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6-Substituted Quinazolinone Angiotensin II Receptor Antagonists

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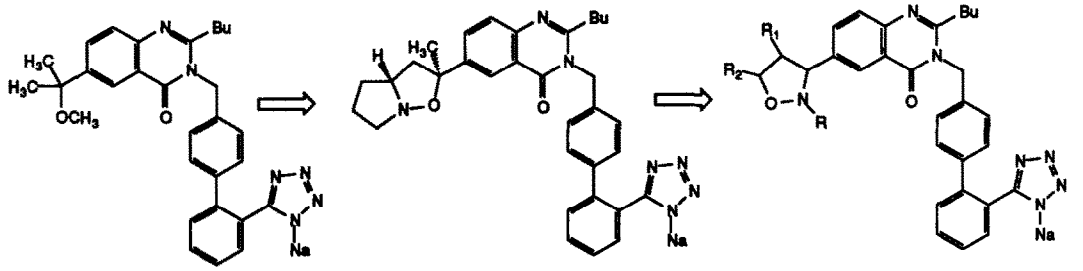
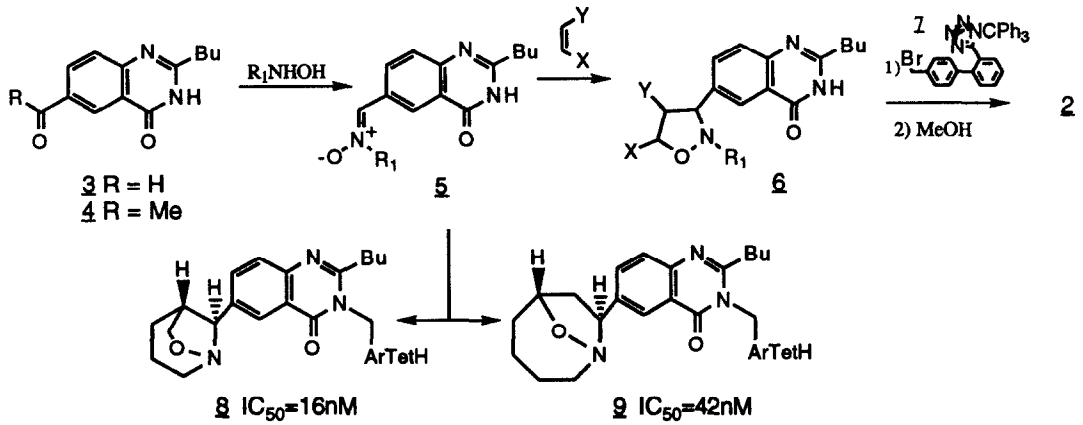
Abstract: 4(3H)-quinazolinones with a variety of heterocyclic substituents bound to the 6-position have been synthesized and evaluated as angiotensin II receptor antagonists both *in vitro* and *in vivo*. Some of these compounds have been shown to be potent, long-lasting, orally active antihypertensives.

We and others have recently reported on several series of quinazolinone based angiotensin II (A II) receptor antagonists, including the clinical candidate CL329,167.[1,2,3] The best of our compounds was 1 (CL332,877), an isoxazolidinyl-substituted quinazolinone[2c] which was more than ten times more potent than DuP 753 *in vitro* and several times more potent than DuP 753 (losartan) on oral dosing in an aorta coarcted rat model of renin-dependent hypertension.[4] Although 1 was potent, orally active and long-lasting, the isoxazolidine ring was extensively metabolized (presumably via initial N-O bond cleavage[2c]) presenting problems for its development into a clinically useful antihypertensive. We therefore began a search for other heterocycles which, when attached to the 6-position of the quinazolinone, would exceed the oral potency of 1 and might also be more robust under physiological conditions.



