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Selenosartans: Novel selenophene analogues of milfasartan and eprosartan

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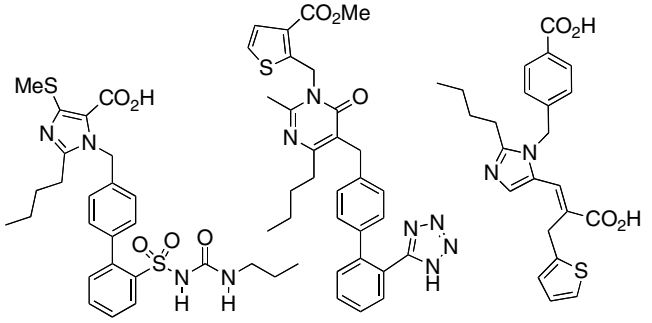
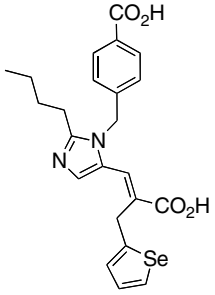
Abstract—A series of selenophene analogues of the thiophene-containing antihypertensives milfasartan and eprosartan were prepared and tested for AT_1 receptor antagonist properties. All four selenophene compounds proved to be potent AT_1 receptor antagonists, with pK_B estimates indicating that these selenides are at least as effective as the thiophene parent compounds at blocking AT_1 receptor mediated responses. These results reveal that replacement of sulfur with selenium in thiophene-containing sartans does not interfere with sartan activity.

Work in our laboratories has been directed towards the synthesis of selenium-containing molecules of potential therapeutic value.[1] In this regard, we recently reported that selenium-containing analogues of the antihypertensive compound, fonsartan (**1**), retained AT_1 receptor blocking activity.[2] We also recently showed that a selenium-containing allosteric enhancer of adenosine A_1 receptor binding was significantly more potent than its thiophene-containing parent,[3] and that a selenium analogue of the A_1 AR agonist, tecadenoson, proved to have similar activity to the parent compound.[4]



1 **2** **3**



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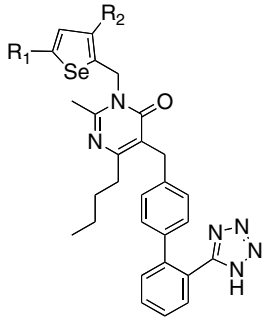

5: $R_1 = R_2 = H$
6: $R_1 = H$, $R_2 = CO_2Me$
7: $R_1 = CO_2Me$, $R_2 = H$

Milfasartan[5] (**2**) and eprosartan[6–9] (**3**) are thiophene-containing selective AT_1 receptor antagonists (sartans).[10] Milfasartan (**2**) reached Phase I clinical trials, while eprosartan (**3**) is on the market in many countries.[6,11,12] Given the outcomes of previous work, we were curious about the effect that sulfur/selenium exchange may have on milfasartan and eprosartan potency. Described herein is the synthesis and preliminary pharmacological testing of selenoeprosartan (**4**) and several selenophene analogues of milfasartan, including the nor-ester (**5**), selenomilfasartan (**6**) and its regioisomer (**7**).

Selenoeprosartan (**4**) was prepared following the general methodology developed by Keenan for the parent

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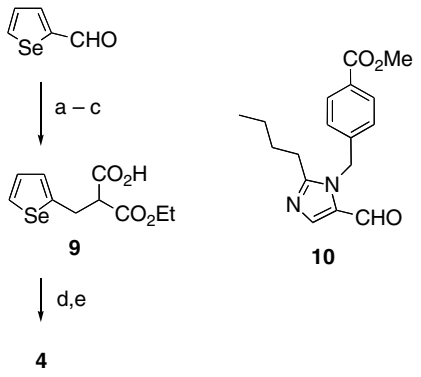


Scheme 1. Reagents and conditions: (a) diethyl malonate, piperidine, benzoic acid, cyclohexane, reflux; (b) $NaBH_4$, EtOH, rt, 49% over two steps; (c) KOH, EtOH, rt, 81%; (d) **10**, Piperidine, benzoic acid, cyclohexane/toluene 9:1, reflux, 76%; (e) NaOH, EtOH, H_2O, rt, 68%.

compound **3** (Scheme 1).[9] Accordingly, 2-selenophenecarboxaldehyde[13] was condensed with diethyl malonate. The resulting alkene was not purified but was rather reduced directly with sodium borohydride to provide the saturated diester (**8**) in 49% yield. Saponification of **8** furnished the required half-acid **9** in 81% yield. Condensation of formylimidazole[8] **10** with three equivalents of half-acid **9** followed by saponification provided the target compound (**4**) in 68% yield.

