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THE SYNTHESIS AND COGNITION ENHANCING EFFECTS OF A SERIES OF DIBENZOYL GUANIDINES. ANALOGS OF N,N'-[[4-(AMINOCARBONYL)PHENYL]CARBONIMIDOYL]BIS[BENZAMIDE]

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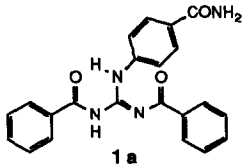
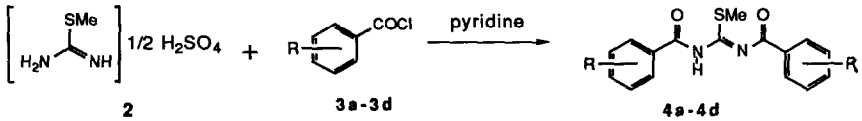
ABSTRACT: A series of both symmetrical and unsymmetrical dibenzoyl guanidines containing a p-aminobenzamide moiety was studied for the reversal of cognition deficits in rats and mice.

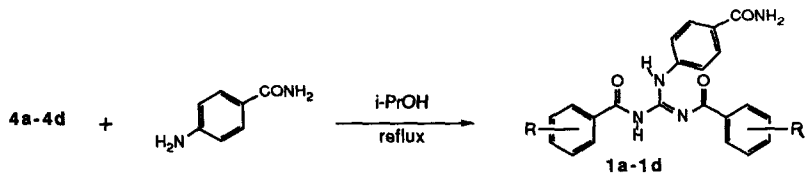


1a

Dibenzoylguanidine **1a**[1] was identified in our laboratories as a potential agent for the improvement of cognition deficits as determined by activity in previously reported Hypoxic Survival and Anoxic Amnesia screens,[2] as well as in a passive avoidance paradigm employing aged rats. We are now disclosing a series of p-aminobenzamide analogs related to **1a** since the synthesis of a large number of dibenzoyl guanidines showed that this substitution in many of the congeners gave compounds that were active in reversing cognition deficits in rats and mice. The general synthesis of dibenzoyl guanidines has been reported in the patent literature.[1]



2 **3a-3d** **4a-4d**



1a-1d

Diaroyl-S-methyl thioureas, **4a-d** were the starting materials for symmetrical analogs. Reaction

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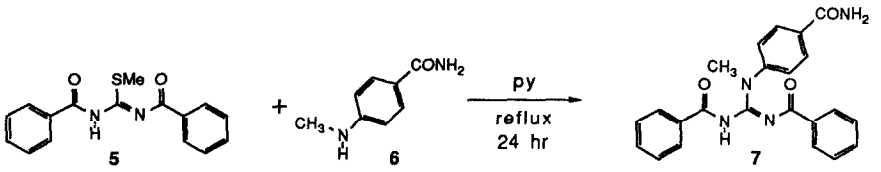
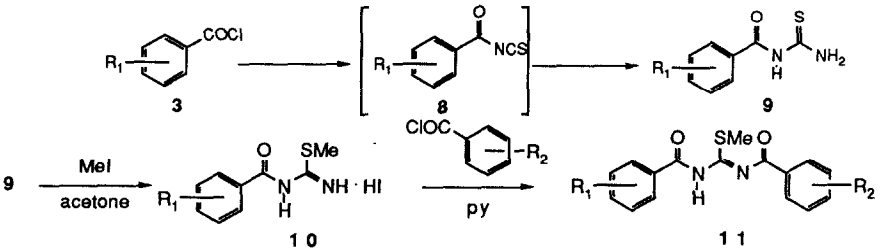
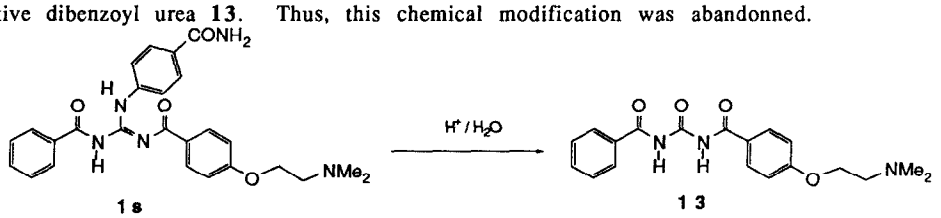


of compounds **4** with p-aminobenzamide gave the desired dibenzoyl guanidines. The preparation of N-alkyl congeners of **1a** was impeded by the low nucleophilicity of N-alkylamino benzamides. p-Methylaminobenzamide derivative **7**, however, was obtained via the reaction of S-ethyl compound **5**[3] with the N-methylaniline derivative **6**[4]. Compound **7** was inactive in all screens.

