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N_1-STERICALLY HINDERED 2H-IMIDAZOL-2-ONE ANGIOTENSIN II RECEPTOR ANTAGONISTS: THE CONVERSION OF SURMOUNTABLE ANTAGONISTS TO INSURMOUNTABLE ANTAGONISTS

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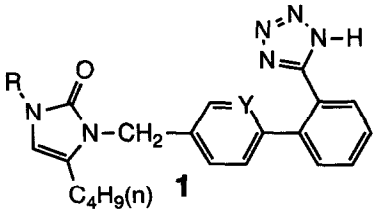
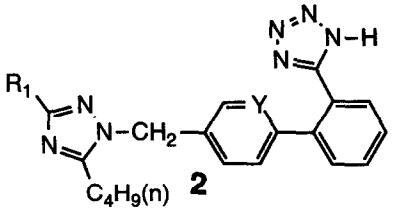
Abstract: The surmountable (competitive) N_1-(2-methylphenyl)-2H-imidazol-2-one angiotensin II receptor antagonist SC-54628 is converted to an insurmountable (noncompetitive) antagonist SC-54629 by the addition of a methyl group at the 6-position of the phenyl ring.

Recently, we reported[1] the presence of a previously unappreciated binding interaction between a postulated secondary lipophilic pocket in the angiotensin II receptor and the substituent at the N_1-position of 1,3-dihydro-2H-imidazol-2-one receptor antagonists **1** (Y= CH), e.g., SC-51895[2]. These observations are consistent with our earlier report[3] for this binding interaction with the substituent at the C_3-position of 1H-1,2,4-triazole angiotensin II receptor antagonists **2** (Y= CH), e.g., SC-50560[4] (IC_{50}= 5.6 nM, pA_2= 8.70). A subsequent investigation of nitrogen containing biphenylmethyl compounds, i.e., phenylpyridinylmethyl and pyridinylphenylmethyl, for 2H-imidazol-2-one receptor antagonists found that a consistent doubling of binding



1

SC-51895: Y = CH, R = C_4H_9(n)
SC-52892: Y = N, R = C_4H_9(n)



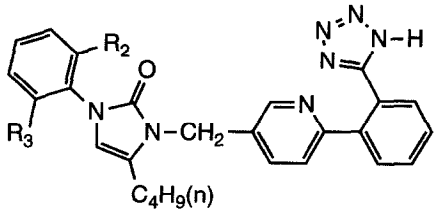
2

SC-50560: Y = CH, R_1 = C_4H_9(n)
SC-52458: Y = N, R_1 = C_4H_9(n)

potencies (IC_{50}) was found for 1-substituted-4-butyl-1,3-dihydro-3-[[6-[2-(1H-tetrazol-5-yl)phenyl]-3-pyridinyl]methyl-2H-imidazol-2-one analogs **1** (Y= N), e.g., SC-52892[5] (IC_{50}= 6.5 nM, pA_2= 8.68), relative to the parent 1-substituted-4-butyl-1,3-dihydro-3-[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-ylmethyl]-2H-imidazol-2-one analogs **1** (Y= CH), e.g., SC-51895 (IC_{50}= 12 nM, pA_2= 8.65), and that both series produced surmountable (competitive) receptor antagonists. This doubling of binding potency was not observed for the corresponding 1H-1,2,4-triazole series **2** (Y= N), e.g., SC-52458[6] (IC_{50}= 6.9 nM, pA_2= 8.18). Using the phenylpyridinylmethyl analogs **1** (Y= N) to explore the potential of the secondary lipophilic pocket, we discovered that surmountable AII antagonists could be converted to insurmountable (noncompetitive) receptor antagonists by the addition of steric hindrance to the N_1-substituent.

Substituting a phenyl ring (Table 1, **1a**) for the butyl group at N_1 caused a seven fold decrease in potency and suggested initially that aromatic substituents do not interact favorably within the secondary lipophilic pocket. However, when a 2-methyl substituent was added to the phenyl ring to give **1b** (SC-54628), the potency was restored to nearly that of the butyl analog SC-52892 (IC_{50}= 6.5 nM). It was hypothesized that the spatial orientation of the phenyl ring in the secondary lipophilic pocket is important in binding. The increase in potency is believed to be caused by the rotation of the aromatic ring due to unfavorable steric interactions between the ortho substituent and the carbonyl oxygen of the 2H-imidazol-2-one ring; this rotation would result in the dihedral angle between the phenyl ring and the 2H-imidazol-2-one ring to be greater for **1b** than for **1a**.