Chinese hamster ovary cells stably expressing the rat AT_{1a} receptor were used to assess the ability of compounds **3** and **4** to inhibit angiotensin II mediated increases in intracellular calcium.[14] Figure 1 shows the rightward shift of angiotensin concentration–response curves by selenoeprosartan at 1, 10 and 100 nM. Similar data were obtained with eprosartan (not shown). The calculated pK_B values were 8.3 for selenoeprosartan compared with 8.8 for eprosartan.

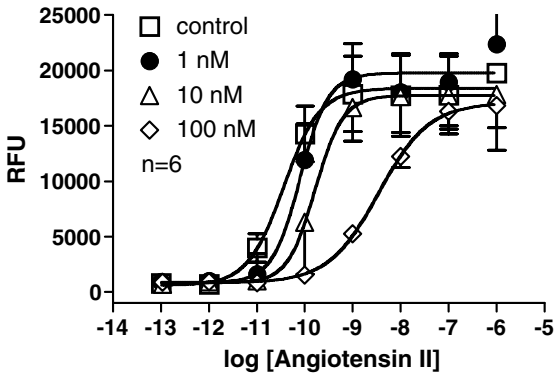
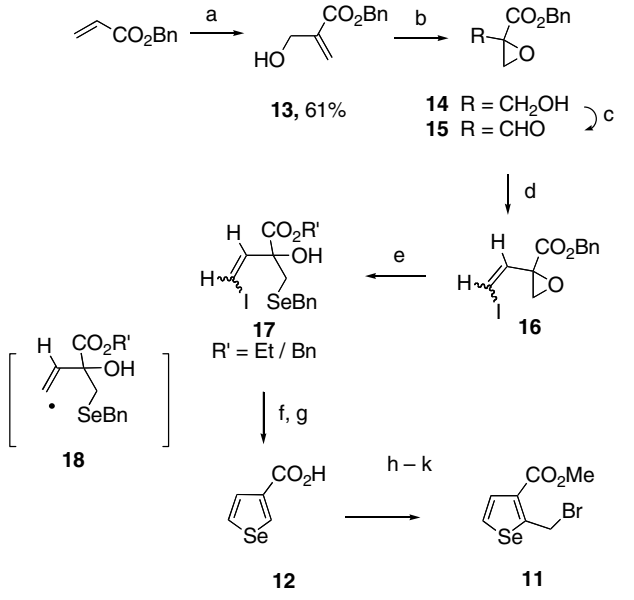


Figure 1. Selenoeprosartan (**4**) inhibits angiotensin II-evoked increases in intracellular calcium in CHO cells stably expressing the AT_{1a} receptor. CHO cells were loaded with Fluo4-AM and then incubated with 1, 10 or 100 nM selenoeprosartan. Changes in intracellular $[Ca^{2+}]$ evoked by increasing concentrations of angiotensin II in the absence and presence of the antagonist were measured over a 3 min period using the Flexstation II (Molecular Devices). RFU, relative fluorescence units.

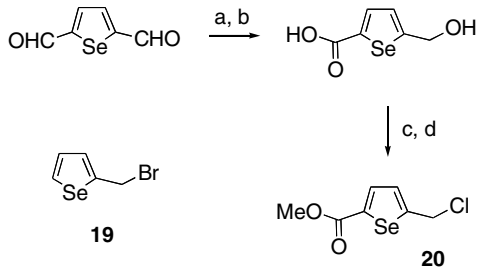
The route to selenomilfasartan (**6**) called for the novel selenophene (**11**) and we envisioned that selenophene **11** could be obtained from selenophene-3-carboxylic acid (**12**). While **12** has been prepared previously via pathways involving regioselective dehalogenation of tri- or tetrahalides of selenophene,[15] none of these procedures were reproducible in our hands. We instead resorted to the free-radical methods developed in our laboratories (Scheme 2).[16]

To that end benzyl acrylate was reacted with paraformaldehyde in a Baylis–Hillman reaction to afford alcohol (**13**) in 61% yield. Epoxidation with *m*-CPBA followed by Swern oxidation provided aldehyde (**15**). Wittig methodology using (iodomethylene)triphenylphosphorane gave iodide (**16**) in 34% overall yield. Our previously established methodology[16] was then applied to iodide (**16**): treatment with sodium benzylselenoate to afford **17**[17] and free-radical mediated ring closure (presumably involving intermediate **18**) followed by ester hydrolysis afforded selenophene-3-carboxylic acid (**12**) in useful quantities. Acid (**12**) is a synthetic intermediate in the preparation of the antitumour agent selenophenfurin[18] and the procedure described above represents a novel synthesis of this useful compound. Selenophene-3-carboxylic acid (**12**) was smoothly converted to the requisite bromide **11** over several routine steps.

