SYNTHETIC ANTICONVULSANTS, ANTIHYPOXICS, AND LIVER MONOOXYGENASE SYSTEM INDUCERS BASED ON AMIDES AND UREA.

V*. SYNTHESIS AND ANTICONVULSIVE AND ANTIHYPOXIC ACTIVITIES OF 1,3 DIBENZHYDRYLUREAS

A. A. Bakibaev, V. K. Gorshkova,
V. V. Shtrykova, A. S. Saratikov,
V. D. Filimonov, and M. P. Krauin'sh

UDC 615.213:547.495.2].012.1]015.4:
612.35.015.1].07

The benzhydryl radical is a key pharmacological fragment of many biologically active compounds, including the benzhydrylureas. We have previously observed high levels of antihypoxic [1] and anticonvulsive activity among the benzhydrylureas [4, 5]. However, there are thus far no reports of pharmacological studies of compounds simultaneously containing two benzhydryl fragments in a carbamide framework.

With the aim of studying the biological activities of benzhydrylureas, and in order to study the effects of single types of substitutions in the benzhydryl fragment on the activity of benzhydrylureas (using data from [1, 4]) and 1,3-dibenzhydrylureas I-XV, we synthesized the second of these groups of compounds and measured their anticonvulsive and antihypoxic activities.

Compounds I-XV were synthesized with high yields (up to 97%) by thermal disproportionation of benzhydrylureas, which were prepared as described in [4]:

$$RC_6H_4(R'C_6H_4)CHNHCONH_2 \rightarrow \underset{I-XV}{[RC_6H_4(R'C_6H)CHNH-]_2CO}$$

R=R'=H(I); R'=H, R=*o*-F(II); R'=H, R=m-F(III); R'=H, R=p-F(IV) R'=H, R=*o*-Cl(V); R'=H, R=m-Cl(VI); R'=H, R=p-Cl(VII); R'=H, R=*o*-Br (VIII); R'=H, R=m-Br (IX); R'=H, R=p-Br (X); R'=H, R=p-MeO (XI); R'=m-F, R=p-Me (XII); R'=Me, R=p-Me (XIII); R'=p-F, R=p-Me (XIV); R'=*o*-Cl, R=p-Cl (XV).

Compounds I-XV were colorless crystals with high melting temperatures; they were insoluble in water, alcohols, ketones, amines, and aromatic hydrocarbons, and had limited solubility in DMSO and DMF. All 1,3-dibenzhydrylureas except compound I were prepared here for the first time. Yields and physicochemical properties of compounds I-XV are shown in Table 1. ^1H and ^{13}C NMR spectra were obtained for compounds I and VI, and values are given below.

A general and favorable property of compounds I-XV was their low toxicity (LD_{50} > 2 g/kg).

The anticonvulsive activity of compounds I-XV was determined using a maximum electric shock (MES) test and by Corazol titration (CT) (Table 2). The fluoro-substituted compounds II-IV, VI, XII, along with compounds X and XIII had relatively high anticonvulsive activity in the CT test, as compared with the unsubstituted parental compound I. In addition, when the anticonvulsive activity was related to the position of each type of substituent, it was found that the m-substituted 1,3-dibenzhydrylureas III, VI, IX, XII, and XIII were more active than the o- and p-substituted analogs. In the MES test (see Table 2), chloro-substituted 1,3-dibenzhydrylureas V-VII had quite high levels of anticonvulsive activity, and the o-chloro derivatives V and XV were the most active of all the chlorine-containing compounds, and also had the greatest therapeutic ratios (see Table 2).

*See [2] for Communication IV.

S. M. Kirov Polytechnical University, Tomsk. Science Research Institute of Pharmacology, Tomsk Scientific Center, Russian Academy of Medical Sciences. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 27, No. 4, pp. 37-39, April, 1993. Original article submitted June 3, 1992.

