Bioorganic & Medicinal Chemistry Letters, Vol. 4, No. 1, pp. 201-206, 1994
Printed in Great Britain

0960-894X/94 $6.00 + .00

ORALLY ACTIVE PRODRUGS OF QUINOLINE-4-CARBOXYLIC ACID ANGIOTENSIN II RECEPTOR ANTAGONISTS

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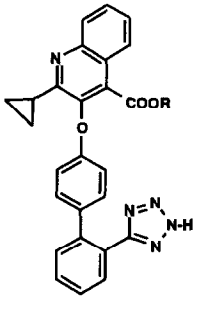
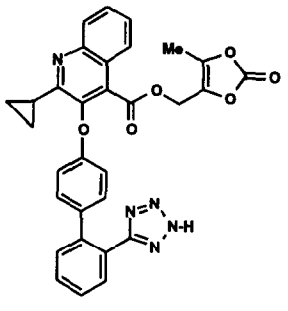
Abstract: Prodrug derivatization of a potent quinoline-4-carboxylic acid angiotensin II receptor antagonist was undertaken as an approach to achieve improved oral activity. A dioxolenone carboxylic ester and an alkylated tetrazole prodrug both showed greater oral antihypertensive activity in the salt-deplete spontaneously hypertensive rat and increased oral bioavailability relative to the parent compound.

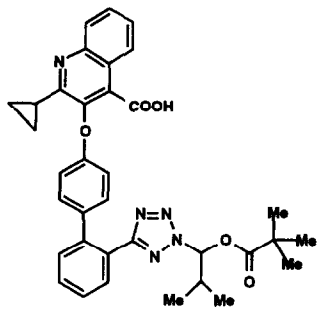
In the preceding paper, we described the design and synthesis of the potent non-peptidic angiotensin II receptor antagonist, quinoline-4-carboxylic acid derivative BMS-183920 (**1a** - *in vitro* inhibition of angiotensin II: K_i = 2.9 nM; K_B = 0.061 nM).[1] Such compounds are of potential utility in the treatment of hypertension and related cardiovascular diseases.[2] Despite excellent intrinsic potency, weak oral activity limited the *in vivo* efficacy of **1a**. This communication describes efforts to improve the oral bioavailability of **1a** by a prodrug approach which ultimately led to the preparation of two compounds with improved oral activity and bioavailability, the dioxolenone carboxylic ester **2** (BMS-184698) and the N-alkyl tetrazole prodrug **3**.



1a, R = -H (BMS-183920)
1b, R = -CH_2CH_3
1c, R = -CH(i-Pr)-O-CO-CH_2CH_3



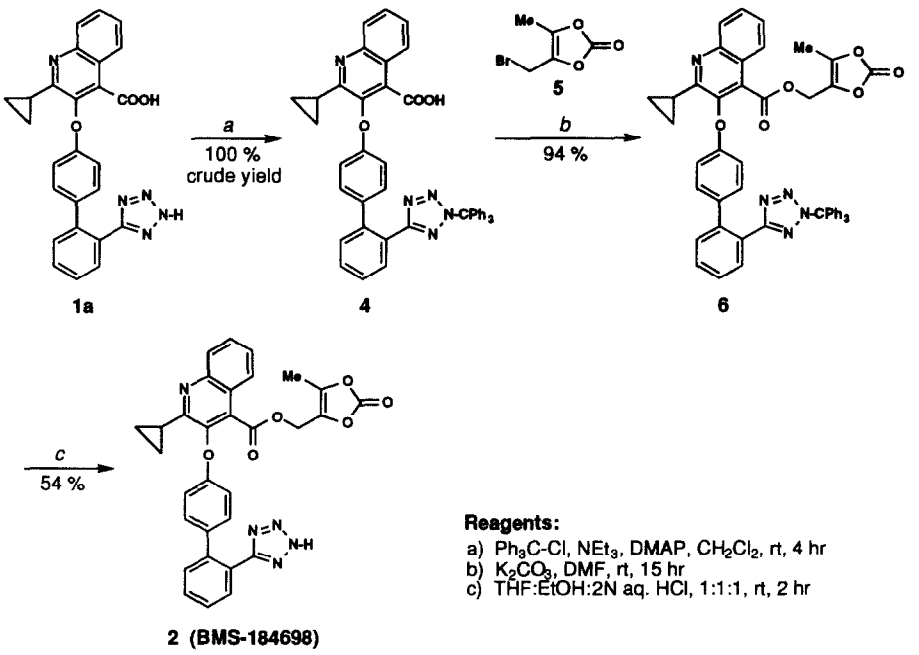
2 (BMS-184698)



