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QUINAZOLINONES 1: DESIGN AND SYNTHESIS OF POTENT QUINAZOLINONE-CONTAINING AT_1-SELECTIVE ANGIOTENSIN-II RECEPTOR ANTAGONISTS

Eric E. Allen*, Stephen E. de Laszlo, Song X. Huang, Carol S. Quagliato, William J. Greenlee, Raymond S. L. Chang†, Tsing-Bau Chen†, Kristie A. Faust†, Victor J. Lotti†,
Exploratory Chemistry, Merck Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065 and
†Department of Pharmacology, Merck Research Laboratories, West Point, Pennsylvania 19486

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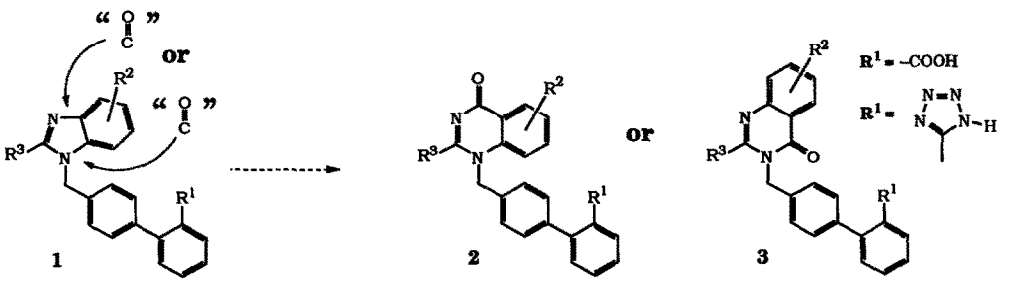
Abstract: We present the design, syntheses, and *in vitro* biological data of a series of substituted quinazolinone containing, AT_1 selective, Angiotensin II (AII) receptor antagonists. Substituents at the 6-position of the quinazolin-4(3H)-ones **3** have pronounced effects on the *in vitro* potency related to both their electronic and lipophilic character.

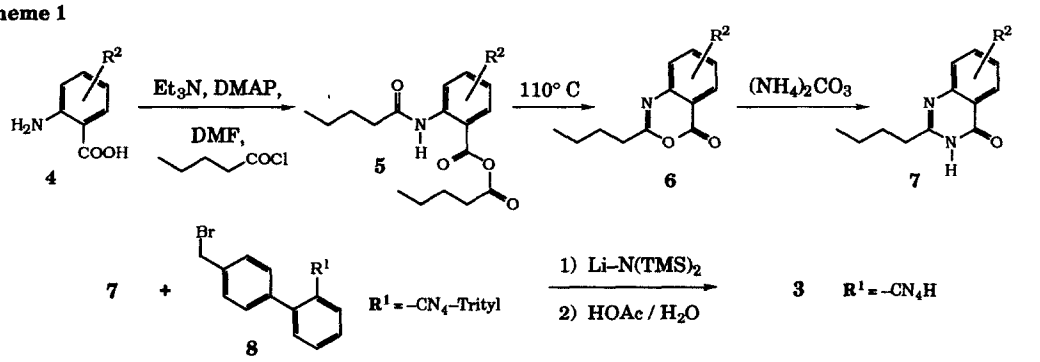
Introduction: Compounds that interrupt the proteolytic enzyme cascade of the renin-angiotensin system (RAS) have been demonstrated to be effective therapeutic agents in the treatment of hypertension. Reduction of AII levels may be achieved by blocking the conversion of the decapeptide Angiotensin I (AI) to the octapeptide hormone AII with angiotensin converting enzyme (ACE) inhibitors.[1] Alternatively, by competitively blocking the binding of AII to the AT_1 receptor, the physiological effects of the AII hormone can be inhibited. Non-peptide AII antagonists such as Losartan are orally active and do not have partial agonist activity as some of the peptide substrate mimics do.[2]

Early work showed that benzo fusion of the DuP-753 (MK-954) imidazole[3] provided potent benzimidazole antagonists **1**.[4] The success encountered with the benzimidazoles prompted us to investigate a related series of 6,6 fused ring systems as replacements of the 6,5 ring system of the benzimidazole. A conceptual insertion of a carbonyl between one or the other of the nitrogens of the imidazole and the benzo ring of **1** would give either **2** or **3**.[5]



