Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 4, No. 9, pp 1141-1146, 1994
Copyright © 1994 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0960-894X/94 $6.00+0.00

0960-894X(94)E0116-V

THE SYNTHESIS OF 2,3-DIHYDRO-4(1H)-QUINAZOLINONE ANGIOTENSIN II RECEPTOR ANTAGONISTS

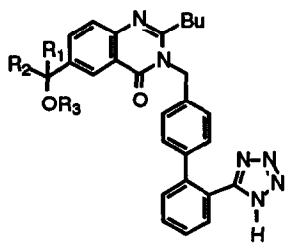
Jeremy I. Levin*, Peter S. Chan, Trina Bailey, Andrew S. Katocs, Jr. and A.M. Venkatesan

American Cyanamid Company
Medical Research Division
Lederle Laboratories
Pearl River, New York 10965

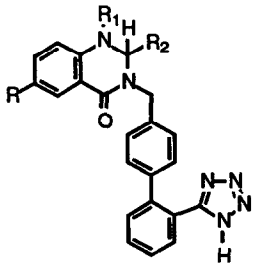
Abstract:. The synthesis and biological evaluation of a series of 2,3,-dihydro-4-(1H)-quinazolinone angiotensin II receptor antagonists is described.

The treatment of essential hypertension by blocking the formation of the octapeptide angiotensin II (A II), a potent endogenous vasoconstrictor,[1] has been proven to be effective in the case of angiotensin converting enzyme (ACE) inhibitors.[2] However, ACE inhibitors are not completely selective for ACE and can therefore cause unwanted side effects which make their use problematic. Renin inhibitors should be more selective than ACE inhibitors, but most still suffer from the problems of poor bio-availability and short half-life. The potential ability of potent, orally active, non-peptide A II antagonists to surmount these problems has made them exceedingly attractive targets for drug development.

We recently described a series of substituted 4(3H)-quinazolinones, 1 , which were potent antagonists of angiotensin II both *in vitro* and *in vivo*.[3] The best of these compounds was CL 329,167, which is presently undergoing clinical trials for the treatment of hypertension. We were therefore interested in ascertaining whether the analogous 2,3-dihydro-4(1H)-quinazolinones, 2 , were also effective A II receptor antagonists. At the time of this work there were few if any non-peptide A II antagonists in which the "head" piece was non-planar.[4]