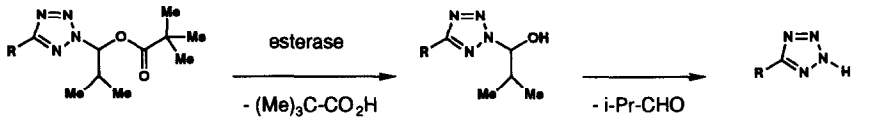
3

Dioxolenone carboxylic ester prodrugs were originally developed for beta-lactam antibiotics. For example, livampicillin is a dioxolenone prodrug of ampicillin approved for human use in Japan.[3] These prodrugs function by an initial esterase-mediated hydrolysis of the cyclic carbonate function followed by decomposition to parent acid and the by-products CO_2 and butane-2,3-dione (biacetyl, a naturally occurring minor component of butter). The preparation of dioxolenone prodrug **2** is depicted in Scheme 1. Selective protection of the tetrazole ring of **1a** was accomplished by tritylation to provide intermediate **4** in high yield. Alkylation with dioxolenone bromide **5**[3] proceeded rapidly and in good yield to give compound **6**. At this point, the trityl group was selectively removed using mild aqueous acid to provide the dioxolenone prodrug **2**.

Scheme 1

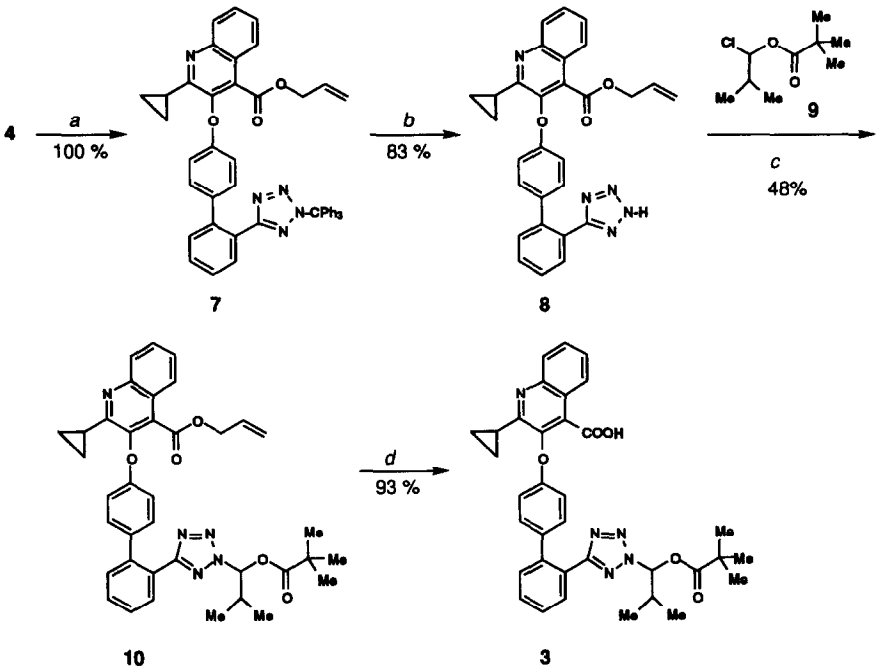


Prodrug modification of tetrazole groups has not been well studied. Nevertheless, we considered that blocking the acidic tetrazole group would be an important complement to carboxylic ester prodrugs. After an attempt to prepare a dioxolenone alkylated tetrazole was frustrated by instability of the final compound, we turned to applying the "double-ester" concept[4] to the problem of temporarily blocking the tetrazole ring. Such a prodrug would presumably unravel in an enzymatically initiated process resembling the scheme shown below.



Tetrazole prodrug **3** was prepared by the route shown in Scheme 2. Again, the selectively protected intermediate **4** was used. Compound **4** was converted to allyl ester **7** in high yield. Acidic removal of the trityl group gave the free tetrazole **8** in good yield. Alkylation of the tetrazole with chloride **9** gave two isomeric products. The major product was assigned structure **10** based upon predominant reaction at the less hindered nitrogen of the tetrazole ring. Palladium catalyzed removal of the allyl ester was best accomplished by the use of dimedone as the trapping agent to provide racemic tetrazole prodrug **3**.