Table 1

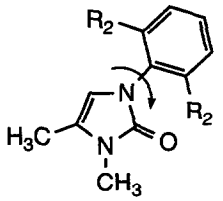


Analog	R_2	R_3	IC_{50} (nM)[7]	pA_2[7]	Mode*
1a	H	H	45	8.1	S
1b	H	CH_3	9.4	8.7	S
1c	H	C_2H_5	4.5	8.7	I
1d	H	$CH(CH_3)_2$	14	8.3	S
1e	H	$C(CH_3)_3$	19	9.0	I
1f	CH_3	CH_3	5.0	9.2	I
1g	C_2H_5	C_2H_5	5.0	8.7	I
1h	$CH(CH_3)_2$	$CH(CH_3)_2$	34	7.1	S

* S = surmountable, I = insurmountable

Molecular mechanics calculations[8] support this contention. Table 2 shows that for 2-substituted phenyl analogs, a progressive increase in the torsional angle between the two rings is observed as the size of the substituent increases. The only apparent exception to this trend is the 2-isopropylphenyl analog whose dihedral angle is smaller than that calculated for the 2-ethylphenyl analog[9]. The trend for 2,6-disubstituted phenyl analogs is not so straightforward. Molecular mechanics calculations suggested that the 2,6-dimethylphenyl analog **1f** (SC-54629) would have a greater dihedral angle than **1b** (71.7° vs. 55.5°), and thus, should be more potent; however, it did not predict the dramatic difference in mode of antagonism observed. Unlike the 2-methylphenyl analog **1b** which was found to be a surmountable antagonist, as were all other 1,3-dihydro-2H-imidazol-2-one analogs synthesized previously, the 2,6-dimethylphenyl analog **1f** was found to be an insurmountable[10] antagonist. We believe that this is the first reported case of a surmountable/insurmountable AII receptor antagonist conversion by the addition of a nonhydrogen bonding moiety.

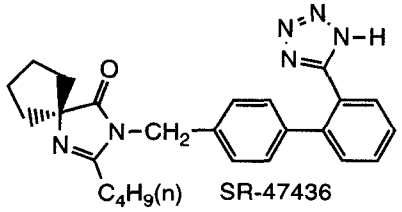
Table 2



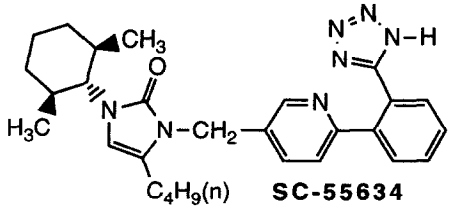
Substituent	Dihedral Angle Between Rings (°)	
	2-Substituted	2,6-Disubstituted
H	38.4	38.4
CH_3	55.5	71.7
C_2H_5	69.6	87.0
$CH(CH_3)_2$	57.7	89.0
$C(CH_3)_3$	75.1	89.0

In an attempt to better define the requirements for insurmountable antagonism, a series of 2-substituted phenyl and 2,6-disubstituted phenyl analogs (Table 1) were synthesized[11] to determine if there is any correlation between the calculated dihedral angle of the two rings and insurmountable antagonism. Comparing Table 1 with Table 2, it appears that there is a very good correlation between the calculated dihedral angle of the two rings and insurmountable antagonism. Analogs which have a dihedral angle of 69° or greater are all insurmountable except for the 2,6-diisopropylphenyl analog **1h**, while analogs with dihedral angles less than 69° are all surmountable. The reason why **1h** is surmountable, instead of insurmountable as predicted by its calculated dihedral angle of 89°, can be rationalized by its relative poor binding and antagonism (IC_{50}= 34 nM, pA_2= 7.1). The actual dihedral angle of this analog bound to the receptor may be much less than calculated due to the steric interactions of the second isopropyl group with some moiety in the receptor which would account for its poor binding. Energetically, these interactions would have to be more costly than the interactions with the carbonyl oxygen of the 2H-imidazol-2-one. There are no exceptions for the 2-substituted phenyl series; moreover, the calculated dihedral angles even correctly predicted the apparent anomaly of the 2-ethylphenyl analog **1c**. Our dihedral angle/mode of antagonism correlation seems to hold for aliphatic substituents as well. Sanofi's 4-spiralcyclopentyl imidazol-5-one SR-47436[12] (IC_{50}= 1.3 nM) is reported to be an insurmountable receptor antagonist. In this analog, the 4-spiralcyclopentyl substituent, which has a fixed dihedral angle of

90°, corresponds to the N_1-substituent of **1f**. In addition, we have found that the N_1-*trans,trans*-2,6-dimethylcyclohexyl analog SC-55634 (IC_{50}= 4.9 nM, pA_2= 9.3) is likewise an insurmountable antagonist.



