.9, 139.0, 138.2, 137.2, 130.9, 130.8, 129.3, 128.8, 128.1, 124.9, 124.7, 123.8, 123.6, 122.8, 122.6, 120.2, 44.1, 34.6, 31.5, 30.7, 22.9, 22.6, 14.0. IR: 1651, 1542 cm^{-1}; HRMS calcd. for $C_{32}H_{30}N_6OS$ ([M+H]$^+$) 547.2281, found 547.2283. (Found: C, 70.2; H, 5.5; N, 15.2. $C_{32}H_{30}N_6OS$ requires C, 70.3; H, 5.5; N, 15.4%).

Methyl 2-[[4-butyl-2-methyl-6-oxo-5-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1(6*H*)pyrimidinyl]methyl-2-benzo[*b*]-selenophene (3, Y = Se). was prepared in identical fashion to **3** (Y = S) and isolated in 89% yield. Mp 124–130 °C (dec.). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J = 7.7, 1H), 7.91 (d, J = 8.0, 1H), 7.70 (d, J = 8.0, 1H), 7.58 – 7.51 (m, 1H), 7.51 – 7.45 (m, 1H), 7.44 – 7.38 (m, 2H), 7.34 (t, J = 7.5, 1H), 7.29 – 7.23 (m, 1H), 7.17 (d, J = 8.1, 2H), 7.09 (d, J = 8.2, 2H), 5.39 (s, 2H), 3.91 (s, 2H), 2.59 (s, 3H), 2.55 – 2.48 (m, 2H), 1.60 – 1.49 (m, 2H), 1.33 (dd, J = 7.4, 14.9, 2H), 0.88 (t, J = 7.3, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.9, 163.1, 156.2, 154.8, 142.4, 141.6, 141.1, 141.0,

140.2, 137.3, 131.4, 130.9, 130.9, 129.2, 129.0, 128.2, 127.7, 125.9, 125.3, 125.2, 124.9, 122.6, 120.1, 46.6, 34.7, 31.5, 30.8, 22.9, 22.7, 14.0; ^{77}Se NMR (95.4 MHz, CDCl3) δ 544.42; IR (neat): 2957, 2927, 1649, 1544 cm^{-1}; HRMS calcd. for $C_{32}H_{31}N_6OSe$ [M+H]+ 595.17191, found 595.17193.

2-Butyl-1-(4-carboxybenzyl)-5-[2-carboxy-3-(benzo[*b*]thiophen-2-yl)prop-1-enyl]-1*H*-imidazole (4, Y = S)

Piperidine (30 μL, 0.30 mmol) and benzoic acid (7.5 mg, 0.061 mmol) were added to a suspension of 2-butyl-1-[(4-carbomethoxyphenyl)methyl]-1*H*-imidazole-5-carboxaldehyde (**14**)[6] (250 mg, 0.90 mmol) and 2-carboethoxy-3-(benzo[*b*]thiophen-2-yl)propanoic acid (**13**, Y = S) (100 mg, 0.33 mmol) in toluene (1 mL) and cyclohexane (7 mL). The mixture was refluxed overnight with azeotropic removal of water. The solvent was then removed *in vacuo* and the residue was purified by flash chromatography (Hex : EtOAc 1 : 1) to provide 2-butyl-1-(4-carbomethoxybenzyl)-5-[2-carboethoxy-3-(benzo[*b*]thiophen-2-yl)prop-1-enyl]-1*H*-imidazole as an oil (79 mg, 46%) which was of sufficient purity for further use.

10% Aqueous sodium hydroxide (1.0 mL, 2.6 mmol) was added to a solution of the freshly prepared diester in ethanol (2.6 mL) and the mixture was stirred at r.t. for 4 h. 10% Aqueous acetic acid (3 mL) was added and the ethanol was removed *in vacuo*. The reaction mixture was extracted with chloroform: *iso*-propanol 9 : 1 (4×). The combined organic layers were dried (sodium sulfate) and concentrated *in vacuo*. The resulting solid was triturated with hexane (2×) and chloroform (2×) to give the title compound as a pale solid (45 mg, 29% over two steps). ^{1}H NMR (DMSO-d$_6$) δ 0.86 (t, J = 7.5 Hz, 3H), 1.30 (sextet, J = 7.5 Hz, 2H), 1.62 (quintet, J = 7.5 Hz, 2H), 2.65 (t, J = 7.5 Hz, 2H), 4.16 (s, 2H), 5.27 (s, 2H), 7.00 (s, 1H), 7.05 (d, J = 8.0 Hz, 2H), 7.22 – 7.30 (m, 2H), 7.34 (s, 1H), 7.39 (s, 1H), 7.56 (s, 1H), 7.62 (d, J = 7.6 Hz, 2H), 7.73 (d, J = 7.6 Hz, 1H), 8.02 (d, J = 8.2 Hz, 1H); ^{13}C NMR (DMSO-d$_6$) δ 13.4, 22.2, 26.7, 29.5, 46.5, 120.7, 121.9, 122.7, 123.5, 123.9, 125.6, 125.9, 127.1, 128.3, 130.3, 130.5, 131.0, 139.3, 139.8, 140.5, 142.0, 151.6, 168.1, 169.2; IR: 2963, 1702 cm^{-1}; Mass spectrum (ESI) 473 ([M + H]$^+$); HRMS calcd. for $C_{23}H_{24}N_2O_4Se$ [M + H]$^+$ 475.1691, found 475.1684.