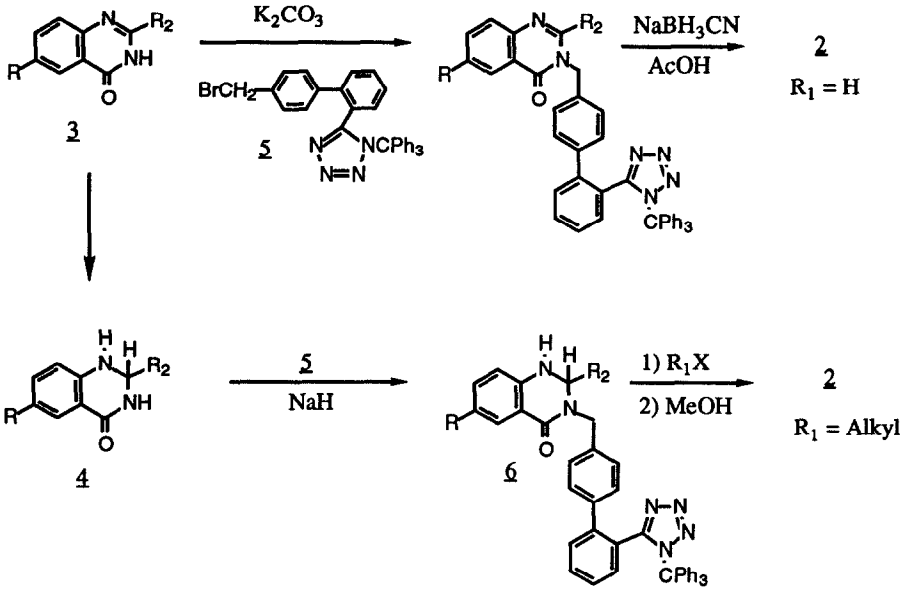


1
CL 329,167 (R_1, R_2, R_3 =CH_3)



2

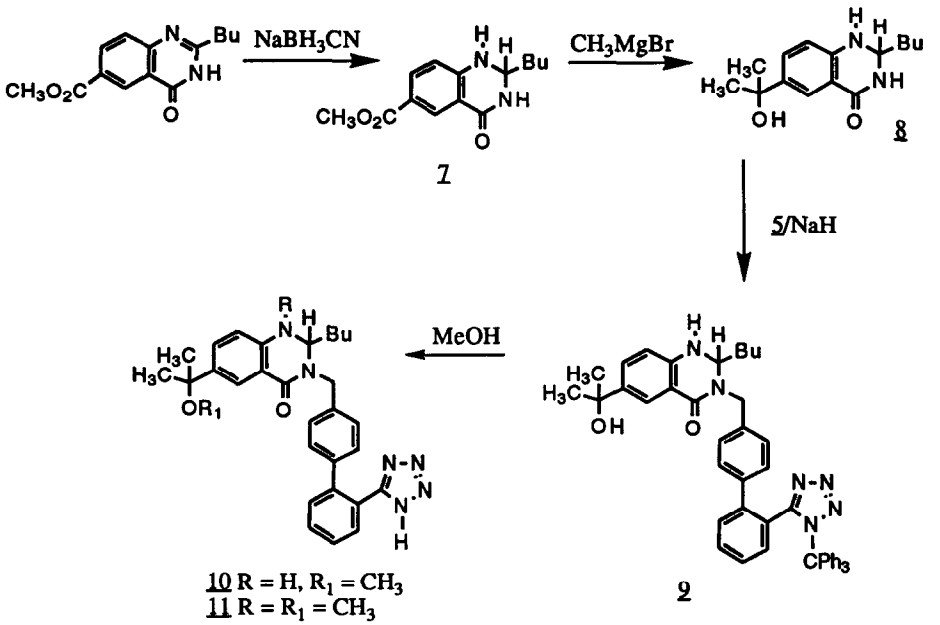
At the outset of this study it was assumed that the C-6 substituted dihydroquinazolinones would be the most active members of this class of compounds, as was the case for the 4(3H)-quinazolinones, 1 , and so only derivatives with substituents at that position were synthesized. The target compounds were made by either of two routes (Scheme 1). The quinazolinones 3 could first be alkylated with the bromomethyl biphenyl "tail" piece, 5, followed by reduction with cyanoborohydride and concommitant detritylation of the tetrazole to give 2 (R_1 = H). Alternatively, the quinazolinones 3 could initially be reduced with sodium cyanoborohydride in acetic acid to provide the corresponding dihydro species 4 which was then alkylated with 5 to give a mixture of 6 and the undesired N-1 alkylated product. Compounds 6 could then be alkylated at N-1 with the desired alkyl halide and sodium hydride in THF followed by detritylation to produce 2 (R_1 = alkyl).



SCHEME 1

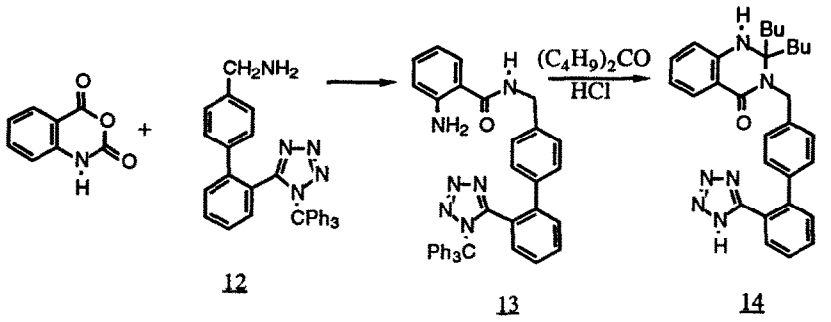
The synthesis of the dihydroquinazolinone analogous to CL 329,167 (i.e. 2, R=$C(CH_3)_2OCH_3$, R_1=H, R_2=Bu) was not directly available by either of these routes since $NaBH_3CN$/AcOH reduction of quinazolinones bearing a benzylic hydroxyl group resulted in concommitant reduction of the quinazolinone ring and the alcohol functionality. It was therefore necessary to reduce the