Unsymmetrical derivatives were prepared by reacting aroyl chlorides **3** with ammonium thiocyanate in acetone to yield the aroyl isothiocyanates **8** which were then reacted *in situ* with ammonium hydroxide to give aroyl thioureas **9**[5] (1.12 mol NH_4NCS, 1.0 mol of **3**, 400 mL acetone, refluxed 15 min, then 200 mL conc. NH_4OH added at a rate to maintain reflux, quenched in ice water, solid collected). Methylation of N-aroyl thioureas **9** with methyl iodide in acetone gave the S-methyl hydroiodides **10.** The second aroyl group was then attached to **10** by the addition of a different acid chloride to the S-methyl hydroiodide in pyridine. Conversion of **11** to **1e-1z**, **1aa**, **1ab** was then carried out in the usual manner.



One of the problems in this series of analogs was their poor solubility, thus producing potential problems for drug development. Compound **1s (Table 1)**, with a dimethylaminoethoxy group, was synthesized to impart aqueous solubility to this class of compound. Although solubility of the compound was enhanced, it had a half-life of 15 minutes[6] in acidic solution. It hydrolyzed to the inactive dibenzoyl urea **13**. Thus, this chemical modification was abandonned.



A radiolabelled sample of **1a** (specific activity = 16.7μCi/mg) was prepared from ^{14}C-2-methyl-2-thiopseudourea sulphate (obtained from ^{14}C-thiourea[8] and dimethyl sulphate).

These compounds[7] were evaluated as cognition activators using three *in vivo* tests.

Table 1. Chemical and Biological Data[a]

Compd	R1	R2	m.p., °C	Yield, %	Hypoxic Survival, i.p., mice			Anoxic Amnesia, i.p. mice		
					% survival	mg/kg	tests[e]	% improvement	mg/kg	tests[e]
1a	H	H	284-285	89	57(45-70)	100	6	50(33-76)	50	3
1a	H	H	-------	----	48	100	13(p.o.)	nt		
1b	p-MeO	p-MeO	265-266	17	15	10	1	nt[b]		
1c	m-CF_3	m-CF_3	220-222	--	5	100	1	nt		
1d	m-CH_3	m-CH_3	252-256	77	40(35-50)	50	4	20	100	1
1e	H	p-Br	291-292	69	60(55-65)	25	3	12	50	1
1f	H	m-CF_3	288-289	52	15	10	1	nt		
1g	H	p-MeO	272-273	85	50(50-50)	10	2	28 (74, -19)	10	2
1h	H	p-Me	277-278	67	5	10	1	nt		
1i	H	p-F	288-289	74	35(5-55)	25	5	nt		
1j	H	m-Br	282-283	68	50(45-55)	10	2	118	25	1
1k	H	p-CN	267-268	82	38(15-50)	100	3	nt		
1l	H	p-NO_2	276-277	78	25(5-45)	100	3	nt		
1m	H	p-CF_3	215-216	76	40(40-40)	100	2	nt		
1n	H	o-CF_3	215-216	54	5	10	1	nt		
1o	H	m-Me	281-283	50	25	100	1	nt		
1p	H	p-*t*-Bu	253-256	44	72(65-80)	100	3	nt		
1q	H	m-NO_2	283-284	65	60(30-95)	100	3	nt		
1r	H	m-EtO	257-259	56	67(50-80)	10	3	nt		
1s	H	p-X[c]	255-256	62	48(40-55)	10	2	R	10	2
1t	H	m-Cl	272-273	62	95(95-95)	100	2	49(53, -8, 102)	50	3
1u	p-MeO	p-F	285-286	59	42(35-50)	100	3	R	50-200	>2
1v	p-F	p-Br	289-290	64	40(25-55)	25	2	nt		
1w	p-F	m-Cl	269-270	49	25	10	1	nt		
1x	p-F	m-F	291	81	68(55-80)	100	2	R	100	1
1y	p-MeO	p-CF_3	269-271	82	55	50	1	nt		
1z	p-MeO	m-Cl	282-284	70	15	10	1	nt		
1aa	p-MeO	m-Me	258-259	90	50(45-55)	10	2	28(65, -8)	10	2
1ab	p-MeO	p-Me	282-285	86	43	100	2	R	50-200	>2
physostigmine					60-80	0.125	>2			
saline					10	---	22	footnote d		