2-Butyl-1-(4-carboxybenzyl)-5-[2-carboxy-3-(benzo[*b*]selenophen-1-yl)prop-1-enyl]-1*H*-imidazole (4, Y = Se). was prepared in identical fashion to **4** (Y = S) from 2-butyl-1-[4(4-carbomethoxyphenyl)methyl] - 1*H* - imidazole - 5 - carboxaldehyde (16.5 mg, 0.055 mmol) and 2-carboethoxy-3-(benzo[*b*]selenophen-2-yl)propionic acid (**13**, Y = Se) (36 mg, 0.110 mmol) and isolated as as colourless solid (14 mg, 51%, 2 steps). ^{1}H NMR (500 MHz, 1 : 1 $CDCl_3$: CD_3OD) δ 0.85 (t, J = 7.5 Hz, 3H), 1.32 (m, 2H), 1.60 (m, 2H), 2.66 (t, J 7.5 Hz, 2H), 4.19 (s, 2H), 5.21 (s, 2H), 7.05 (d, J = 8 Hz, 2H), 7.16 (m, 2H), 7.27 (td, J = 7.5, 1 Hz, 1H), 7.38 (s, 1H), 7.55 (s, 1H), 7.60 (d, J = 7.5 Hz, 1H), 7.77 (d, J = 8 Hz, 1H), 7.99 (d, J = 7.5 Hz, 2H); ^{13}C NMR (126 MHz, 1 : 1 $CDCl_3$: CD_3OD) δ 13.2, 22.2, 26.7, 29.6, 31.9, 46.6, 123.8, 124.3, 124.4, 124.5, 125.1, 125.7, 127.4, 129.3, 130.5, 130.7, 130.8, 140.7, 140.9, 142.3, 145.9, 151.6, 168.3, 169.3; ^{77}Se NMR (95.4 MHz, 1 : 1 $CDCl_3$: CD_3OD) δ 534.59; HRMS calcd. for $C_{27}H_{26}N_2O_4Se$ [M+H]$^+$ 523.1131, found 523.1130.

Acknowledgements

This work would not have been possible without the generous support of the Australian Research Council through the Centres of Excellence Scheme. We thank Mark Ross-Smith, Department of Pharmacology, University of Melbourne, for conducting the CHO cell assays.