CL329,167; IC_{50}=31nM 1 (CL332,877; IC_{50}=27nM) 2

Initially we focused on isoxazolidines such as 2 produced by 1,3-dipolar cycloaddition of quinazolinone-nitrones with substituted olefins as shown in Scheme 1. These compounds were analogs of 1 in which the spatial orientation of the N-O atom pair was reversed. Nitrones 5 were readily available by condensation of the quinazolinone aldehyde 3 with the appropriate hydroxylamine. 1,3-Dipolar cycloaddition of 5 in the presence of an olefin gave isoxazolidinyl-quinazolinones, 6 (mixtures of diastereomeric products were separated by flash chromatography on silica gel). Alkylation of 6 with the trityl protected bromomethyl biphenyl tetrazole tail piece,[5] 7, and subsequent detritylation gave the desired compounds 2. Two bridged bicyclic isoxazolidines, 8 and



Scheme 1

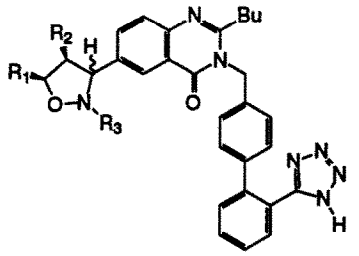
9, synthesized by intramolecular nitrone cycloadditions {5, R_1= $(CH_2)_3CH=CH_2$ and 5, R_1= $(CH_2)_4CH=CH_2$}, were also prepared.[6] Both the N-methyl and N-benzyl nitrones were synthesized with the expectation that the N-benzyl series could later be used to access the N-H isoxazolidines. However, all attempts to remove the N-benzyl group while keeping the isoxazolidine ring intact failed. In addition, we were unable to construct nitrones derived from methyl ketone 4, which would have provided isoxazolidines having a quaternary carbon bonded to the quinazolinone ring as in 1. The final compounds of this series were each tested *in vitro* in a binding assay using bovine adrenal cortex. The IC_{50}'s for the isoxazolidines are shown in Table 1.[7]

The most potent compounds of the series, *in vitro*, were the bridged isoxazolidines 8 and 9 which compared favorably with 1.[2c] This is a further indication of the large amount of steric bulk tolerated at this position of the parent quinazolinone. The remaining isoxazolidines in this series are somewhat less potent *in vitro* than the congeners of 1 with the exception of examples 10b and 12a. In general it appears that activity decreases with increasing size of the substituent on the isoxazolidine nitrogen (methyl vs. benzyl) as well as with increasing steric bulk of the ring derived from the dipolarophile.

The isoxazolidines listed in Table 1 were also active *in vivo* on oral dosing in an A II challenge model[4] and a renin-dependent aorta coarcted rat model of hypertension.[4] The best of these compounds were examples 12a and 14b which produced a 95% blockade of the vasopressor response to A II (0.05mcg/kg i.v.) at a dose of 5mg/kg p.o. In the aorta coarcted rat model a 3mg/kg p.o. dose of 14b produced a 60mm Hg decrease in mean arterial blood pressure (MABP) after two hours which was sustained for over 3 additional hours (end of experiment).

The next series of analogs that we explored were derivatives of the 6-dihydrofuran-quinazolinones 19 and 20 which had previously been shown[2c] to be potent A II receptor antagonists *in vitro*, but were not exceptionally active *in vivo*. We hoped that by annelation of a heterocyclic ring onto the dihydrofuran moiety the oral activity of the original compounds would be

