Bioorganic & Medicinal Chemistry Letters, Vol.2, No.4, pp. 349-352, 1992
Printed in Great Britain

0960-894X/92 $5.00 + .00

SYNTHESIS AND ACTIVITY IN COGNITION-RELATED TESTS OF NOVEL 2-BENZOYLAMINO-4-OXOQUINAZOLINES

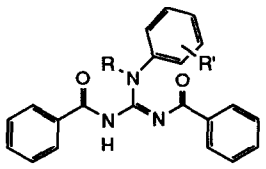
J. I. Levin*, W. J. Fanshawe, J. W. Epstein, B. Beer,♦ R. T. Bartus† and R. L. Dean III†

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

(*Received* 20 *December* 1991)

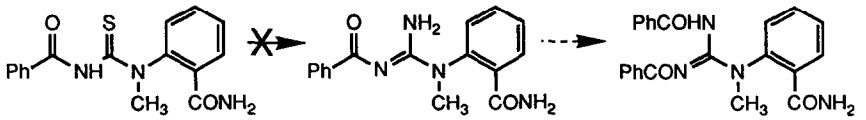
Abstract: A series of 1-alkyl and 3-alkyl-2-benzoylamino-4-oxo-quinazolines has been prepared and found to have activity in tests for cognition enhancement in rats and mice.

In the course of a project aimed at the synthesis of dibenzoylguanidines, **1**, as cognition enhancing agents[1] we wished to synthesize the N-methyl compound **2**. One of the synthetic routes



1, R = H, R' = p-$CONH_2$
2, R = CH_3, R' = o-$CONH_2$

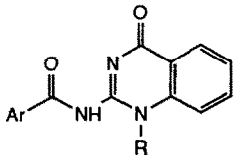
that we pursued was the reaction of benzoyl isothiocyanate with 2-(methylamino)benzamide to provide the expected benzoylthiourea **3**. In our reaction scheme we anticipated that treatment of **3** with hydrogen peroxide/ammonia (Method A)[2,3] would yield the guanidine derivative, **4**, followed by reaction with benzoyl chloride to yield the desired product, **5**. However, compound **4** apparently was not formed. A high melting (252-253° C) crystalline solid was obtained instead. Spectral and elemental analyses demonstrated that it was N-benzoyl aminoquinazolinone **6a**. The



3 **4** **5**

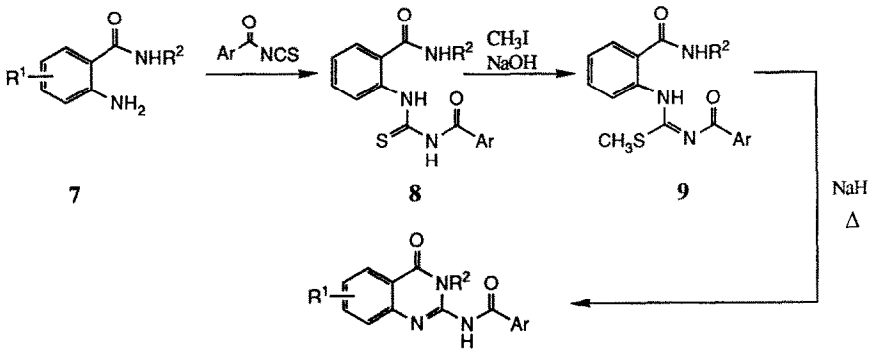
six-membered ring of **6** had formed via the displacement of the sulfinic or sulfonic acid of **3** by the amide nitrogen.[4] Although benzoylaminoquinazolinones, e.g. **6b** are reported in the literature,[5] there are no examples of N-alkyl derivatives. The biological activity of compound **6a** in a Hypoxic Survival screen prompted further analog synthesis.

♦ Head, CNS Biology. †Current address: Cortex Pharmaceutical, Inc.; Irvine, CA 92718



6a, Ar = phenyl, R = CH_3

Although the oxidation/cyclization of thioureas **3** to the 1-alkyl quinazolinones **6a-6i, and 10a, 10b** was expedient, the yields for this method were generally poor (8-48%). The alternative route (Method B) shown below, was used to prepare the 3-alkyl quinazolinones **10c-e**. The yield in each step was high. Method B works for a variety of alkyl groups, whereas Method A was only applicable for H and methyl.



7 **8** **9**

10c-10e

Anthranilamides **7** were reacted with the appropriate aroyl isothiocyanate in refluxing tetrahydrofuran to give the thioureas **8** in excellent (80-98%) yield. The thioureas were then S-methylated using methyl iodide-NaOH-DMF to provide compounds **9** in greater than 90% yield. Cyclization to form **10c-10e** was conducted by the addition of 1.8 to 2.2 equivalents of sodium hydride to the S-methyl compounds in THF or dioxane, followed by refluxing the resulting solutions. Compounds **6** and **10**[6] were evaluated as cognition activators using three *in vivo* tests.

Hypoxic Survival Test (Table 1).[7] Activity in this screen is demonstrated by the enhanced survival rates of test animals subjected to a hypoxic environment after treatment with drug, as compared to saline-treated control animals. A compound is judged to be active if greater than 40% of test animals survive.