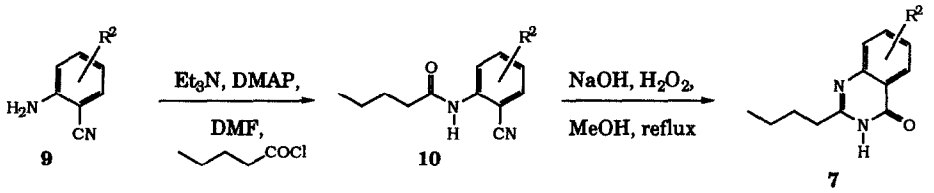
Chemistry: The quinazolinone nuclei of **2** and **3** were readily accessible from commercially available anthranilic acids or anthranilonitriles.[6] Quinazolinone **2a** (R^1 = -COOH, R^2 = H) was prepared by a route different from those outlined in the ensuing schemes, but since it had poor binding affinity for the AT_1 receptor, the synthetic route will not be described here.

Scheme 1



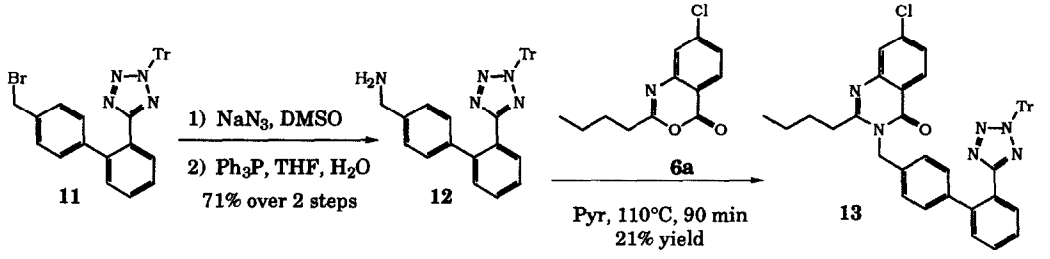
Scheme 1 illustrates the first of three general routes to **3**. Anthranilic acids **4** were doubly acylated to give the amide mixed anhydrides **5** that, upon heating, gave the benzoxazones **6**. Addition of ammonium carbonate[7] to the hot solutions provided the quinazolinones **7** that were then alkylated using **8** and lithium hexamethyldisilazide in DMF.[8] Other bases such as NaH worked well, but we have found that smaller amounts of O-alkylated materials were produced when using lithium hexamethyldisilazide.[9] The sequences from the anthranilic acids **4** to the quinazolinones **7** may be conducted in a single reaction vessel in high yield. However, benzoxazones **6** may be isolated and used in applications such as the one shown in Scheme 3.

Scheme 2



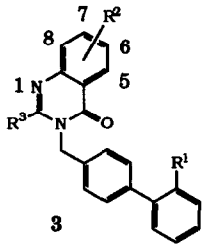
Scheme 2 depicts the other major route we used to prepare quinazolinones **7**. Anthranilonitriles **9** were acylated in either DMF or methylene chloride. The amide nitriles **10** were then hydrolyzed and cyclized to give **7** in 40-70% yields over two steps.[10]

Scheme 3



Scheme 3 outlines the route used to prepare the 7-chloro derivative **13**. The corresponding 7-chloroquinazolinone **7a** could not be alkylated with **8** as shown in Scheme 1. The yield of the condensation of **6a** with **12** was not optimized since the reaction was not used extensively.[11] The reaction is useful for rapid, single-vessel generation of analogs and for correcting regiochemical problems that are encountered with the alkylation of **7** (Scheme 1).[12]

Discussion: The first compounds in this series were made with R^1 = -COOH (Table 1, **3a** through **3f**).[13] Substitution with methyl in positions 5, 7, and 8 gave compounds with decreased binding affinity relative to the unsubstituted quinazolinone **3a**, with substitution of position 8 being particularly detrimental. In contrast, substitution of position 6 with methyl gave a 2-fold increase in binding over the parent carboxylic acid **3a**. Tetrazol-5-yl (-CN_4H) was substituted for the carboxylic acid at R^1 with a concomitant 15 to 23-fold increase in binding affinity. Compounds **3i** through **3m** are examples of halogen substitution in the 5, 6, and 7 positions. Analogs with halogen in the 5 and 7 positions showed little or no difference in *in vitro* activity from the parent tetrazole **3g**. However, analogs with fluorine or chlorine in the 6 position suffered a loss of binding affinity. The 6-iodo and 6-trifluoromethyl analogs (**3m** and **3n**[14]) were equipotent to the parent tetrazole and the 6-nitro analog **3o** had binding affinity similar to the 6-fluoro and 6-chloro analogs. The last three examples show the effect of changing the length of the 2-position alkyl chain. Both the propyl analog **3u** and the pentyl analog **3w** were slightly



