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2-ARYL-1,2-DIHYDRO-6,7-DIMETHOXYQUINAZOLINE-3-OXIDES WITH POSITIVE INOTROPIC ACTIVITY

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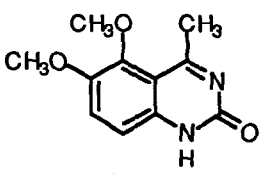
Abstract: A series of 2-aryl-1,2-dihydro-6,7-dimethoxyquinazoline-3-oxides was found to possess cardiotonic and blood pressure lowering activity in an open chest anesthetized dog model. Increases in cardiac force of greater than 150% at 10 mg/kg intraduodenally were recorded with the 2-phenyl analog.

Non-steroidal, non-catecholamine positive inotropic agents represent a potential new class of drugs for treating congestive heart failure without the use of toxic digitalis glycosides.[1] Our laboratories have been actively searching for new structural classes that can act as potent oral cardiotonic agents. This search has led to the discovery of bemarinone[2] **1** and bemoradan[3] **2** which is the subject of further development.



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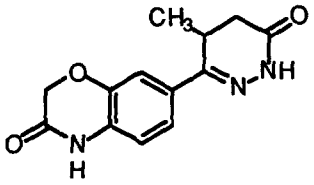

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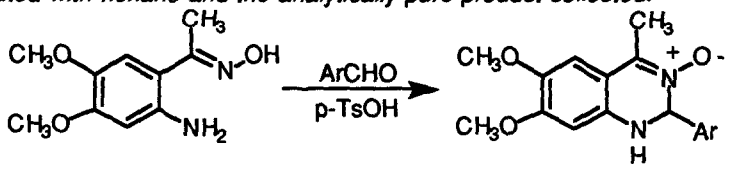
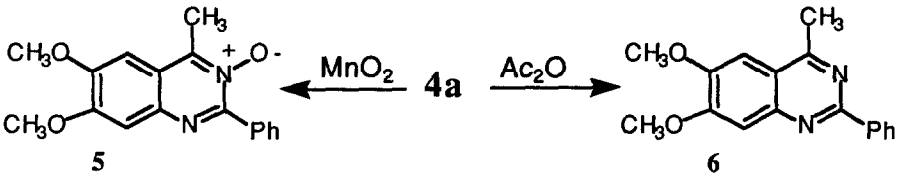
During our investigations we discovered a new class of cardiotonic agents structurally similar to bemarinone, namely the 2-aryl-1,2-dihydro-6,7-dimethoxy-quinazoline-3-oxides[4] **(4a-4k)**. The starting material for all of the reported compounds, 2-amino-4,5-dimethoxyacetophenone oxime **3**, was made from the corresponding acetophenone by the method of Simpson[5]. The method of Kovendi and Kurtz[6], who synthesized halogenated quinazoline-3-oxides, was modified to prepare our methoxy substituted analogues. The oxime **3** was suspended in toluene and the appropriate aldehyde added followed by a catalytic amount of p-toluenesulfonic acid. After 0.5 h at 25°C, the mixture was diluted with hexane and the analytically pure product collected.



3 **4 a - k**

For comparison in the test system, the aromatized quinazoline-3-oxide **5**[7] was made by treatment of **4a** with activated manganese dioxide[8] in chloroform at room temperature for 2 hours while the deoxy compound **6**[9] was prepared by treatment of **4a** with acetic anhydride at 100°C for 2 hours. Yields and melting points are given in the table.



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During biochemical screening of this series of N-oxides, we found that **4a** inhibited the canine cardiac fraction III phosphodiesterase isozyme with an IC_{50} of 40 μM. Due to the established relationship between inhibition of this enzyme and positive inotropic activity[10], we investigated the *in vivo* activity of 2-phenyl-1,2-dihydro-6,7-dimethoxy-quinazoline-3-oxide **4a** and related compounds. When administered intravenously, we find that these analogues have the ability to increase cardiac force in a dose related fashion in anesthetized open chest dogs as measured by a Walton-Brodie strain gauge[11] sewn into the heart muscle. Compound **4a** was also examined by the intradoudenal route. There was also a moderate dose related increase in heart rate and a decrease in blood pressure which is typical of this class of compounds[2]. The table presents the observations from these experiments using various aryl groups and other structural variations of the heterocycle.

TABLE. Inotropic Activity of 2-Aryl-1,2-dihydro-6,7-dimethoxyquinazoline-3-oxides

Compd[a]	Ar	mp°C	%Yield	CF[b]	HR[c]	MABP[d]	Dose[e]	n[f]
4a	C_6H_5	178-182	67	42	12	-3	1.87	3
				137	47	-28	8.75	3
				157	37	-15	10 (id)	3
4b	4-C_6H_4Me	155-158	37	45	10	-6	1.87	3
4c	3,4-$OCH_2OC_6H_3$	186-189	20	124	39	-38	8.75	1
4d	2,3-$OCH_2OC_6H_3$	185-189	10	45	13	10	8.28	1
4e	6-NO_2-3,4-$OCH_2OC_6H_2$	200-202	65	17	4	0	8.75	1
4f	4-C_6H_4OMe	161-163	15	29	8	-6	1.87	1
4g	C_6F_5	178-180	99	33	8	2	1.87	1
4h	2-furyl	191-195	16	123	20	-14	8.75	1
4i	2-thienyl	180-185	24	75	21	-31	8.75	1
4j	2-pyridyl	187-189	75	45	16	0	8.75	1
4k	4-pyridyl	179-182	47	29	8	0	8.75	1
5	C_6H_5	163-165	64[g]	29	5	0	8.75	1
6	C_6H_5	161-162	37[h]	-14	-4	-20	1.87	1

a. All compounds had satisfactory elemental analysis (CHN); b. CF = maximum % increase in cardiac force at the given dose; c. HR = % change in heart rate; d. MABP = % change in mean arterial blood pressure; e. iv dose in mg/kg; f. n = number of experiments; g. Made by oxidation of **4a**; h. From **4a** by reaction with acetic anhydride.