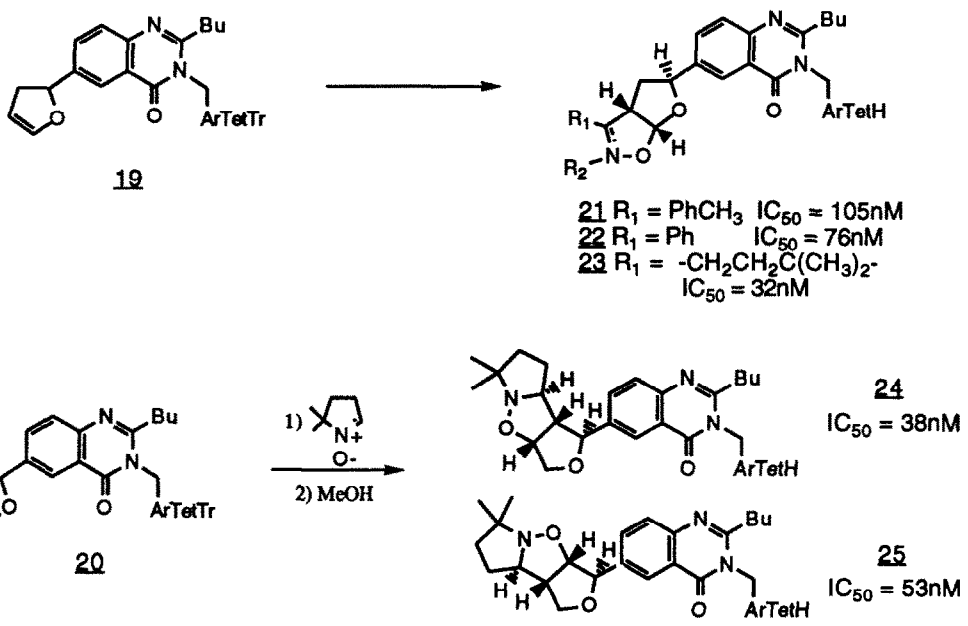
Table 1: In Vitro Binding of Substituted Isoxazolidines.



Compound #	R_1	R_2	R_3	2-H	IC_{50}(nM)
10a	CH_2OH	H	CH_3	α-H	61
10b	CH_2OH	H	CH_3	β-H	43
11	$-(CH_2)_3-$		CH_3	β-H	98
12a	$-CH_2CH_2CO-$		CH_3	α-H	42
12b	$-CH_2CH_2CO-$		CH_3	β–H	98
13	$-CH_2CH_2CO-$		CH_2Ph	β-H	79
14a	$-CH_2OCO-$		CH_3	α-H	150
14b	$-CH_2OCO-$		CH_3	β-H	68
15a	$-CH_2OCO-$		CH_2Ph	α-H	94
15b	$-CH_2OCO-$		CH_2Ph	β-H	177
16	$-CH_2CH_2CH_2CO-$		CH_3	β-H	900
17	-1,3-cyclopentyl-		CH_3	β-H	154
18	$-(CH_2)_6-$		CH_3	β-H	180
losartan					330

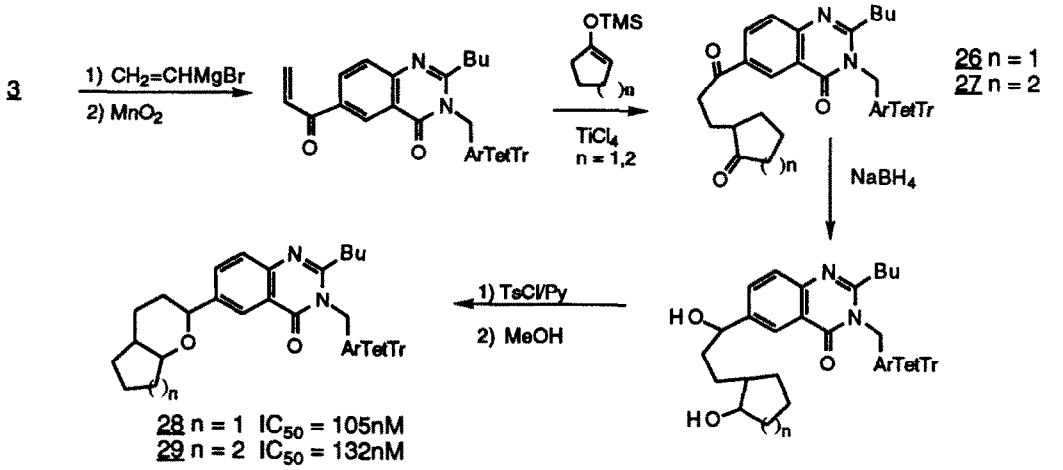
improved. Thus, reaction of p-tolyl nitrile oxide and phenyl nitrile oxide with 2,3-dihydrofuran 19, followed by deprotection of the tetrazole provided the bicyclic compounds 21 and 22 respectively (Scheme 2). Similarly, 5,5-dimethyl-1-pyrroline-N-oxide reacted with 19 to give the tricyclic compound 23 after deprotection of the tetrazole. In the same manner, 5,5-dimethyl-1-pyrroline-N-oxide reacted with 2,5-dihydrofuran derivative 20 followed by removal of the trityl group to yield a 1:1 mixture of tricyclics 24 and 25. Surprisingly, despite the large steric requirements of these C-6 substituents on the quinazolinone, all of these compounds were potent A II receptor antagonists *in vitro*, being at least three times more active than DuP 753 in the same assay. However, these compounds were not significantly more potent than the parent dihydrofurans on oral dosing *in vivo*. A 3mg/kg oral dose of compound 24 caused a slow 45mm Hg drop in MABP over the course of 5 hours in the aorta coarcted rat model of hypertension.