quinazolinone prior to the introduction of alcohol (Scheme 2). Thus, the dihydroquinazolinone ester 7 was converted into the desired tertiary alcohol 8 in moderate yield on reaction with 10 equivalents of methylmagnesium bromide. Subsequent alkylation of alcohol 8 with 5 in the presence of sodium hydride gave a 33% yield of the N-3 alkylated product along with 10% of the N-1 alkylated compound. Compound 9 was then converted into the corresponding methyl ether 10 in 27% yield simply by refluxing in methanol, which also deprotected the tetrazole. N- and O-Methylation of 9 with NaH/MeI followed by methanolysis produced methyl ether 11.



SCHEME 2

An alternate route was used for the synthesis of a 2,2-disubstituted 2,3-dihydroquinazolinone. Thus, reaction of the amino-methyl biphenyl tetrazole 12 with isatoic anhydride gave amino-amide 13 in 90% yield. Aniline 13 was then reacted with 5-nonanone in ethanolic HCl to give the dihydroquinazolinone 14 in 33% yield (Scheme 3).

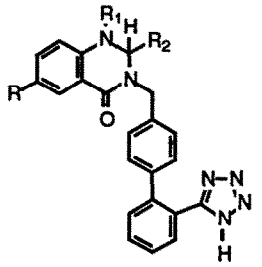


SCHEME 3

The results of the *in vitro* binding assay[5], using rat adrenal cortex tissue, are shown in Table 1. In most cases there is a large loss of binding affinity when the 4(3H)-quinazolinone "head" piece is replaced by the analogous 2,3-dihydro-4(3H)-quinazolinone. For instance, Example 18 is fifty times less potent than CL 329,167 (IC_{50} = 6nM), its 4(3H)-quinazolinone congener. Nevertheless, two extremely potent compounds were found in this series, which evidently has a very different SAR than the 4(3H)-quinazolinone series. Thus, for R =R_1=H an n-propyl substituent at R_2 provides optimal activity (Example 3) with potency falling off dramatically if this side chain is lengthened or shortened (Example 3 vs. Examples 2 and 4). Interestingly, there is no loss in binding affinity when two bulky groups occupy R_2 (Example 4 vs. 5). However, a different trend was apparent when either R or R_1 was an alkyl substituent, a requirement for optimal *in vitro* potency in the 2,3-dihydroquinazolinone series. If a bulky substituent occupies R, and R_1=H, then activity increases as R_2 increases in length from ethyl to n-butyl (Examples 7,8 and11). Finally, if R and R_2 are constant within a series, binding decreases as the size of R_1 increases, so long as R_1 is not hydrogen. The ten-fold decrease in affinity seen when R_1 is changed from methyl to hydrogen is perhaps due to the fact that N-1 is required as a hydrogen bond acceptor rather than a hydrogen bond donor (Examples 13 and 14 vs. 3 and 4). The only instance in which substituting a methyl for hydrogen at R_1 is detrimental is Example 17 where R and R_2 are both bulky groups, implying a finite volume for that area of the receptor.

The 2,3-dihydroquinazolinones were next tested for their ability to inhibit the vasoconstrictor response to exogenous angiotensin II in rats.[6] The best compounds of the series were Examples 11, 14 and 17, which produced inhibitions of 92, 88 and 95% respectively when administered at 15 mg/kg intravenously. Unfortunately, these compounds were only minimally active upon oral administration in this screen, including those with the tertiary alcohol methyl ether at C-6 (Examples 18 and 19) which had proven so effective in providing potent, orally active compounds in the 4(3H)-quinazolinone series.