3

Table 1

Compd #	R^1	R^2	R^3	AT_1 IC_{50} (nM) §
3a	$-CO_2H$	–H	*n*–Bu	200
3b	$-CO_2H$	5–Me	*n*–Bu	370
3c	$-CO_2H$	6–Me	*n*–Bu	92
3d	$-CO_2H$	7–Me	*n*–Bu	370
3e	$-CO_2H$	8–Me	*n*–Bu	1400
3f	$-CO_2H$	6,7–benzo fused	*n*–Bu	380
3g	$-CN_4H$	–H	*n*–Bu	10
3h	$-CN_4H$	6–Me	*n*–Bu	4
3i	$-CN_4H$	5–F	*n*–Bu	10
3j	$-CN_4H$	6–F	*n*–Bu	26
3k	$-CN_4H$	6–Cl	*n*–Bu	29
3l	$-CN_4H$	7–Cl	*n*–Bu	15
3m	$-CN_4H$	6–I	*n*–Bu	12*
3n	$-CN_4H$	6–CF_3	*n*–Bu	12*
3o	$-CN_4H$	6–NO_2	*n*–Bu	28
3p	$-CN_4H$	6–NH_2	*n*–Bu	1.3
3q	$-CN_4H$	6–NHCOMe	*n*–Bu	9
3r	$-CN_4H$	6–NHCOBu	*n*–Bu	2
3s	$-CN_4H$	6–OMe	*n*–Bu	5
3t	$-CN_4H$	6,7–dimethoxy	*n*–Bu	13
3u	$-CN_4H$	6–Me	*n*–Pr	10
3v	$-CN_4H$	6–Me	–Et	>100
3w	$-CN_4H$	6–Me	*n*–Pen	6.4

§ Rabbit aortic tissue. Except where noted with an asterisk (*), the binding assay was run with 0.2% bovine serum albumin (BSA); this generally shows no effect on this class of monoacidic compounds.

less potent than the butyl analog **3h**. The ethyl analog **3v**, however, lost binding affinity by a factor of 25 or more. This is in direct contrast to the experience with imidazo[4,5-*b*]pyridines[15] where shortening the 2-position alkyl from butyl to ethyl slightly enhanced binding affinity.

Table 2

#	R^2	AT_1 IC_{50} (nM)	F	R	π
3p	6–NH_2	1.3	0.38	-2.52	-1.23
3h	6–Me	4	-0.01	-0.41	0.56
3s	6–OMe	5	0.54	-1.68	-0.02
3q	6–NHCOMe	9	0.77	-1.43	-0.97
3g	–H	10	0.00	0.00	0.00
3m	6–I	12	0.65	-0.12	1.12
3n	6–CF_3	12	0.64	0.76	0.88
3j	6–F	26	0.74	-0.60	0.14
3o	6–NO_2	28	1.00	1.00	-0.28
3k	6–Cl	29	0.72	-0.24	0.71

It is apparent that at least two factors affect the potency contributions of a particular substituent: (a) the electron donating or withdrawing capacity and (b) the lipophilicity of the particular substituent. Lipophilic π-electron donors appear to enhance potency, and conversely, hydrophilic π-electron withdrawers seem to decrease potency. Table 2 contains a subset of the compounds listed in Table 1. The compounds are identical with the exception of the substituent at the 6 position. The compounds are listed in order of increasing IC_{50}. The constants F and R are the *field* and *resonance* components of substituents taken from the published table of C. G. Swain, *et al.*[16] The constant π is the *lipophilicity* component of the substituent taken from the published table of C. Hansch, *et al.*[17] Some correlation between IC_{50} and substituent constants may be made from the table. Very strong π-electron donors such as amino and methoxy enhance potency. Weaker π-electron donors with positive lipophilic character such as methyl are also potency enhancing. Acetamide is a strong π-electron donor but also has a large positive field constant (electron withdrawing) as well as negative lipophilic character giving it an overall neutral effect on potency relative to hydrogen. Valeramido (not included in Table 2 because no F, R, or π values were available) is likely electronically similar to acetamido. Its increased lipophilicity would explain its greater potency over acetamido. Iodo is a very weak π-electron donor and has the highest lipophilic character. It also has a significant positive field constant balancing its lipophilicity making it a neutral effect substituent. Fluoro is a weaker π-electron donor similar to methyl, has a small lipophilic component, and is a strong σ-electron withdrawing substituent giving it an overall negative effect on potency relative to hydrogen. Nitro has negative lipophilic character and large electron withdrawing constants F and R. One would predict it to have the lowest IC_{50} of all the substituents listed. Chloro is a weaker π-electron donor, has significant lipophilic character, but also has a high positive field constant similar to that of fluoro also making it a potency detracting substituent.