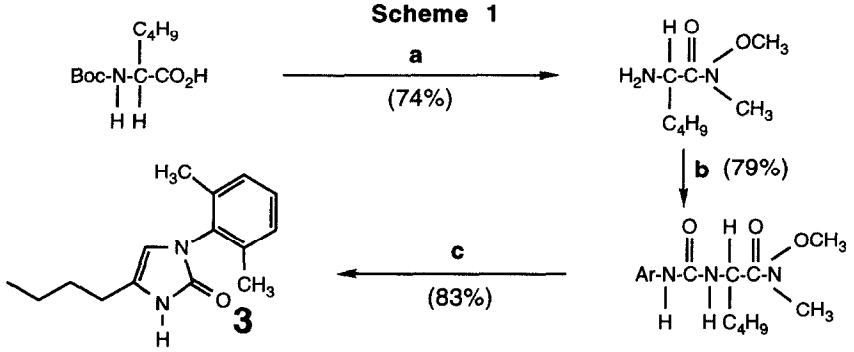
SR-47436



SC-55634

The synthesis of 2H-imidazol-2-one AII antagonists **1** (Y= N) is exemplified by the synthesis of SC-54629. Scheme 1 shows the synthesis of the 2H-imidazol-2-one **3** in 48% overall yield from commercially available N-BOC-norleucine.

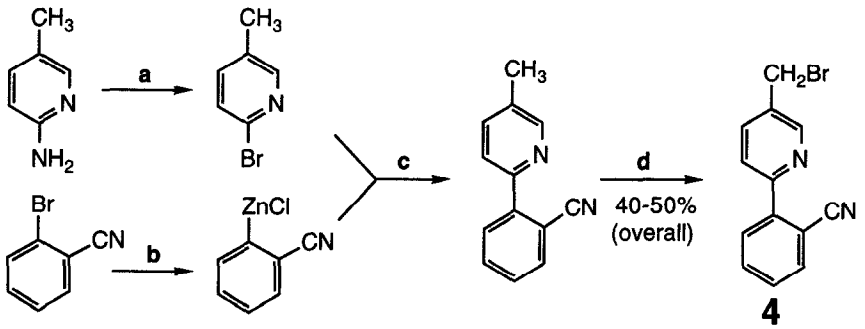
Scheme 1



a. 1. Cl-CO-$OCH_2CH(CH_3)_2$, $N(C_2H_5)_3$, 0°, 2. $HN(CH_3)OCH_3$, 3. TFA, Δ, 4. NaOH, $(C_2H_5)_2O$; **b**. $(CH_3)_2H_3C_6NCO$; **c**. 1. LAH, 0°, 2. TFA, $CHCl_3$, Δ.

Scheme 2 shows the synthesis of the phenylpyridinylmethyl alkylating reagent **4** in 40-50% overall yields from commercially available 2-amino-5-picoline and 2-bromobenzonitrile by means of a Pd° catalyzed coupling reaction.

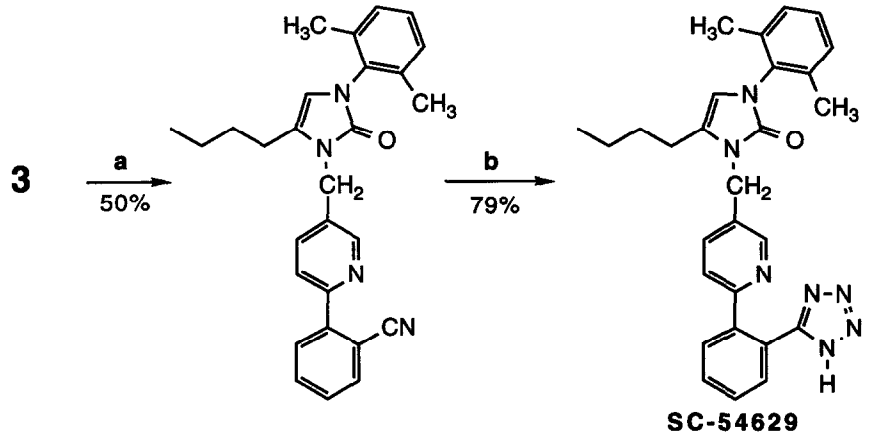
Scheme 2



a. $NaNO_2$, HBr, 0°; **b**. n-BuLi, -78°, $ZnCl_2$; **c**. $Pd[P(C_6H_5)_3]_4$; **d**. NBS, CCl_4, Δ

Scheme 3 shows the alkylation reaction in which the anion of the 2H-imidazol-2-one was reacted with the bromide **4**. Subsequent conversion of the resulting nitrile analog to the corresponding tetrazole produced SC-54629 in 39% overall yield.