TABLE 1: *In vitro* binding data for 2,3-dihydroquinazolinones 2.



Example#	R	R_1	R_2	$IC_{50}(\mu M)^{5a,b}$
1	H	H	Me	90
2	H	H	Et	27
3	H	H	nPr	0.54
4	H	H	nBu	14
5	H	H	$(nBu)_2$	13
6	Me	H	Et	20
7	iPr	H	Et	45
8	iPr	H	nPr	12
9	Et	H	nBu	0.37
10	Bn	H	nBu	3.7
11	iPr	H	nBu	0.09
12	CO_2Me	H	nBu	4.1
13	H	Me	nBu	1.1
14	H	Me	nPr	0.05
15	H	Et	nPr	7.5
16	H	Bn	nPr	100
17	iPr	Me	nBu	0.65
18	$C(Me)_2OMe$	H	nBu	2.7
19	$C(Me)_2OMe$	Me	nBu	2.0
CL 329,167				0.006
DuP 753				0.082

In summary, we have disclosed a series of 2,3-dihydroquinazolinones, some of which are potent inhibitors of angiotensin II *in vitro*. These compounds were devoid of any significant oral activity and so were not pursued further.

References and Notes:

1) Peach, M. J. *Biochem. Pharmacol.* **1981**, *30*, 2745.

2) a) Ondetti, M. A.; Rubin B.; Cushman, D. W. *Science* **1977**, *196*, 441.
b) Ondetti, M. A.; Cushman, D. W. *J. Med. Chem.* **1981**, *24*, 355.
c) Patchett, A. A.; Harris, E.; Tristram, E. E.; Wyvratt, M. J.; Wu, M. T.; Taub, D.; Peterson, E. R.; Ikeler, T. J., Ten Broecke, J.; Payne, L. G.; Ondeyka, D. L.; Thorsett, E. D.; Greenlee, W. J.; Lohr, N. S.; Hoffsommer, R. D.; Joshua, H.; Ruyle, W. V.; Rothrock, J. W.; Aster, Maycock, A. L.; S. D. Robinson; Hirshmann, R. F. M.; Seet, C. S.; Ulm, E. H.; Gross, D. M.; Vassil, T. C.; Stone, C. A. *Nature* **1980**, *288*, 280.

3) Levin, J. I.; Venkatesan, A. M.; Baker, J. S.; Francisco, G.; Chan, P. S.; Bailey, T.; Vice, G.; Katocs, A. *Bioorg. & Med. Chem. Lett.* in press.

4) a)Buhlmayer, P. *Curr. Opin. Thera. Patents* **1992**, *2*, 1693.
b)Atwal,K.S.; Ahmed,S.Z.; Bird,J.E.; Delaney,C.L.; Dickinson,E.J.; Ferrara,F.N.; Hedberg,A.; Miller,A.V.; Moreland,S.; O'Reilly,B.C.; Schaeffer,T.R.; Waldron,T.L.; Weller,H.N. *J. Med. Chem.* **1992**, *35*, 4751.
c) Murray,W.V.; Lalan,P.; Gill,A.; Addo,M.F.; Lewis,J.M.; Lee,D.K.H.; Rampulla,R.; Wachter,M.P.; Hsi,J.D.; Underwood,D.C. *Biorg. & Med. Chem. Lett.*, **1992**, *2*, 1775.

5) a) Chiu, A. T.; Duncia, J. V.; McCall, D. E.; Wong, P. C.; Price, W. A.; Thoolen, M. J. M. C.; Carini, D. J.; Johnson, A. L.; Timmermans, P. B. M. W. M. *J. Pharmacol. Exp. Ther.* **1989**, *250*, 867.
b) All IC_{50} values were obtained using rat adrenal cortex tissue. DuP 753 had an IC_{50} of 82nM in this assay.

6) Chan, P. D.; Cervoni, P.; Accomando, R. C.; Quirk, G.; Ronsberg, M. J. *Hypertension* **1986**, *4*, 749.

(*Received in USA* 24 *February* 1994; *accepted* 25 *March* 1994)