The IC_{50} of trifluoromethyl can not be fully rationalized using the same explanations as used above. It is both strongly σ- and π-electron withdrawing. It has high positive lipophilic character that may overcome the F and R deficits, but one would not predict it to have the same potency as iodo since it is so much more π-electron withdrawing than iodo. In this analysis we have, however, disregarded possible interactions between the receptor and the substituent itself. An in-depth analysis would have to include other factors such as steric bulk, dipolar interactions, and hydrogen bonding. While not complete, our simple analysis taking into account the electronic and lipophilic character of the substituents does have some predictive value.

In conclusion, incorporation of quinazolinones in place of the Losartan imidazole provides potent AII receptor antagonists. Lipophilic and/or π-electron donating substituents at the quinazolinone 6 position enhance potency. Work at Merck continues in this area and we will present some of these compound's *in vivo* results elsewhere.

Sample Procedures:

2-butyl-6-iodoquinazolin-4(3H)-one from 5-iodoanthranilic acid: To a solution of 20 g 5-iodoanthranilic acid (76 mmol), 37 mL Et_3N (266 mmol), and ~1 g DMAP in 500 mL DMF in a 1000 mL, three-neck, round-bottom flask fitted with a reflux condenser, was added 19 mL valeryl chloride (160 mmol). After 10 minutes, the mixture was heated to 110-120° C for 2.5 hours. To the hot mixture was added 57 g $(NH_4)_2CO_3$ chips (~1-5 mm dia., 456 mmol) portionwise (**CAUTION:** Frothing occurs from rapid release of ammonia and CO_2 gas from the $(NH_4)_2CO_3$). After 30 minutes, the mixture was allowed to cool to room temperature. The mixture was poured into 500 mL water. The product was removed by filtration on a fritted funnel, was washed with water, was suction dried on the funnel, then was vacuum oven dried for two days at 80° C to give 19.5 g of the title compound, 78% yield.[18] ^{1}H-NMR (300 MHz, $CDCl_3$): ∂ 11.06 (br s, 1H), 8.59 (d, J = 1.9 Hz, 1H), 8.02 (dd, J_1 = 1.9 Hz, J_2 = 8.7 Hz, 1H), 7.43 (d, J = 8.7 Hz, 1H), 2.75 (3 line m, 2H), 1.85 (5 line m, 2H), 1.49 (6 line m, 2H), 1.00 (t, J = 7.3 Hz, 3H).

2-butyl-6-nitroquinazolin-4(3H)-one from 5-nitroanthranilonitrile: To a solution of 30 g 5-nitroanthranilonitrile (184 mmol), 34 mL Et_3N (239 mmol), and 2.25 g DMAP (18.4 mmol) in 500 mL DMF was added 24 mL valeryl chloride (202 mmol). After 1 hour, the mixture was poured into 500 mL water. The solid product was collected on a fritted funnel and was washed with water. The solid was redissolved in 500 mL MeOH. To this mixture was added 220 mL 2.5 *N* NaOH followed by portionwise addition of 125 mL H_2O_2 (1.2 mol). (**CAUTION:** Rapid exothermic reaction follows the addition of H_2O_2. Ice-water should be kept on hand to control the exotherm if necessary). The reaction was refluxed for 1 hour. The mixture was allowed to cool, was poured into aqueous 10% citric acid, then was filtered on a fritted funnel. The solid product was recrystallized from $CHCl_3$ then was vacuum oven dried for two hours at 70° C to give 29.0 g of the title compound, 64% yield. ^{1}H-NMR (300 MHz, DMSO-d_6): ∂ 12.69 (br s, 1H), 8.78 (m, 1H), 8.50 (m, 1H), 7.78 (m, 1H), 2.66 (3 line m, 2H), 1.73 (5 line m, 2H), 1.36 (6 line m, 2H), 1.00 (3 line m, 3H).