The next extension of the dihydrofuran analogs 19 and 20 which we pursued were the tetrahydropyran derivatives. These compounds could also be viewed as analogs of CL329,167 in which the ether linkage has been incorporated into a ring. It was hoped that the tetrahydropyran would have enhanced metabolic stability compared to the relatively labile isoxazolidine. The bicyclic tetrahydropyrans were synthesized in a straightforward manner starting from aldehyde 3 as shown in Scheme 3. Thus, Mukaiyama aldol[8] reaction of the TMS-enol ethers of cyclopentanone or



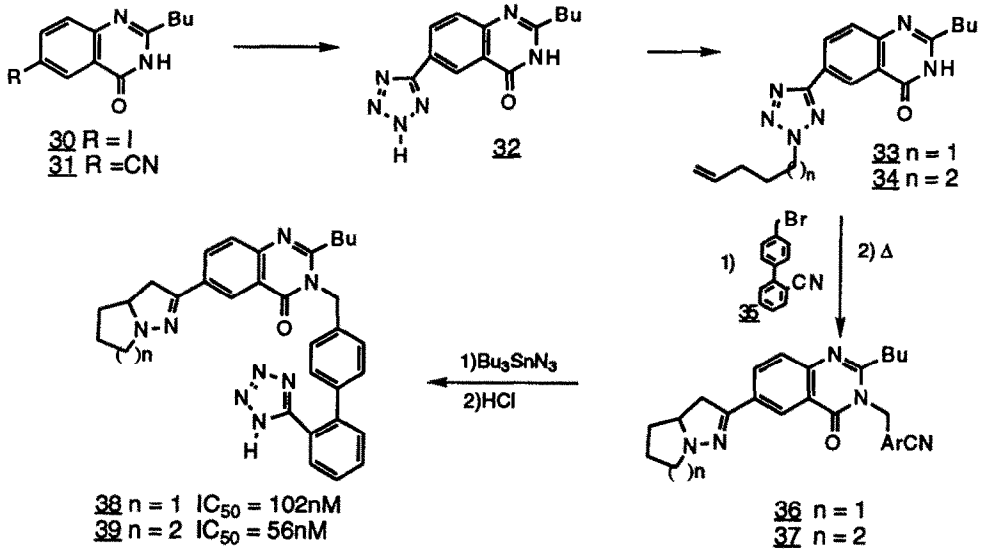
Scheme 2

cyclohexanone on enone 25 provided diones 26 and 27 respectively. Reduction of the dione followed by tosylation, cyclization and deprotection of the tetrazole gave tetrahydropyrans 28 and 29 as inseparable mixtures of diastereomers. In contrast to several other series of quinazolinone A II receptor antagonists we had synthesized, the tetrahydropyrans were only moderately active *in vitro*, but quite potent *in vivo*. In the aorta coarcted rat model of hypertension a 3 mg/kg oral dose of 29 produced a steady reduction of MABP during 4 hours (15mm Hg/hour) to a maximum decrease of 70mm Hg which was then sustained for an additional hour (end of experiment).