Scheme 2



Reagents: a) allyl-Br, K_2CO_3, DMF, 50°C, 2 hr b) THF:EtOH:2N aq. HCl, 1:1:1, rt, 2 hr c) **9**, Ag_2O, THF, 65 °C, 18 hr d) dimedone, THF, cat $Pd(Ph_3P)_4$

Oral activity was determined using the salt-deplete spontaneously hypertensive rat (SHR), a model particularly responsive to inhibitors of the renin-angiotensin system.[5] A comparison of the oral activity of **1a** with prodrugs **2** and **3** is shown in Table 1 below, along with the results for a carboxylic ethyl ester (**1b**) and propanoyloxyisobutyl double ester (**1c**) (both synthesized by means similar to those described in Scheme 1). The simple ethyl ester **1b** failed to show improved oral activity relative to **1a** when both compounds were dosed *p.o.* at 30 μmol/kg. However, both dioxolenone prodrug **2** and tetrazole prodrug **3** showed oral activity at 10 μmol/kg equal to that of **1a** at a three-fold higher dose. The carboxylic double ester **1c** was less active than both **2** and **3** at the 10 μmol/kg oral dose. All of the prodrugs possessed significantly less *in vitro* activity than compound **1a** in receptor binding affinity and/or functional antagonism.

Table 1. Oral Activity in the Salt-Deplete Spontaneously Hypertensive Rat.

compound	*p.o.* dose (μmol/kg)	% maximum decrease in mean arterial pressure 0-6 hr	6-12 hr	12-18 hr	18-24 hr
1a (BMS-183920)	30	14	14	21	23
1b	30	17	19	25	26
1c	10	7	5	9	19
2 (BMS-184698)	10	19	19	23	24
3	10	17	17	20	19

Oral bioavailabilities of compounds **1a**, **2**, and **3** were estimated by measurement of the circulating plasma levels of **1a** after *i.v.* and *p.o.* dosing to rats. The results summarized in Table 2 indicate that both prodrugs provide significantly improved bioavailability of parent drug. Since oral bioavailability was similar for both **2** and **3**, the dioxolenone prodrug **2** was selected for further study because of its easier chemical synthesis and structural simplicity (lack of a chiral center) relative to the tetrazole prodrug **3**.

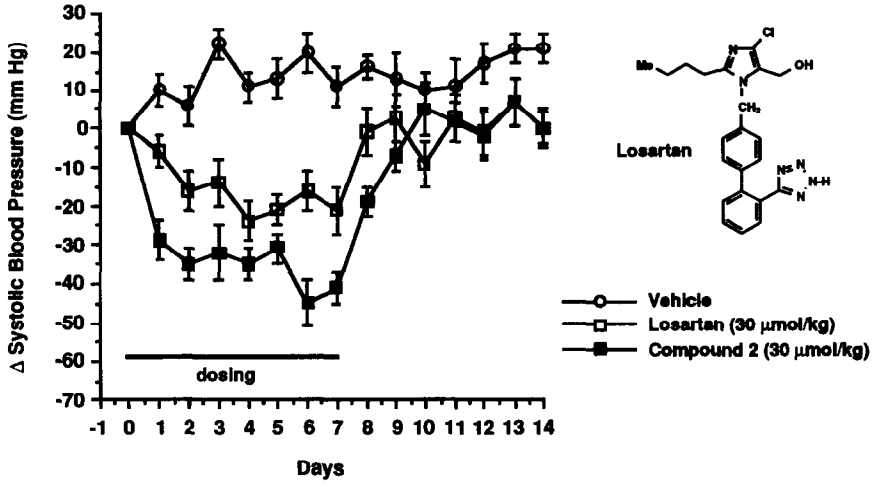
Table 2. Estimated oral bioavailability in the rat for 1a and prodrugs 2 and 3.

compound		% oral bioavailability[6]
1a (BMS-183920)	parent drug	11 (n=4)
2 (BMS-184698)	dioxolenone	27 ± 6 (n=6)
3	tetrazole prodrug	39 ± 11 (n=6)

The dioxolenone prodrug BMS-184698 (**2**) was taken on to a comparison of its oral antihypertensive activity with that of losartan, the first non-peptidic angiotensin II antagonist to be advanced to clinical trials.[7] This study was conducted in sodium-replete SHR with both

compounds dosed at 30 μmol/kg *p.o.* at 24 hour intervals for 7 days, followed by 7 days of further observation. The results of this study are shown in Figure 1. BMS-184698 achieved ca. 45 mm Hg fall in blood pressure by the sixth and seventh day of dosing that compared favorably to ca. 20 mm Hg reduction achieved with losartan from the fourth through seventh days of dosing. Significantly, no rebound hypertension was observed for BMS-184698 (as well as losartan) as blood pressure appeared to normalize within about 2 days after cessation of dosing.

Figure 1. Effects of once-daily treatment with BMS-184698 (2) and losartan on systolic blood pressure in SHR.