The route to selenomilfasartan analogues (**5**, **7**) required the preparation of 2-(bromomethyl)selenophene (**19**)[19] and methyl 5-(chloromethyl)selenophene-2-carboxylate



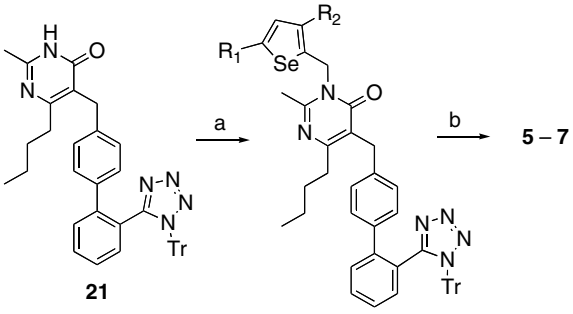
Scheme 2. Reagents and conditions: (a) $(CHO)_n$, NMe_3 (aq), H_2O, 60 °C, 61%; (b) *m*-CPBA, 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide, CCl_4, reflux, 73%; (c) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C; (d) $(Ph_3PCH_2I)^+I$, NaHMDS, HMPA, THF, −78 °C → rt, 34%; (e) $(SeBn)_2$, $NaBH_4$, EtOH, rt; (f) TTMSS, AIBN, benzene, reflux; (g) LiOH, THF, H_2O, 26% from **16**; (h) ^{s}BuLi, −78 °C, THF; (i) MeI, rt, 90%; (j) K_2CO_3, MeI, acetone, rt, 87%; (k) NBS, AIBN, CCl_4, reflux, 45% (NMR yield).



Scheme 3. Reagents and conditions: (a) $NaBH_4$, EtOH, rt, 84%; (b) $AgNO_3$, NaOH, H_2O, 0 °C, 80%; (c) $SOCl_2$, benzene, reflux; (d) MeOH, rt, 85%.

(**20**). The former compound was readily prepared from 2-selenophenecarboxaldehyde[13] through a sequence involving reduction and bromination, while **20** was prepared from 2,5-selenophenedicarboxaldehyde[20] via a sequence consisting of selective reduction, oxidation, double chlorination and esterification (Scheme 3). The precursors (**11**, **19**, **20**) were coupled to the common trityl-protected biphenyl core structure (**21**) following the procedure of Salimbeni.[5] Subsequent deprotection afforded the selenosartans (**5**–**7**) in acceptable quantities (Scheme 4).

During the course of the biological testing of these selenomilfasartan analogues, it became apparent that contrary to expectation,[5] regioisomer (**7**) was a potent AT_1 receptor antagonist (Fig. 2). The rightward shift of the angiotensin concentration–response curve and the depression of the maximum response are characteristic of many of the high affinity competitive AT_1 antagonists.[21] We therefore chose to synthesize the analogous thiophene (**22**) for direct comparison with **7**; **22** was not tested by Salimbeni but was expected to be less effective than **2** as an AT_1 receptor antagonist on the basis of substituent effect studies.[5] The thiophene (**22**) was prepared from methyl 5-(bromomethyl)thiophene-2-carboxylate, itself obtained from methyl 5-methylthiophene-2-carboxylate[22] by NBS bromination, in an identical manner to that described for **7**.



Scheme 4. Reagents and conditions: (a) **11**, **19** or **20**, NaH, LiBr, DMF, 0 °C → rt; (b) MeOH, reflux. Overall yields: 40–50%.

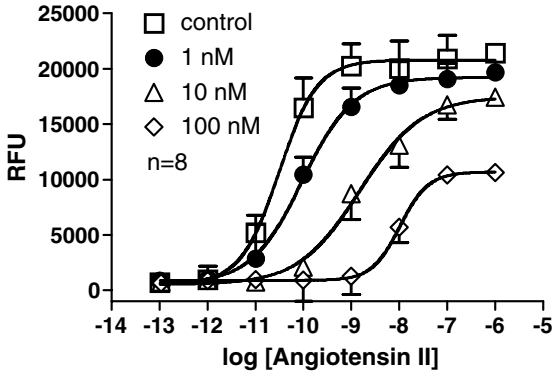


Figure 2. Inhibition of angiotensin II-evoked increases in intracellular calcium in CHO cells stably expressing the AT_{1a} receptor by selenomilfasartan regioisomer (**7**). Methods as described in Figure 1. RFU, relative fluorescence units.