Scheme 3

The final group of derivatives investigated were bicyclic compounds in which an N-N bond had been substituted for the N-O bond in the two isoxazolidine series we had previously prepared. It was hoped that the N-N bond of these analogs would be less labile than the N-O bond, thereby increasing the half-life of these agents. The pyrazole derivatives analogous to 1 were synthesized by the route shown in Scheme 4.[9] Thus, 6-iodoquinazolinone 30 was converted into the corresponding nitrile, 31, followed by reaction with tributyltin azide to provide the tetrazole 32. Compound 32 was then alkylated with 1-bromo-4-pentene or 1-bromo-5-hexene to give 33 and 34 respectively. Alkylation of these olefin-tetrazoles with the bromomethyl biphenyl nitrile 35 and subsequent thermolysis in refluxing diphenyl ether produced the desired bicyclic tetrahydropyrazole derivatives, 36 and 37, via an intramolecular nitrile imine cycloaddition reaction. Next, conversion of the biphenyl nitrile into the requisite tetrazole moiety gave the final products 38 and 39. Compound 39 was roughly twice as active as 38 *in vitro*, but only one-half as potent as 1. Both compounds were slightly less potent than DuP 753, and several fold less potent than 1 in the renin-dependent aorta coarcted rat model of hypertension.

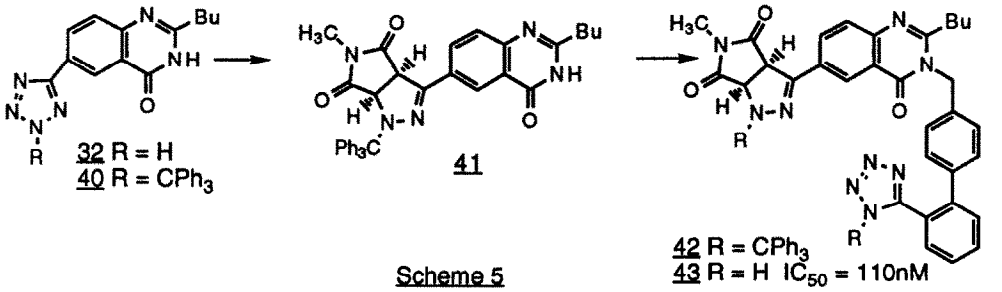


Scheme 4

The intermolecular variant of the nitrile imine reaction was used to synthesize dihydropyrazoles analogous to structure 2. Thus, tritylation of tetrazole-quinazolinone 32 gave 40 which was then reacted with N-methyl maleimide in refluxing xylenes to yield 41 (Scheme 5). Alkylation of compound 41 with the tail piece, 7, followed by removal of both trityl protecting groups gave 43. Compound 43 is still three-fold more potent than DuP 753 *in vitro*, but only moderately active on oral dosing. The corresponding tetrahydropyrazoles were not synthesized.

In summary, we have extended our original series of 6-substituted quinazolinones to include several additional heterocyclic groups which display improved oral potency as A II receptor

antagonists relative to our initial quinazolinone clinical lead CL329,167.[2a] Many of these compounds are extremely potent, long-lasting, orally active agents worthy of further study as



Scheme 5

possible treatments for hypertension and congestive heart failure. However, we have been unable to exceed the oral potency level of the isoxazolidinyl-quinazolinone 1.