Scheme 3



a. $KOC(CH_3)_3$, -78°, DMF, **4**; **b.** $(CH_3)SnN_3$, xylene, Δ.

The reason why N_1-substituted phenyl 1,3-dihydro-2H-imidazol-2-one analogs with dihedral angles of 69° or greater are insurmountable is unknown at this time; however, we speculate that it is due to a difference in dissociation rates[10] caused by the spatial dispensation of the N_1-substituent. We are currently conducting experiments which should help clarify this phenomenon.

References and Notes

1. Reitz, D.B.; Garland, D. J.; Norton, M. B.; Chen, B. K.; Olins, G. M.; Corpus, V. M.; McMahon, E. G.; Palomo, M.A.; Koepke, J. P.; Moore, G. K.; Smits, G. J.; McGraw, D. E.; Blaine, E. H.; Manning, R. E. 204th ACS National Meeting, **1992**, MEDI-31.
2. Reitz, D. B.; Manning, R. E. U.S. Patent 5,087,634 (2/11/92); Eur. Patent Appl. WO 92/07834 (5/14/92).
3. Reitz, D.B.; Penick, M. A.; Brown, M. S.; Reinhard, E. J.; Olins, G. M.; Corpus, V. M.; McMahon, E. G.; Palomo, M. A.; Koepke, J. P.; Moore, G. K.; Smits, G. J.; McGraw, D. E.; Blaine, E. H. 203rd ACS National Meeting, **1992**, MEDI-189.
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5. Reitz, D. B.; Manning, R.E. U.S. Patent 5,164,403 (11/17/92); Eur. Patent Appl. WO 92/17469 (10/15/92).

6. Reitz, D.B. U.S. Patent 5,155,117 (10/13/92); Eur. Patent Appl. WO 92/18092 (10/29/92).
7. Inhibition of [^{125}I]AII to rat uterine membranes (IC_{50}) had standard errors of 10% or less and antagonism of AII-contracted rabbit aortic rings (pA_2 and mode of antagonism) were the average of two rabbit aortas; in our assays, Dup-753 had an IC_{50}= 36 nM and a pA_2= 8.1. The experimental details for both assays are described in: Olins, G. M.; Corpus, V. M.; McMahon, E. G.; Palomo, M. A.; Schuh, J. R.; Blehm, D. J.; Huang, H.-C.; Reitz, D. B.; Manning, R. E.; Blaine, E. H. *J. Pharmacol. Exp. Ther.* **1992**, 261, 1037. The experimental biological data will be published elsewhere.
8. Molecular mechanics calulations were done using MacroModel MM2, Version 2.5.
9. In ethyl benzene, the low energy conformation has the ethyl group perpendicular to the phenyl ring (c-c-C-C torsional angle= 90°; (c= aromatic carbon, C= aliphatic carbon). In isopropyl benzene, the phenyl ring bisects the C-C-C angle of the isopropyl side chain (c-c-C-C angle= 120°; c-c-C-H angle equals 0°). In the 2-isopropylphenyl-2H-imidazol-2-one analog, the terminal methyl groups of the isopropyl side chain are orientated away from the 2H-imidazol-2-one ring and the methine hydrogen atom is pointed towards the 2H-imidazol-2-one ring system. From the point of view of the 2H-imidazol-2-one ring, the 2-isopropyl-phenyl group is effectively smaller than the 2-ethylphenyl group due to its orientation in its low energy conformation.
10. (a) Wong, P. C.; Timmermans, P. M. W. M. *J. Pharmacol. Exp. Ther.* **1991**, 258, 49; (b) Liu, Y. J.; Shankley, N. P.; Welsh, N. J.; Black, J. W. *Br. J. Pharmacol.* **1992**, 106, 233; (c) Robertson, M. J.; Barnes, J. C.; Drew, G. M.; Clark, K. L.; Marshall, F.H.; Michel, A.; Middlemiss, D.; Ross, B. C.; Scopes, D.; Dowle, M. D. *Br. J. Pharmacol.* **1992**, 107, 1173.
11. All new compounds were fully characterized spectrally; purity was established by a combination of analytical HPLC and HRMS and/or combustion analysis. Complete synthetic procedures with thorough AII analog characterization will be published elsewhere.
12. Cazaubon, C.; Gougat, J.; Guiraudou, P.; Broussier, D.; Lacour, C.; Roccon, A.; Galindo, G.; Barthelemy, G.; Gautret, B.; Nisato, D. *Am. J. Hypertens.* **1992**, 5, 19A.