References

1 G. Beevers, G. Y. H. Lip and E. O'Brien, *ABC of Hypertension*, BMJ Books, London, 2001.
2 P. B. M. W. M. Timmermans, P. C. Wong, A. T. Chiu and W. F. Herblin, *Trends Pharmacol. Sci.*, 1991, **12**, 55; P. B. M. W. M. Timmermans, P. C. Wong, A. T. Chiu, W. F. Herblin, P. Benfield, D. J. Carini, R. J. Lee, R. R. Wexler, J. M. Saye and R. D. Smith, *Pharmacol. Rev.*, 1993, **45**, 205; T. L. Goodfriend, M. E. Elliott and K. J. Catt, *N. Engl. J. Med.*, 1996, **334**, 1649; C. I. Johnston, M. Naitoh and L. M. Burrell, *J. Hypertens.*, 1997, **15**, S3; M. Burnier and H. R. Brunner, *Lancet*, 2000, **355**, 637; R. R. Wexler, W. J. Greenlee, J. D. Irvin, M. R. Goldberg, K. Prendergast, R. D. Smith and P. B. M. W. M. Timmermans, *J. Med. Chem.*, 1996, **39**, 625.
3 A. Salimbeni, R. Canevotti, F. Paleari, D. Poma, S. Caliari, F. Fici, R. Cirillo, A. R. Renzetti, A. Subissi, L. Belvisi, G. Bravi, C. Scolastico and A. Giachetti, *J. Med. Chem.*, 1995, **38**, 4806.
4 G. W. Robins and L. J. Scott, *Drugs*, 2005, **65**, 2355.
5 J. Weinstock, R. M. Keenan, J. Samanen, J. Hempel, J. A. Finkelstein, R. G. Franz, D. E. Gaitanopoulos, G. R. Girard, J. G. Gleason, D. T. Hill, T. M. Morgan, C. E. Peishoff, N. Aiyar, D. P. Brooks, T. A. Fredrickson, E. H. Ohlstein, R. R. Ruffolo, E. J. Stack, A. C. Sulpizio, E. F. Weidley and R. M. Edwards, *J. Med. Chem.*, 1991, **34**, 1514.
6 R. M. Keenan, J. Weinstock, J. A. Finkelstein, R. G. Franz, D. E. Gaitanopoulos, G. R. Girard, D. T. Hill, T. M. Morgan, J. M. Samanen, J. Hempel, D. S. Eggleston, N. Aiyar, E. Grifin, E. H. Ohlstein, E. J. Stack, E. F. Weidley and R. M. Edwards, *J. Med. Chem.*, 1992, **35**, 3858.
7 R. M. Keenan, J. Weinstock, J. A. Finkelstein, R. G. Franz, D. E. Gaitanopoulos, G. R. Girard, D. T. Hill, T. M. Morgan, J. M. Samanen, C. E. Peishoff, L. M. Tucker, N. Aiyar, E. Griffin, E. H. Ohlstein, E. J. Stack, E. F. Weidley and R. M. Edwards, *J. Med. Chem.*, 1993, **36**, 1880.
8 C. Csajka, T. Buclin, K. Fattinger, H. R. Brunner and J. Biollaz, *Clin. Pharmacokinet.*, 2002, **41**, 137.
9 R. Catalioto, R. Porchia, A. R. Renzetti, M. Criscuoli, A. Subissi and A. Giachetti, *Eur. J. Pharmacol.*, 1995, **280**, 285.
10 R. L. Grange, J. Ziogas, A. J. North, J. A. Angus and C. H. Schiesser, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 1241.
11 R. L. Grange, J. Ziogas, J. A. Angus and C. H. Schiesser, *Tetrahedron Lett.*, 2007, **48**, 6301.
12 C. Kaiser and C. L. Zirkle, South African Patent ZA6800682 (1968)See also: P. V. Podea, M. I. Tosa, C. Paizs and F. D. Irimie, *Tetrahedron: Asymmetry*, 2008, **19**, 500.
13 J. W. Ellingboe, T. R. Alessi, T. M. Dolak, T. T. Nguyen, J. D. Tomer, F. Guzzo, J. F. Bagli and M. L. McCaleb, *J. Med. Chem.*, 1992, **35**, 1176.
14 V. P. Mamaev and O. P. Shkurko, *Zh. Obsh. Khim.*, 1961, **31**, 3288.
15 A. Ruwet and M. Renson, *Bull. Soc. Chim. Belg.*, 1970, **79**, 75; A. Ruwet and M. Renson, *Bull. Soc. Chim. Belg.*, 1970, **79**, 593.
16 C. H. Schiesser, *Chem. Commun.*, 2006, 4055 and refs. cited therein.
17 M. K. Staples and C. H. Schiesser, *Chem. Commun.*, 2010, **46**, 565.
18 S. Lobachevsky, C. H. Schiesser and V. Gupta, *Tetrahedron Lett.*, 2007, **48**, 9077.
19 R. Leardini, G. F. Pedulli, A. Tundo and G. Zanardi, *J. Chem. Soc., Chem. Commun.*, 1985, 1390.
20 M. W. Carland, R. L. Martin and C. H. Schiesser, *Org. Biomol. Chem.*, 2004, **2**, 2612.
21 M. P. Doyle and W. J. Bryker, *J. Org. Chem.*, 1979, **44**, 1572.
22 K. Prasad, *Int. J. Angiol.*, 2004, **13**, 59.
23 F. Tian, Z. Yu and S. Lu, *J. Org. Chem.*, 2004, **69**, 4520.
24 H. Sashida, K. Sadamori, K. and T. Tsuchiya, *Synth. Commun.*, 1998, **28**, 713.
25 L. Christiaens and M. Renson, *Bull. Soc. Chim. Belg.*, 1968, **77**, 153.
26 P. Cagniant and G. Kirsch, *C. R. Seances Acad. Sci. C*, 1971, **272**, 1978.