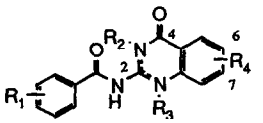


Table 1. Chemical and Biological Data[a]

Compd	R_1	R_2	R_3	R_4	m.p., °C	Yield, %	Method	Hypoxic Survival, i.p., mice[b]		
								% survival	mg/kg	tests
6a	H	-	Me	H	252-253d	27	A	70 (50-95)	100	3
6b	H	-	H	H	227-228d	40	A	73 (65-80)	100	2
6c	4-Me	-	Me	H	235-238	8	A	55 (45-65)	100	2
6d	4-MeO	-	H	H	235-236	11	A	63 (50-75)	10	2
6e	4-Me	-	H	H	238-239d	17	A	63 (50-75)	10	2
6f	4-Cl	-	H	H	239-241d	48	A	55 (30-80)	10	2
6g	3-Me	-	H	H	211-213	27	A	83 (80-85)	100	2
6h	3-Me	-	Me	H	266-269	43	A	R[d]	10-100	1
6i	H	-	H	6,7-MeO	226-227d	48	A	70 (50-90)	100	2
10a	4-Me	Me	-	H	189-191	42	A	85 (80-90)	50	2
10b	H	H-	-	6-Me	243-244d	11	A	55 (55-55)	100	2
10c	H	Me	-	H	185-187	94	B	78 (75-80)	100	2
10d	H	i-Pr	-	H	156-158	65	B	55	100	1
10e	H	n-Pr	-	H	133-135	56	B	nt[c]		
physostigmine								60-80	0.125	>2
saline								10		22

[a]Data for the doses with the best response is shown, data averages are listed, ranges are in parenthesis, [b]Groups of 20 mice /test. [c]nt = not tested, [d]R = inactive

Passive-Avoidance Anoxic-Induced-Amnesia Test.[7] This test is used to determine the attenuation of anoxic-induced amnesia in mice treated with drug, as compared to saline treated control animals. A shock-motivated, single trial, step-through passive avoidance procedure is used.

Compounds **6b**, **6c**, **10a**, and **10c** were active in the Anoxic Amnesia test (130%, 224%, and 116% improvement at 50 mg/kg, and 78% at 100 mg/kg, i.p., respectively). However, only **10c** was evaluated further (**Table 2**).

Passive Avoidance Retention in Aged (20-25 month-old) Rats:[1a] The same general passive avoidance procedure used in the mouse anoxic-induced amnesia was employed in this test, except that the test animals were memory-impaired, aged rats.[8]

Compound **10c** showed significant reversal effects in Anoxic Amnesia in the 10 and 25 mg/kg, i.p. range, and was particularly effective (1369% improvement) in old rats at 10 mg/kg, i.p.

In this test 5 of 6 aged rats delayed to the test endpoint of 600 sec. However, poor results obtained in the initial screen with oral dosing precluded further development of this compound.

Table 2. Passive Avoidance

Treatment	dose, mg/kg	post training hours	Anoxic Amnesia, mice, i.p			Aged Rat, i.p.[c]		
			delay[a] seconds	no.[b] tests	% improvment	delay seconds	no.[b] tests	% improv.
none	----	1				480	5	
none	----	24				[580	5	young rats]
saline	----	24				36	7	0
10c	10	24	218	4	94 (-19 to 248)	529 (173-600)	6[d]	1369
10c	25	24	341	2	105 (79 to 131)	300 (46-600)	7[e]	733

[a]Delay for untreated anoxic mice done on day of test, data averages are shown, ranges are in parenthesis. [b]groups of 21 mice /test. [c]% improvement is defined as [(delay, sec) - (saline control, sec)] x 100/(saline control, sec). Saline control represents 0% improvement. [d]5/6 responded at 600 seconds. [e]3/7 responded at 600 seconds. Test endpoint = 600 sec.

In conclusion, some novel 1- and 3-alkyl 2-benzoylaminoquinazolinones have been prepared and have been found to possess activity as agents for the improvement of cognition deficits in rats and mice when administered intraperitoneally. These compounds do not bind at the muscarinic receptor (^{3}H-quinuclidinyl benzylate assay). No mechanism of action can be proposed at this time.

References and Notes

1 a) See preceding paper. b) Tomcufcik, A. S.; Dixon, J. S.; Epstein, J. W.; Birnberg, G. H.; and Fanshawe, W. J. U. S. Patent 4,977,189 (December 11, 1990), and patents cited therein.

2. Maryanoff, C. A.; Stanziove, R. C.; Plampin, J. N.; and Mills, J. E. *J. Org. Chem.* **1986**, *51*, 1882.

3. Pfleiderer, W.; Baur, R.; Bartke, M.; Lutz, H. "Reactivity of Pteridines", in "Chemistry and Biology of Pteridines", Gruyter & Co., 1983; p. 94.

4. For an alternative route to 2-aminoquinazolones see: Molina, P.; Alajarín, M.; and Vidal, A. *Tetrahedron Lett.* **1988**, *29*, 3849-3852.

5. Shakidoyatov, Kh. M.; Oripov, E. O.; Yun, L. M.; Yamankulov, M. Ya.; and Kadyrov, Ch. Sh. *Fungitsidy* **1980**, 66-81.

6. All compounds had satisfactory ^{1}H NMR, IR, MS and elemental analyses. Spectral data for **6a**: ^{1}H-NMR(DMSO-d_6, 80 MHz,δ): 3.90(s, 3H), 7.35-8.30(m, 9H); IR(KBr) 1695, 1580, 1360cm^{-1}; mass spectrum (EI) m/z 279, 251, 202.

7. Levin, J. I.; Epstein, J. W.; Beer, B.; Dean, W. D.; Dusza, J. P.; Tseng, S.-S.; Schweitzer, H. J.; Francisco, G. D.; Cain, W. T.; Bartus, R. T.; and Dean III, R. L. *Bioorg. and Med. Chem. Lett.* **1991**, *1*, 435-440.

8. Lippa, A. S.; Pelham, R. W.; Beer, B.; Critchett, D. J.; Dean III, R. L.; and Bartus, R. T. *Neurobiology of Aging* **1980**, 10-16.