In summary, a prodrug strategy was successfully implemented to develop BMS-184698, a dioxolenone carboxylic ester of the quinoline-4-carboxylic acid angiotensin II receptor antagonist **1a**. This prodrug modification more than doubled the oral bioavailability of the parent compound.[8] Furthermore, BMS-184698 was shown to be an effective, orally active antihypertensive agent in the sodium-replete spontaneously hypertensive rat. Compared to losartan at 30 μmol/kg *p.o.* once-daily doses, BMS-184698 was the better antihypertensive agent.

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

References and Notes

1. Lloyd et al., preceding paper in this issue. Receptor binding affinity determined from competitive binding assay using ^{125}I labelled [Sar^1,Ile^8] angiotensin II in rat adrenocortical membranes with inhibition constants (K_i) for the AT_1 receptor population calculated by curve fitting. Functional antagonism (K_B) was measured by the ability of a single concentration of antagonist to block angiotensin II induced contractions in rabbit aortic smooth muscle strips.

2. For example, see: Duncia, J. W.; Chiu, A. T.; Carini, D. J.; Gregory, G. B.; Johnson, A. L.; Price, W. A.; Wong, P. C.; Calabrese, J. C.; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1990**, *33*, 1312-1329; Mantlo, N. B.; Chakravarty, P. K.; Ondeyka, D. L.; Siegl, P. K. S.; Chang, R. S.; Lotti, V. J.; Faust, K. A.; Chen, T.-B.; Shorn, T. W.; Sweet, C. S.; Emmert, S. E.; Patchett, A. A.; Greenlee, W. J. *J. Med. Chem.* **1991**, *34*, 2919-2922; Weinstock, J.; Keenan, R. M.; Samanen, J.; Hempel, J.; Finkelstein, J. A.; Franz, R. G.; Gaitanopoulos, D. E.; Girard, G. R.; Gleason, J. G.; Hill, D. T.; Morgan, T. M.; Peishoff, C. E.; Aiyar, N.; Brooks, D. P.; Frederickson, T. A.; Ohlstein, E. H.; Ruffolo, R. R.; Stack, E. J.; Sulpizio, A. C.; Weidley, E. F.; Edwards, R. M. *J. Med. Chem.* **1991**, *34*, 1514-1517; Middlemiss, D.; Drew, G. M.; Ross, B. C.; Robertson, M. J.; Scopes, D. I. C.; Dowle, M. D.; Akers, J.; Cardwell, K.; Clark, K. L.; Coote, S.; Eldred, C. D.; Hamblett, J.; Hilditch, A.; Hirst, G. C.; Jack, T.; Montana, J.; Panchal, T. A.; Paton, J. M. S.; Shah, P.; Stuart, G.; Travers, A. *Biorg. Med. Chem. Lett.* **1991**, *1*, 711-716.

3. Sakamoto, F.; Ikeda, S.; Tsukamoto, G. *Chem. Pharm. Bull.* **1984**, *32*, 2241-2248.

4. Bundgaard, H. *Drugs of the Future* **1991**, *16*, 443-458.

5. Weeks, J. R.; Jones, J. A. *Proc. Soc. Exp. Biol. Med.* **1960**, *104*, 646-648; Laffin, R. J.; Goldberg, M. E.; High, J. T.; Schaeffer, T. R.; Waugh, M. H.; Rubin, B. *J. Pharmacol. Exp. Ther.* **1978**, *204*, 281-288.

6. Bioavailability was estimated by measurement of circulating plasma levels of parent drug (compound **1a**) as determined by hplc analysis.

7. Duncia, J. V.; Carini, D. J.; Chiu, A. T.; Johnson, A. L.; Price, W. A.; Wong, P. C.; Wexler, R. R.; Timmermans, P. B. M. W. M. *Med. Res. Rev.* **1992**, *12*, 149-191.

8. Examples of other successful applications of prodrugs in the AII receptor antagonist area include: (a) Mizuno, K.; Niimura, S.; Tani, M.; Saito, I.; Sanada, H.; Takahashi, M.; Okazaki, K.; Yamaguchi, M.; Fukuchi, S. *Life Sciences* **1992**, *51*, PL 183-187; and (b) Middlemiss, D.; Watson, S. P.; Ross, B. C.; Dowle, M. D.; Scopes, D. I. C.; Montana, J. G.; Shah, P.; Hirst, G. C.; Panchal, T. A.; Paton, J. M. S.; Pass, M.; Hubbard, T.; Hamblett, J.; Cardwell, K. S.; Jack, T. I.; Stuart, G.; Coote, S.; Bradshaw, J.; Drew, G. M.; Hilditch, A.; Clark, K. L.; Robertson, M. J.; Bayliss, M. K.; Donnelly, M.; Palmer, E.; Manchee, G. R. M. *Biorg. Med. Chem. Lett.* **1993**, *3*, 589-594.

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