References and Notes:

1. For recent reviews on A II receptor antagonists see:
   a)Baldwin, J. J. *Current Opinion in Therapeutic Patents*, **1993**, 137.
   b)Buehlmayer, P. *Current Opinion in Therapeutic Patents*, **1992**, 1693.
2. a)Levin, J. I.; Venkatesan, A. M.; Chan, P. S.; Baker, J. S.; Fransisco, G.; Bailey, T.; Vice, G.; Katocs, A.; Lai, F.; Coupet, J. *Bioorg. & Med. Chem. Lett.* **1994**, *4*, 1135.
   b)Levin, J. I.; Chan, P. S.; Bailey, T.; Katocs, A.; Venkatesan, A. M. *Bioorg. & Med. Chem. Lett.* **1994**, *4*, 1141.
   c)Levin, J. I.; Chan, P. S.; Coupet, J.; Bailey, T. K.; Vice, G.; Thibault, L.; Lai, F.; Venkatesan, A.M. *Bioorg.& Med. Chem. Lett.* in press.
   d)Levin, J. I.; Chan, P. S.; Coupet, J.; Thibault, L.; Venkatesan, A. M.; Bailey, T. K.; Vice, G.; Cobuzzi, A.; Lai, F.; Mellish, N. *Bioorg.& Med. Chem. Lett.* in press.
3. a)Allen, E. E.; de Laszlo, S. E.; Huang, S. X.; Quagliato, C. S.; Greenlee, W. J.; Chang, R. S. L.; Chen, T.-B.; Faust, K. A.; Lotti, V. J. *Bioorg. & Med. Chem. Lett.* **1993**,*3*, 1293.
   b)de Laszlo, S. E.; Allen, E. E.; Quagliato, C. S.; Greenlee, W. J.; Patchett, A. A.; Nachbar, R. B.; Siegl, P. K. S.; Chang, R. S.; Kivlighn, S. D.; Schorn, T. S.; Faust, K. A.; Chen, T.-B.; Zingaro, G. J.; Lotti, V. J. *Bioorg. & Med. Chem. Lett.* **1993**,*3*, 1299.
   c)de Laszlo, S. E.; Quagliato, C. S.; Greenlee, W. J.; Patchett, A. A.; Chang, R. S. L.; Lotti, V. ;Chen, T.-B.; Scheck, S. A.; Faust, K. A.; Kivlighn, S. S.; Schorn, T. S.; Zingaro, G. J.;Siegl, P. K. S. *J. Med. Chem.* **1993**,*36*, 3207.
4. Chan, P. S.; Cervoni, P.; Ronsberg, M. A.; Scully, P. A.; Quirk, G. J.; McLendon, T. K.*Drug Development Res.* **1989**,*18*, 75.
5. Carini, D. J.; Duncia, J .V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella,III, J. B.; Wells, G. J.; Wexler, R. R.; Wong, P. C.; Yoo, S.-E.; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1991**,*34*, 2525.
6. For similar examples see:
   a)Oppolzer, W.; Siles, S.; Snowden, R. L.; Bakker, B. H.; Petrilka, M. *Tetrahedron* **1985**,*41*, 3497.
   b)Baldwin, S. W.; Wilson, J. D.; Aube,J. *J.Org. Chem.* **1985**,*50*, 4432.
   c)Lumma,Jr., W. C. *J. Am. Chem. Soc.* **1969**,*91*, 2820.
7. a)Chiu, A. T.; Duncia, J. V.; McCall, D. E.; Wong, P. C.; Price, W. A.; Thoolen, M. J. N. C.; Carini, D. J.; Johnson, A. L.; Timmermans, P. B. M. W. M. *J. Pharmacol. Exper. Therap.* **1989**, *250*, 867.
   b)Binding assay done using bovine adrenal cortex tissue. DuP 753 IC_{50}=330nM in this assay.
8. Narasaka, K.; Soai, K.; Aikawa, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 779.
9. Padwa, A.; Nahm, S.; Sato, E. *J.Org.Chem.* **1978**, *43*, 1664.

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