Bioorganic & Medicinal Chemistry Letters, Vol. 4, No. 1, pp. 195-200, 1994
Printed in Great Britain

0960-894X/94 $6.00 + .00

QUINOLINE-4-CARBOXYLIC ACIDS AS ANGIOTENSIN II RECEPTOR ANTAGONISTS

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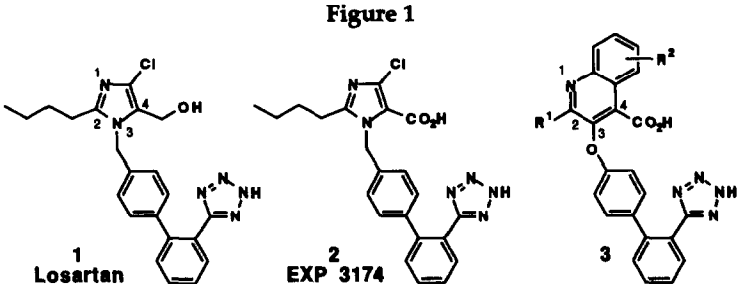
Abstract: We have synthesized a series of quinoline-4-carboxylic acids that are potent antagonists of the angiotensin II receptor. They show high receptor binding affinities and functional antagonism in rabbit aortic strips. They are also effective in blocking the hypertensive effects of AII *in vivo*.

The renin-angiotensin system plays an important role in the pathophysiology of cardiovascular disease and agents such as angiotensin converting enzyme (ACE) inhibitors are effective for the treatment of hypertension.[1] Antagonism of angiotensin II (AII) AT_1 receptors may also be a useful strategy for the treatment of hypertension and several groups have disclosed non-peptidic AII antagonists.[2] We would like to report the development of quinoline-4-carboxylic acids as antagonists of the AII receptor.

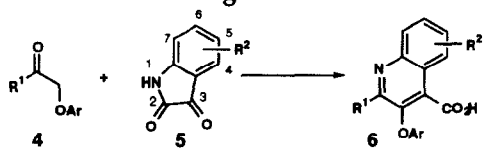
Many reported AII antagonists (Figure 1), such as losartan (**1**)[2a] and its more pharmacologically active metabolite EXP 3174 (**2**)[2b], share structural features believed to be important for activity. These include a heterocycle with one or more basic nitrogen atoms, an alkyl substituent in the 2-position relative to the basic nitrogen, an aryl substituent with an acidic group in the 3-position and an acid or its metabolic equivalent in the 4-position. Quinoline-4-carboxylic acids (**3**) appeared to accommodate all these structural features.

Figure 1



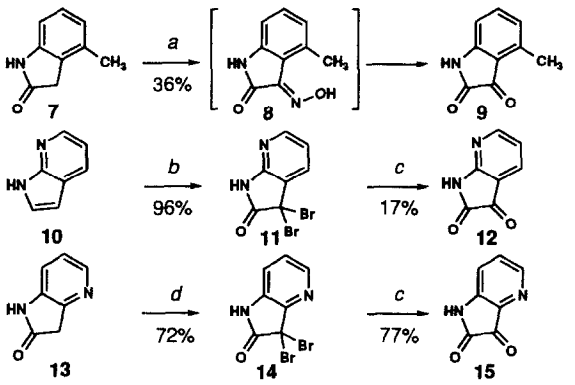
The Pfitzinger quinoline synthesis (Figure 2) is quite general for the reaction of ketones (**4**) with isatin or substituted isatins (**5**) under strongly basic conditions to give quinoline-4-carboxylic acids (**6**) substituted in the 2 and 3 positions.[3] The alkyl substituents (R^1) are contained on the ketone component and substituents on the carbocyclic ring of the quinoline (R^2) arise from substituents on the isatin. We hoped to optimize the activity of these compounds by variation of the these substituents.

Figure 2



Isatin, 5-fluoroisatin, 5-methoxyisatin and 7-methylisatin are commercially available or readily synthesized by known methods.[4] The other isatins were obtained by oxidation of oxindoles (Scheme 1). The 4-methylisatin (**9**) was synthesized from 4-methyloxindole (**7**)[5] by oxidation to the oxime (**8**) followed by hydrolysis.[6] The azaisatins (**12, 15**) were prepared by oxidation of 7-azaindole (**10**)[7] or 4-azaoxindole (**13**)[8] to the 3,3-dibromooxindoles (**11, 14**) followed by hydrolysis.[9]