Sample alkylation/deprotection procedure: To a suspension/solution of 1.00 g 2-butyl-6-iodoquinazolin-4(3H)-one (3.05 mmol) in 20 mL DMF was added 3.1 mL 1.0 *M* $LiN(TMS)_2$ in THF (3.1 mmol) followed by 1.95 g 87% **11** (3.05 mmol). The mixture was stirred overnight, then was poured in ~50 mL water/brine mixture. This mixture was extracted 3 times with CH_2Cl_2. The combined organic material was dried over $MgSO_4$, was stripped of solvent *in vacuo*, then was purified by flash chromatography on silica gel eluting with 15% ethyl acetate/hexane to give 1.61 g of the N-3 alkylated product as a foam (from CH_2Cl_2 under 1 Torr vacuum), 66% yield. This product was redissolved in 20 mL methanol and 3 mL conc. HCl was added.[19] After 30 minutes, the mixture was neutralized with 10% NaOH using phenolphthalein as an indicator, then was reacidified with 10% citric acid. Water was added and the mixture was extracted 3 times with ether. The combined organic material was dried over $MgSO_4$, stripped of solvent *in vacuo*, then was purified by flash chromatography on silica gel eluting with 1/12/87 NH_4OH/MeOH/CH_2Cl_2 to give 1.03 g of **3m**, 92% yield. ^{1}H-NMR (400 MHz, $CDCl_3$): ∂ 8.50 (br s, 1H), 7.97 (m, 2H), 7.49 (m, 2H), 7.36 (m, 2H), 7.06 (m, 4H), 5.30 (s, 2H), 2.72 (3 line m, 2H), 1.76 (5 line m, 2H), 1.40 (6 line m, 2H), 0.91 (3 line m, 3H).[20] MS-FAB m/e 563 (M + 1).

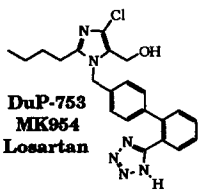
References and Notes:

1 (a) Smith R. D.; Chiu, A. T.; Wong, P. C.; *Annual Reviews of Pharmacology and Toxicology* **1992**, *23*, 135-165. (b) Greenlee, W. J.; Siegl, P. K. S.; *Annual Reports in Medicinal Chemistry* **1992**, *27*, 59-68.

2 (a) Khosla, M. C.; Smeby, R. R.; Bumpus, F. M.; *Structure Activity Relationship in Angiotensin II Analogs*; in *Angiotensin*; Page, I. H.; Bumpus, F. M.; Eds.; Springer Verlag: Heidelberg, 1973; pp 126-161. (b) Streeten, D. H. P.; Anderson, G. H.; *Angiotensin-Receptor Blocking Drugs*; in *Clinical Pharmacology of Antihypertensive Drugs, Handbook of Hypertension*; Doyle, A. E.; Ed.; Elsevier: New York, 1984; Vol. 5, pp 246-271. (c) Bovy, P. R.; Blaine, E. H. *Peptidic and Non-peptidic Angiotensin II Competitive Antagonists*; in *Current Cardiovascular Patents* **1989**, *1*, 2044-2056.

3 (a) Chiu, A. T.; McCall, D. E.; Price, W. A.; Wong, P. C. Carini, D. J., Duncia, J. V.; Johnson, A. L.; Wexler, R. R.; Yoo S. E.; Timmermans, P. B. M. W. M.; *J. Pharmacol. Exp. Ther.* **1990**, *252*, 711-718. (b) Wong, P. C.; Price, W. A.; Chiu, A. T.; Duncia, J. V.; Carini, D. J., Wexler R. R., Johnson, A. L., Timmermans, P. B. M. W. M.; *J. Pharmacol. Exp. Ther.* **1990**, *255*, 211-217.

4 (a) Chakravarty, P. K.; Camara, V. J.; Chen, A.; Marcin, L. M.; Greenlee, W. J.; Patchett, A. A.; Chang, R. S. L.; Lotti, V. J.; Siegl, P. K. S.; *Substituted Benzimidazoles as Novel Non-*



DuP-753
MK954
Losartan

References and Notes (cont.):

Peptide Angiotensin II Receptor Antagonists; *Book of Abstracts*, 200th National Meeting of the American Chemical Society, Washington, DC, Aug. 26-31, 1990; American Chemical Society: Washington, DC, 1990; MEDI # 90. (b) Thomas, A. P.; Allott, C. P.; Gibson, K. H.; Major, J. S.; Masek, B. B.; Oldham, A. A.; Ratcliffe, A. H.; Roberts, D. A.; Russell, S. T.; Thomason, D. A.; *J. Med. Chem.* **1992**, *35*, 877-885. (c) Zhang, J.; Entzeroth, M.; Wolfgang, W.; Van Meel, J. C. A.; *European J. Pharmacology* **1992**, *218*, 35-41. (d) For current patent activity related to benzimidazoles, see: Bühlmayer, P.; *Current Opinion in Therapeutic Patents*, Oct. 1992, pp. 1693-1718.