Figure 3a compares the ability of the selenomilfasartans (compounds **5**–**7**) each at a concentration of 30 nM to inhibit the angiotensin II-evoked increases in intracellular calcium in CHO cells stably expressing the AT_{1a} receptor. The estimated pK_B values were 10.1, 9.8 and 9.9 for compounds **5**, **6** and **7**. Figure 3b shows the ability of the corresponding sulfur-containing sartans (com-

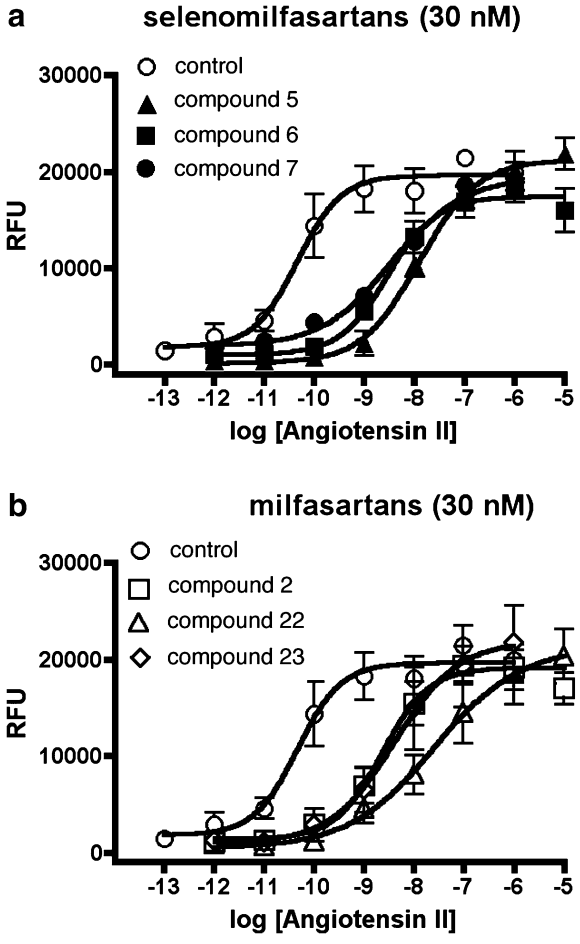
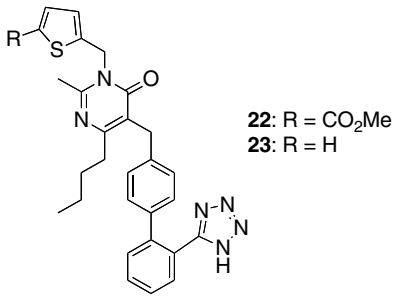


Figure 3. Inhibition of angiotensin II-evoked increases in intracellular calcium in CHO cells stably expressing the AT_{1a} receptor by (a) selenomilfasartans **5**–**7**; and (b) the parent sulfur-containing milfasartans **2**, **22** and **23**. A similar shift in the angiotensin concentration–response curve was elicited by 30 nM of each of the compounds. Methods as described in Figure 1. $n = 3$–4 RFU, relative fluorescence units.

pounds **2**,[5] **22**, **23**[5]) to inhibit AT_{1a} receptor mediated responses in the CHO cell assay. The estimated pK_B values for the corresponding sulfidemilfasartan analogues were 10.0, 9.6 and 10.1. These data suggest that the selenomilfasartans are each as effective as the corresponding sulfur-containing parent and suggest that replacing the thiophene sulfur with selenium does not interfere with the AT_1 receptor antagonist capabilities of the sartans.



22: R = CO_2Me
23: R = H

These findings are consistent with our earlier report that replacing the sulfur with selenium in the non-thiophene fonsartan also does not interfere with AT_1 receptor antagonist potency.[2] The finding that the regioisomers (**7**, **22**) of selenomilfasartan and milfasartan are effective antagonists of AT_1 receptor mediated responses contrasts with the substituent effect studies of Salimbeni et al. and warrants further investigation.

Acknowledgments

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