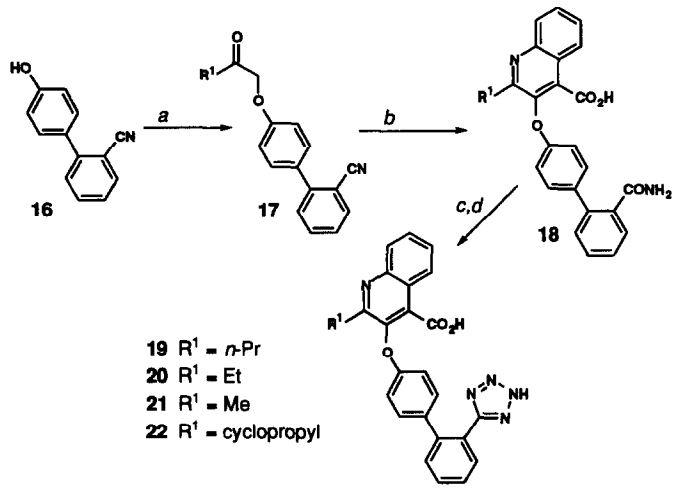
Scheme 1



Reagents: a) $NaNO_2$, HCl, H_2O, b) pyridinium bromide perbromide, *t*-BuOH, H_2O, c) AgOTFA, MeCN, H_2O, d) NBS, *t*-BuOH.

The ketone components were obtained by reaction of a chloromethyl ketone with 2-(4-hydroxyphenyl)benzonitrile (**16**)[10] (Scheme 2). Our initial approach to the quinolines condensed the ketone component (**17**) and isatin in 30% potassium hydroxide at elevated temperature. Unfortunately, this treatment also led to hydrolysis of the nitrile to the amide (**18**). The nitrile then was reformed and the tetrazole was obtained by the usual means.

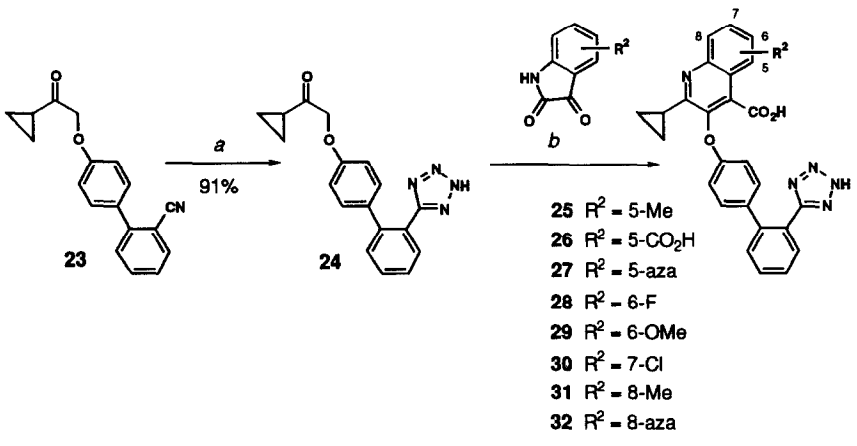
Scheme 2



Reagents: a) R^1COCH_2Cl, K_2CO_3, acetone, 50°, b) isatin, 30% KOH, 105°, c) $(CF_3CO)_2O$, pyridine, dioxane, d) Bu_3SnN_3, xylene, 110°.

In later syntheses, we found it more efficient to form the tetrazole at an earlier stage (Scheme 3). Pfitzinger reaction of a ketone component already functionalized with a tetrazole (**24**) resulted in higher yields and eliminated the dehydration step.

Scheme 3



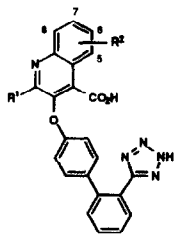
Reagents: a) Bu_3SnN_3, xylene, 110°, b) 30% KOH, 105°

In vitro testing included receptor binding affinity as well as functional antagonism. The binding affinity was determined by a competitive binding assay using ^{125}I labeled [Sar^1,Ile^8] angiotensin II bound to AII receptors in rat adrenocortical membranes and inhibition constants

(K_i) for the AT_1 receptor population were calculated by iterative curve fitting.[11] Functional antagonism (K_B) was evaluated by the ability of a single concentration of antagonist to block AII induced contractions in rabbit aortic smooth muscle strips.[12]

Our initial study was modification of the alkyl group (R^1) at the 2-position of the quinoline. The activity of the compound where R^1 is n-propyl (**19**), confirmed the hypothesis that the quinoline-4-carboxylic acids can be high affinity ligands for the AII receptor. Reducing the size of the substituent to ethyl (**20**) had little effect on binding affinity or functional potency but substitution of a methyl group (**21**) reduced functional potency by 10 fold. The most interesting compound in this study was the 2-cyclopropyl compound (**22**, BMS-183920) which showed very potent and insurmountable antagonism in the functional assay (Table).

Table. *In vitro* activity of quinoline-4-carboxylic acids.