5 Other related "oxo" heterocycles have provided potent AII antagonists: (a) Atwal, K. S.; Ahmed, S. Z.; Bird, J. E.; Delaney, C. L.; Dickinson, K. 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*, 4751-4763. (b) 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. Pharmacology and Experimental Therapeutics* **1992**, *261*, 1037-1043. (c) See ref. 4(d) for additional examples.

6 Armarego, W. L. F.; *Part 1: Quinazolines; Fused pyrimidines, The chemistry of heterocyclic compounds*; Brown, D. J.; Ed.; John Wiley & Sons: New York, 1967, pp. 74-116.

7 Bogert, M. T.; Hand, W. F.; *J. Am. Chem. Soc.* **1906**, *28*, 94-104.

8 For a synthesis of **8**, see Allen, E. E.; de Laszlo, S. E.; Greenlee, W. J.; Patchett, A. A.; Chakravarty, P. K.; Walsh, T. F.; Eur. Pat. Appl. 411,766, **1991**.

9 O-alkylated material is generally less polar on silica gel than the N-alkylated material. If the synthesis has a subsequent step that uses an acid equivalent to or stronger than TFA or has a subsequent hydrogenation step, the O-alkylated material will decompose to the free quinazolinone and corresponding biphenylmethanol or biphenylmethyl, respectively.

10 (a) Taylor, E. C.; Knopf, R. J.; Borror, A. L.; *J. Am. Chem. Soc.* **1960**, *82*, 3152-3157. (b) McKee, R. L.; McKee, M. K.; Bost, R. W.; *J. Am. Chem. Soc.* **1946**, *68*, 1902-1903.

11 Parmar, S. S.; Singh, S. P.; *J. Heterocyclic Chem.* **1979**, *16*, 449-452.

12 For a synthesis of **12**, see ref. 8.

13 For *in vitro* assay protocol, see (a) Chang, R. S. L.; Lotti, V. J.; Chen, T. B.; *Biochem. Biophys. Res. Commun.* **1988**, *151*, 1213-1219. (b) Chang, R. S. L.; Siegl, P. K. S.; Clineschmidt, B. V.; Mantlo, N. B.; Chakravarty, P. K.; Greenlee, W. J.; Patchett, A. A.; Lotti, V. J.; *J. Pharmacology and Experimental Therapeutics* **1992**, *262*, 133-138. (c) The AT_2 potencies for the compounds in Table 1 were measured to be between 4 and 100 μM on the rat midbrain AT_2 receptor assay. (d) On the basis of the results of several standard compounds having three or more determinations, the standard error (expressed as percent of means) of the IC_{50} measurement in this assay is estimated to be less than 30%. In some cases the reported IC_{50} values represent an average of two or more determinations from separate assays.

14 Prepared from the trityl protected tetrazole precursor of **3m** and potassium trifluoroacetate, CuI, and DMF. Lin, R. W.; Davidson, R. I.; U.S. Pat. 4,808,748, **1989**.

15 Mantlo, N. B.; Chakravarty, P. K.; Ondeyka, D. L.; Siegl, P. K. S.; Chang, R. S. L.; Lotti, V. J.; Faust, K. A.; Chen, T. B.; Schorn, T. W.; Sweet, C. S.; Emmert, S. E.; Patchett, A. A.; Greenlee, W. J.; *J. Med. Chem.* **1991**, *34*, 2919-2922.

16 Swain, C. G.; Unger, S. H.; Rosenquist, N. R.; Swain, M. S.; *J. Am. Chem. Soc.* **1983**, *105*, 492-502.

17 Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J.; *J. Med. Chem.* **1973**, *16*, 1207-1216.

18 Some quinazolinone products were recrystallized from hexane/acetone, methanol/water, hexane/methylene chloride or chloroform.

19 The trityl protecting group may also be removed by stirring the compound in ~90/10 $AcOH/H_2O$ overnight.

20 The N-3 alkylated product may be easily distinguished from the O-alkylated material using NMR. The NMR signal corresponding to the benzylic protons of the N-alkylated material is generally broader, shorter, and upfield from that of the O-alkylated product.