TABLE 1. Properties of 1,3-Di(benzhydryl)-ureas I-XV

Compound	Yield (%); melting temperature (°C)	Atomic formula	IR spectrum, ν_{max}, cm^{-1}	
			C=O	NH
I	92 269—271	$C_{27}H_{24}N_2O$	1630	3328
II	94 295—296	$C_{27}H_{22}F_2N_2O$	1642	3365
III	95 286—287	$C_{27}H_{22}F_2N_2O$	1638	3343
IV	93 290—291	$C_{27}H_{22}F_2N_2O$	1635	3340
V	92 296—298	$C_{27}H_{22}Cl_2N_2O$	1635	3352
VI	95 272—273	$C_{27}H_{22}Cl_2N_2O$	1632	3346
VII	89 297—298	$C_{27}H_{22}Cl_2N_2O$	1640	3353
VIII	97 322—323	$C_{27}H_{22}Cl_2N_2O$	1644	3335
IX	95 254—255	$C_{27}H_{22}Br_2N_2O$	1642	3340
X	92 297—298	$C_{27}H_{22}Br_2N_2O$	1638	3332
XI	95 305—206	$C_{27}H_{22}F_2N_2O$	1648	3354
XII	93 255—256	$C_{31}H_{32}N_2O$	1650	3343
XIII	93 270—271	$C_{29}H_{26}F_2N_2O$	1642	3345
XIV	95 321—322	$C_{27}H_{20}Cl_4N_2O$	1639	3340
XV	97 1646	$C_{29}H_{28}N_2O_3$	3350	

TABLE 2. Anticonvulsive Activity of 1,3-Di(benzhydryl)ureas I-XV

Compound	LD_{50}, mg/kg	Therapeutic index (LD_{50}/ED_{50} in MES test)	Dose, mg/kg	Maximum electric shock			Corazol convulsive threshold, mg/kg		
				% prevention of convulsion	% survival	ED_{50}, mg/kg	$M \pm m$	P	ACI
I	2000	—	200	0	100	—	114,5±6,0	0,502	1,05
			300		83,3				
II	2000	6,2	200	16,7	100	322	117,5±6,2	0,024	1,20
			350	50,0	66,7				
III	2000	6,2	200	16,7	100	322	124,3±10,4	0,034	1,3
			350	50,0	100				
IV	2000	8,9	200	33,3	16,7	225	124,6±9,4	0,022	1,3
			300	50,0	50,0				
			350	66,7	100				
V	2000	20,4	200	100	100	98	92,8±3,1	0,016	0,9
			100	50,0	83,3				
			75	33,3	66,7				
VI	2000	9,2	200	33,3	83,3	217	152,8±8,1	0,001	1,53
			250	83,3	100				
VII	2000	7,6	200	33,3	50,0	266	101,9±5,9	0,563	1,00
			300	50,0	83,3				
VIII	2000	5,6	200	16,7	50,0	360	113,9±5,2	0,031	1,2
			350	33,3	66,7				
IX	2000	6,4	200	33,3	66,7	315	117,1±2,3	0,004	1,2
			350	50,0	66,7				
X	2000	6,1	200	16,7	66,7	330	141,3±8,8	0,000	1,5
			300	33,3	66,7				
XI	2000	11,6	200	50,0	100	173	113,3±9,2	0,442	1,1
			150	50,0	83,3				
XII	2000	5,2	300	50,0	100				
XIII	2000	5,2	200	16,7	16,7	384	137,1±8,0	0,002	1,4
			300	50,0	83,3				
XIV	2000	—	200	16,7	66,7	—	96,3±7,6	0,259	0,9
			400	0	100				
XV	2000	15,4	200	80,0	80,0	130	108,3±6,0	0,770	1,00
			100	33,3	100				
Chloracon	1360	5,7	200	50,0	83,3	240	132,4±11,4	0,026	1,30
			100	16,7	83,3				
			400	66,7	100				

Note. ACI is the anti-Corazol index (ratio of convulsive Corazol thresholds with and without drug).

Among compounds I-XV, we found that IV-VI, XI, and XV had greater anticonvulsive activity (in the MES test) than Chloracon (β-chloropropionic acid amide).

Comparison of the anticonvulsive activities of compounds I-XV with those of benhydrylureas with the same types of substitutions [4, 5] showed that the latter were significantly more active than compounds I-XV. The main reason for this difference is probably connected with the low solubility of I-XV compared with that of the benzhydrylureas, which prevents enzymatic hydrolysis and metabolism of compounds I-XV. On the other hand, the lower anticonvulsive activities of compounds I-XV are probably associated with their steric bulk, which considerably alters their ability to reach their biological targets. We have previously [2] noted the important role of spatial factors in the benzhydrylureas in determining their anticonvulsive properties.

