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Selenofonsartan analogues: novel selenium-containing antihypertensive compounds

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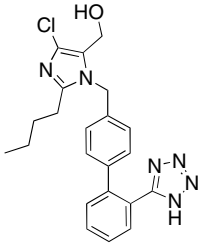
Abstract—2-Butyl-4-(methylseleno)-1-[[2′-(1*H*-tetrazol-5-yl)-1,1′-biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylic acid (**4**) and 2-butyl-4-(phenylseleno)-1-[[2′-(1*H*-tetrazol-5-yl)-1,1′-biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylic acid (**5**) have been prepared and tested for AT_1 receptor antagonist properties. Both compounds proved to be potent AT_1 receptor antagonists, with pK_b estimates indicating that these selenides are very effective at blocking AT_1 receptor mediated responses.

The renin–angiotensin cascade is responsible for the conversion of the protein angiotensinogen to the octapeptide hormone angiotensin II.[1] Interaction of angiotensin II with its type 1 receptors (AT_1 receptors) results in vasoconstriction (narrowing of the blood vessels), vascular remodeling (structural alterations to resistance arteries), renal sodium reabsorption and norepinephrine release.[1] All these responses raise blood pressure and can lead to hypertension (high blood pressure). Consequently, suppressing the renin–angiotensin cascade is an effective strategy for alleviating hypertension.[2]

The most direct and specific method for inhibiting the renin–angiotensin cascade is to antagonize angiotensin II at its AT_1 receptors.[3] The family of drugs[4–9] that achieve this are known as sartans (selective AT_1 receptor antagonists). Important advantages of sartans over other antihypertensives include a relative lack of side effects and an ability to protect completely against angiotensin II.[3] Losartan (**1**)[10] was the first sartan to be marketed as an antihypertensive,[9] and inspired the development of many more drugs. For example, workers at Hoechst Roussel patented a number of compounds, including tetrazole (**2**) and fonsartan (**3**). These compounds proved to be potent, orally active AT_1 receptor antagonists, with fonsartan (**3**) being ten times more potent than losartan (**1**).[11,12]

Work in our laboratories has been directed towards the synthesis of selenium-containing compounds of potential therapeutic value.[13] With this in mind, we were curious about the effect that sulfur/selenium exchange may have in sulfur-containing sartans such as fonsartan (**3**) and analogues (**2**). Described herein is the synthesis and preliminary pharmacological testing of selenofonsartan analogues 2-butyl-4-(methylseleno)-1-[[2′-(1*H*-tetrazol-5-yl)-1,1′-biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylic acid (**4**) and 2-butyl-4-(phenylseleno)-1-[[2′-(1*H*-tetrazol-5-yl)-1,1′-biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylic acid (**5**).



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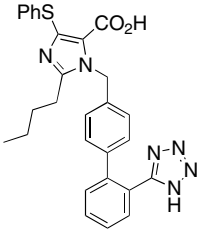

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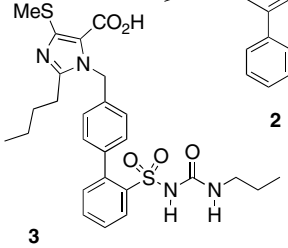

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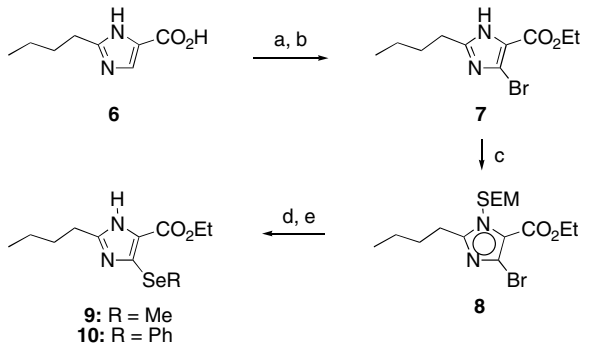
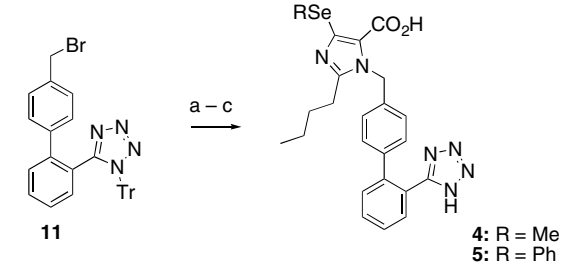


Scheme 1. Reagents and conditions: (a) $SOCl_2$ then $EtOH/CH_2Cl_2$ (91%); (b) Br_2, $KHCO_3$, DMF, 70 °C (90%); (c) NaH then SEM-Cl (73%); (d) ^tBuLi then RSeSeR, THF, −78 °C (52%: R = Me, 67%: R = Ph); (e) TFA/CH_2Cl_2 (81%: R = Me, 92%: R = Ph).