[a]Data for the dose with the best response is shown, ranges are in parenthesis, [b]nt = not tested, [c]X = $OCH_2CH_2NMe_2$, [d]Delay for untreated anoxic mice done on day of test. % improvement is defined as [(delay, sec) - (saline control, sec)] x 100/(saline control, sec). Saline control represents 0% improvement. [e]20 mice/test.

Hypoxic Survival Test.[2] 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. Among the compounds **1a-1ab**, some showed activity in the Hypoxic Survival screen (% survival >40%), however, no strict SAR was observed. Furthermore, the data did not follow a dose-response course. We decided to pursue the development of the original lead compound, **1a**, based on its ease of synthesis and reproducibility of test results. By the i.p. route at 0.5 hours **1a** produced 57% survival at 100 mg/kg. Oral dosing required 4 hours for a peak effect with 48% surviving at 100 mg/kg.

Passive-Avoidance Anoxic-Induced-Amnesia Test.[2] 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. Evaluations in the Anoxic-Induced Amnesia Test produced fewer active compounds, e.g. **1a,j,t**, and this test is perhaps more predictive of the propensity of a compound to reverse amnestic effects in the compromised brain of mammals.

Passive Avoidance Retention in Aged (20-25 month-old) Rats: The passive avoidance procedure used in mice was employed in this test, except that the animals were memory-impaired, aged rats[9]. These exhibit a time-related deficit in retention of the avoidance task, as compared to young control rats. Compound **1a** produced significant improvement in retention of the avoidance task in aged rats at 24 hours by both p. o. [391% improvement (627-21, median 464%), 25 mg/kg, 5 rats], and i.p. [1,088% improvement (1835-874, median 1,751%), 5 mg/kg, 5 rats]. The reference was old rats on saline at 24 hrs. This activity suggests its potential value in treating cognition deficits such as Alzheimer's disease in humans.

Compound **1a** did not interact at muscarinic cholinergic, histamine(H_1), or 5-HT_2 receptors, nor did it effect precursor availibility for acetylcholine synthesis. It had no effect on serotonin, norepinephrine, or dopamine uptake in rat brain synaptosomes, *in vitro*. The CNS activity of **1a** in spite of its low aqueous solubility and the very low absorption of ^{14}C-**1a** in rats, p.o.[10] is presently unexplained, and a mechanism of action is unknown. A recent review describes current research in the cognition field.[11]

References and Notes

1. a) 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. b) Birnberg, G. H.; Fanshawe, W. J.; Levin,J. I.; Epstein, J. W.; and Francisco, G. D. "Abstracts of Papers", 199th National Meeting of the American Chemical Society, Boston, MA, Apr 1990; American Chemical Society: Washington, DC, 1990; Abstr MEDI 121.
2. 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 DeanIII, R. L. *Bioorg. and Med. Chem. Lett.* **1991**, *1*, 435-440.
3. Siano, M. L. and Di Giaimo, M. P. U. S. Patent 3,535,256 (October 20, 1970).
4. Kadim, S. B. *J. Org. Chem* **1973**, *38*, 1349.
5. Frank, R. L. and Smith, P. V. In "Org. Syntheses"; Wiley: New York, 1955; Collect Vol. III, p. 735.
6. Private communication from Dr. P. Niphardkar, these laboratories.
7. All new compounds exhibited satisfactory IR, MS, ^{1}H-NMR and elemental analyses.
8. New England Nuclear, Boston, MA 02118
9. 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.
10. Private communication from Dr. G. Nicolau, these laboratories.
11. Pavia, M. R.; Davis, R. E.; and Schwarz, R. D. In "Annual Reports in Medicinal Chemistry"; Bristol, J. A., Ed.; Academic Press, Inc.: San Diego, CA, 1990; Vol. 25, Chapter 3.