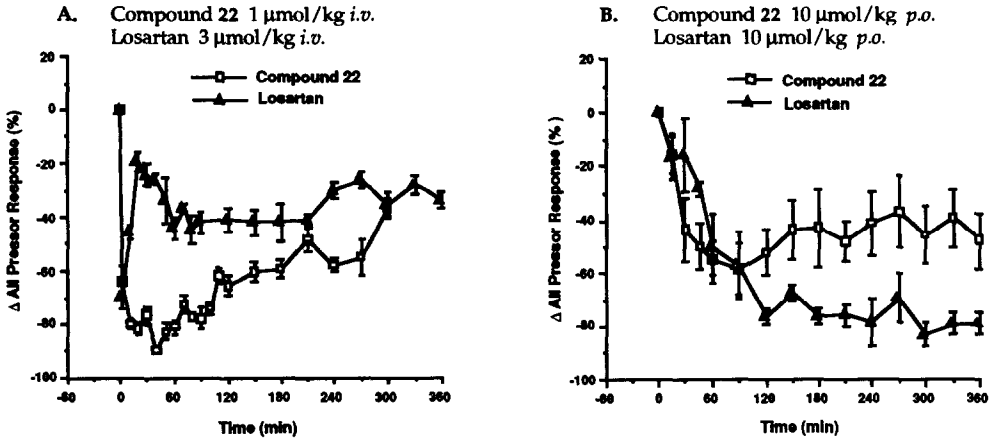


Compound	R^1	R^2	K_i (nM)	K_B (nM)
19	n-Pr	H	3.4 ± 1.0	0.091 ± 0.051
20	Et	H	5 9 ± 1.2	0 12 ± 0 023
21	Me	H	3.2 ± 0.4	1 1 ± 0.18
22	cyclo-Pr	H	2 9 ± 0.5	0 061 ± 0 034
25	cyclo-Pr	5-Me	12 ± 1	0 40 ± 0 09
26	cyclo-Pr	5-CO_2H	120 ± 7	2 0 ± 0.30
27	cyclo-Pr	5-aza	2 1 ± 0 2	0.67 ± 0.13
28	cyclo-Pr	6-F	14 ± 0.5	0.61 ± 0.055
29	cyclo-Pr	6-OMe	33 ± 4	0 20 ± 0.091
30	cyclo-Pr	7-Cl	32 ± 2.9	0 18 ± 0.20
31	cyclo-Pr	8-Me	1,300 ± 120	8.3 ± 3 7
32	cyclo-Pr	8-aza	4.6 ± 2.1	0.76 ± 0.19

In the cyclopropyl series, we examined substitution of the quinoline ring with halogen, alkyl, alkoxy, and carboxyl substituents as well as ring nitrogens. Although many of these compounds displayed high binding affinity and functional antagonism, in no case did substitution in the carbocyclic ring of the quinoline lead to greater potency in both *in vitro* assays.

Compounds that were potent in the functional assay were tested *in vivo* both *i.v.* and *p.o.* by measuring the ability to block an AII induced increase in blood pressure in normotensive rats. The results are expressed as the percent change of the response to AII relative to the response in the absence of the test compound. The most potent antagonist in our *in vivo* tests was the cyclopropyl compound (**22**, BMS-183920). Upon *i.v.* administration, this compound lowered the AII response to a greater degree and at a lower dose than losartan, however, losartan was more active upon oral administration (Figure 3). Unfortunately, all of the other compounds with different alkyl groups (R^1) and quinoline ring substituents (R^2) showed similar pharmacology. This lack of oral potency suggested that these compounds are readily metabolized and/or poorly absorbed. Poor oral absorption may be due to the diacidic nature of the compounds and losartan may have better oral performance because it is absorbed as a monoacid before it is metabolically activated to the diacidic EXP 3174. This hypothesis suggests that a strategy of forming a prodrug at one of the two acidic sites of the quinoline-4-carboxylic acids would improve oral efficacy.

Figure 3. Inhibition of the AII pressor response by compound 22 (BMS-183920) and losartan in normotensive rats.



In summary, we have synthesized a series of quinoline-4-carboxylic acids as AII antagonists that have excellent *in vitro* and *i.v.* potency.[13] The problem of oral activity will be addressed in the following paper.

Acknowledgments: We thank the Bristol-Myers Squibb Department of Analytical Chemistry for microanalysis and mass spectra.

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13. Subsequent to the completion of this study, similar compounds were disclosed by researchers at Merck. No biological data were reported. Greenlee, W. J.; Johnston, D. B. R.; MacCoss, M. U.S. Patent 5,157,040.

(*Received* 21 *July* 1993; *accepted* 15 *September* 1993)