Scheme 2. Reagents and conditions: (a) **9** or **10**, K_2CO_3, DMF, 70 °C (47%: R = Me, 41%: R = Ph); (b) EtOH, reflux (86%: R = Me, 97%: R = Ph); (c) NaOH, EtOH, H_2O, reflux (50%: R = Me, 70%: R = Ph).

Our preparation of selenosartans (**4**, **5**) began with 2-butyl-1*H*-imidazole-4(5)carboxylic acid (**6**), prepared as described by Yanagisawa,[14] which was esterified and subsequently treated with bromine in DMF to afford ethyl 5(4)-bromo-2-butyl-1*H*-imidazole-4(5)-carboxylate (**7**) in a good yield (Scheme 1). It is interesting to note that bromide **7** appears to be novel and that similar attempts to chlorinate ethyl 2-butyl-1*H*-imidazole-4(5)-carboxylate met with a failure.[15] Further reaction with SEM chloride afforded the protected imidazole **8**,[16] contaminated with 20% of the alternative nitrogen-regioisomer. After flash chromatography, the major isomer was further treated with *tert*-butyllithium and then either dimethyl or diphenyl diselenide to afford, after deprotection, imidazoles **9** and **10** in moderate yields.

With imidazoles **9** and **10** in hand, they were smoothly coupled to the trityl-protected biphenyl core structure **11**, prepared according to the protocol of Carini and co-workers[17] to afford, after deprotection, selenofonsartan analogues **4** and **5** in moderate yields (Scheme 2).[18]

Chinese hamster ovary cells stably expressing the rat AT_1A receptor[19] were used to assess the potency of the fonsartan analogues. Angiotensin II-induced increases in intracellular calcium were effectively inhibited by 30 nM of each of the compounds synthesized. In preliminary experiments, an estimate of 10.3 for the pK_b of the known fonsartan analogue **2** compares favourably with previous estimates obtained for fonsartan in vascular tissue.[20] The pK_b estimates of 10.5 and 9.9 for compounds **4** and **5** confirm that the selenosartans remain potent AT_1 receptor antagonists. Further results on the characterization of the AT_1 receptor antagonist properties of these compounds will be reported in due course.

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18. Compound **4**: white solid (50%): mp = 137–139 °C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 0.88 (t, $J = 7.4$ Hz, 3H), 1.35 (sextet, $J = 7.1$ Hz, 2H), 1.62 (quintet, $J = 7.6$ Hz, 2H), 2.43 (s, 3H), 2.63–2.66 (m, 2H), 5.52 (s, 2H), 6.91 (d, $J = 8.0$ Hz, 2H), 7.07 (d, $J = 7.6$ Hz, 2H), 7.45 (d, $J = 7.2$ Hz, 1H), 7.51 (t, $J = 7.4$ Hz, 1H), 7.59 (t, $J = 7.4$ Hz, 1H), 7.81 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 4.7, 13.6, 22.3, 26.8, 29.9, 48.0, 119.6, 123.0, 125.7, 128.0, 129.3, 130.6, 130.8, 131.1, 136.9, 138.2, 140.8, 141.3, 154.5, 155.1, 162.5; ^{77}Se NMR ($CDCl_3$/CD_3OD) δ 195.2; Mass spectrum (ESI) 497 ($[M+H]^+$); HRMS calcd for $C_2H_{25}N_6O_2Se$ $[M+H]^+$ 497.1205, found 497.1196; ν_{max} 1691, 1482 cm^{-1}. Compound **5**: yellow crystals (70%): mp = 143–144 °C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 0.84 (t, $J = 7.4$ Hz, 3H), 1.29 (sextet, $J = 7.5$ Hz, 2H), 1.56 (quintet, $J = 7.6$ Hz, 2H), 2.57–2.61 (m, 2H), 5.50 (s, 2H), 6.69 (d, $J = 8.0$ Hz, 2H), 7.09 (d, $J = 8.0$ Hz, 2H), 7.30–7.33 (m, 3H), 7.45 (d, $J = 7.6$ Hz, 1H), 7.50–7.54 (m, 1H), 7.57–7.62 (m, 1H), 7.64–7.66 (m, 2H), 7.86 (d, $J = 7.2$ Hz, 1H); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 13.5, 22.1, 26.6, 29.6, 48.2, 120.8, 122.9, 125.8, 127.7, 128.0, 128.6, 128.8, 129.4, 130.6, 130.8, 131.2, 134.3, 136.8, 138.3, 139.8, 140.8, 154.6, 155.1, 161.9; ^{77}Se NMR ($CDCl_3$/CD_3OD) δ 383.8; Mass spectrum (ESI) 559 ($[M+H]^+$); HRMS calcd for $C_{28}H_{27}N_6O_2Se$ $[M+H]^+$ 559.1361, found 559.1334; ν_{max} 1687, 1478 cm^{-1}.
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