Although the number of compounds made was insufficient for an exhaustive QSAR study, we were able to draw some conclusions based on the data collected. We found that the oxidation state of the heterocycle was critically important to activity since oxidation to the quinazoline-3-oxide **5**, as well as removal of the N-oxide oxygen to give **6**, both resulted in inactive compounds. Indeed, the quinazoline without the 3-oxide (**6**) depressed cardiac force and thus was a negative inotrope. If these compounds are metabolites of the active moiety, they do not lend activity to the *in vivo* profile. Replacement of the pendant phenyl ring of **4a** with substituted phenyl rings bearing an ortho substituent such as **4d** and **4e**, or replacement of the phenyl ring with 2-thienyl (**4l**) or an electron deficient heterocycle, (pyridinyl analogues **4j** and **4k**) gave compounds with reduced activity. The 4-tolyl, 3,4-methylenedioxyphenyl, 4-methoxyphenyl, pentafluorophenyl and 2-furyl analogues (**4b,4c, 4f, 4g** and **4h**, respectively) were comparable to the parent compound in activity but the introduction of a nitro group to the 2-position of the methylendioxyphenyl ring of **4c** to give **4e**, resulted in loss of activity. Also, even though the 3,4-methylenedioxyphenyl analogue, **4c** had good activity, the 2,3 isomer **4d** did not. A factor which may account for these activity differences is the size of the dihedral angle formed by N3 and C2 of the quinazoline ring and C1 and C2 of the phenyl ring. Those compounds which contain ortho substituents such as **4d** and **4e** have lowered activity. This may be due to the inability of these compounds to adopt a conformation in which the two rings have a low dihedral angle. The steric interaction of the N-oxide oxygen with the 2-substituent would force the two rings to be orthogonal. Compounds without an ortho substituent can more easily exist in low energy conformations in which the two rings are closer to planarity (assuming that the phenyl ring is in an equatorial position). These compounds all have a chiral center at C-2 of the quinazoline ring. No attempt was made to resolve the enantiomers. In all cases positive inotropic activity was accompanied by an increase in heart rate and a decrease in blood pressure.

A new series of non-gylcoside positive inotropic agents related to bemarinone (**1**), and which presumably act through elevation of c-AMP levels due to inhibition of cardiac phosphodiesterase fraction III, has been described. The most potent compound, **4a**, has good *in vivo* cardiotonic activity, and is orally active with a 157% increase in cardiac force at 10 mpk by the intraduodenal route. Since a maximal effect of 137% was achieved at an iv dose of 8.75 mpk, the bioavailability of the compound is excellent. The discovery of more potent inhibitors of the phosphodiesterase fraction III enzyme which possess more selectivity for heart rate have led us to pursue other chemical leads for the management of congestive heart failure in humans.

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References and Notes

1. Weishaar, R. E.; Cain, M. H.; Bristol, J. A. *J. Med. Chem.*,**1985**, 28, 537; and Erhardt, P. W. *J. Med. Chem.*, **1987**, 30, 231.
2. Bandurco, V. T. ; Schwender, C. F.; Bell, S. C.; Combs, D. W.; Kanojia, R. M.; Levine, S. D.; Mulvey, D. M.; Appollina, M. A.; Reed, M. S.; Malloy, E. A.; Falotico, R., Moore, J. B.; Tobia, A. J. *J. Med. Chem.*,**1987**, 30, 1421.
3. Combs, D. W.; Rampulla, M. S.; Bell, S. C.; Klaubert, D.; Tobia, A. J.; Falotico, R.; Haertlien, B.; Lakas-Weiss, C.; Moore, J. B. *J. Med. Chem.*, **1990**, 33, 380.
4. US Patent 4,963,554, Oct **1990**
5. Simpson, J. C. E. *J. Chem. Soc.* **1946**, 94.
6. A. Kovendi and M. Kircz, Chem Ber. **1965**, 98, 1049.
7. Japan 70 00,499 Jan **1970**.
8. Pratt E. F.; McGovern, T. P. *J. Org. Chem.*, **1964**, 29, 1540.
9. Surprisingly, this compound has not previously been reported in the literature.
10. Weishaar, R. E.; Quade, M. M.; Schenden, J. A.; Evans,D. E. *J. Cyclic Nucleotide and Protein Phosphorylation Res.*,**1985**, 10, 551.
11. Falotico, R.; Moore, J. B.; Bandurco, V.; Bell, S. C.; Levine S. D.; Tobia, A. J. *Drug Devel. Res.*, **1988**, 12, 241.