TABLE 3. Antihypoxic Activities of 1,3-Di(benzhydryl)ureas I-XV (200 mg/kg) (M ± m)

Compound	Sodium nitrite 300 mg/kg			Sodium nitroprusside 25 mg/kg			Hermetic chamber		
	control	exptl.	AHI	control	exptl.	AHI	control	exptl.	AHI
I	24,2±0,5	31,0±2,1 0,011	1,28	11,3±1,6	11,2±0,7 0,922	0,99	33,0±2,2	35,2±1,6 0,442	1,10
II	22,0±2,2	18,7±1,2 0,223	0,90	13,5±0,7	13,0±0,8 1,000	1,00	29,5±1,9	29,5±1,6 1,000	1,00
III	22,0±2,2	18,2±1,4 0,192	0,80	13,5±1,1	11,5±0,8 0,500	0,90	29,5±1,9	28,0±1,3 0,258	0,90
IV	22,0±2,2	19,3±1,4 0,344	0,90	12,5±1,1	11,5±0,3 0,389	0,9	29,5±1,9	34,8±2,9 0,165	1,20
VI	18,8±1,2	15,7±0,8 0,052	0,80	11,3±1,6	8,8±0,7 0,389	0,80	33,0±2,2	35,0±2,1 0,500	1,10
VII	22,0±2,2	23,3±1,6 0,628	1,10	12,5±1,1	10,8±0,8 0,258	0,90	28,3±1,1	30,8±3,00 0,442	1,10
VIII	19,5±1,6	15,3±0,8 0,044	0,80	11,2±0,7	8,3±0,4 0,004	0,70	29,5±1,9	31,7±2,1 0,442	1,10
IX	19,5±1,6	14,3±0,7 0,016	0,70	11,2±0,7	10,2±0,9 0,389	0,90	29,5±1,9	30,7±1,4 0,628	1,10
X	19,5±1,6	18,0±2,1 0,562	0,90	11,2±0,7	14,6±2,5 0,192	1,30	29,5±1,9	28,8±1,4 0,770	0,98
XI	25,2±2,2	19,0±3,5 0,172	0,80	13,5±0,7	16,6±2,7 0,303	1,20	30,6±1,7	31,8±1,6 0,631	1,00
XII	22,0±2,2	18,7±1,4 0,258	0,85	12,5±1,1	12,6±0,95 0,500	1,00	29,5±1,9	31,8±2,6 0,500	1,10
XIII	22,0±2,2	16,7±1,5 0,073	0,80	13,5±0,7	16,0±1,5 0,148	1,20	30,6±1,7	33,7±1,6 0,223	1,10
XV	22,2±2,2	20,8±1,9 0,693	0,90	12,5±1,1	11,7±0,6 0,562	0,90	29,0±1,9	29,8±1,2 0,771	1,00
Guthimine	19,0±1,7	21,0±2,1 0,442	1,11	10,0±1,0	11,0±1,1 0,500	1,10	29,9±3,4	33,0±1,6* 0,347	1,17

Note. AHI is the antihypoxic index; asterisks indicate survival after treatment with guthimine (100 mg/kg).

The antihypoxic activities of compounds I-XV were determined using three models of hypoxia: acute hemic, acute histotoxic, and acute hypercapnic (Table 3). Overall, analysis of the antihypoxic activities of compounds I-XV shows that most were inactive. Compound I had some activity in the hemic hypoxia model, as did compounds X, XI, and XIII in the histotoxic hypoxia model. The lower antihypoxic activities of compounds I-XV in comparison with that of the single-type-substituted benzhydrylurea I may result from the same factors that reduce the anticonvulsive activities of compounds I-XV, as discussed above.

CHEMICAL METHODS

1,3 Di(benzhydryl)urea I. Benzhydrylureas (0.008 mole) were heated to 200-210°C for 10-16 h. Reaction mixes were cooled, dissolved in DMF, and diluted with water; the resulting precipitates of 1,3-di(benzhydryl)ureas were collected by filtration, washed with water, and dried.

1,3-Di(benzhydryl)ureas II-XV. These were synthesized and extracted using methods similar to that used for I.

Yields and physicochemical properties of compounds I-XV are shown in Table 1. Elemental analyses agreed with calculated values.

BIOLOGICAL METHODS

Pharmacological studies were carried out on white mongrel mice (18-25 g) of both sexes. Compounds were given p.o. as suspensions in 1% starch paste 1.5-2 h before dosage with convulsive agents. Anticonvulsive activity was assessed in terms of blockade of convulsions elicited by maximum electric shock [7], i.e. prevention of tonic extension of the hind limbs in mice, and in terms of increases in the convulsive threshold in the Corazol test [6]; calculations were performed by the indirect differences method [3] and determination of the anti-Corazol index (ratio convulsive thresholds with and without drug).

Antihypoxic activity were studied using three models of hypoxia: hemic (sodium nitrite 300 mg/kg), histotoxic (sodium nitroprusside 25 mg/kg), and hypoxic with hypercapnia (in a hermetic chamber) (Methodological Recommendations for Identification of Antihypoxic Agents, Moscow, 1990). Efficacy was evaluated in terms of the survival times of mice in experimental groups compared with those in control groups, and in terms of the protective index (i.e. the ratio of these values).

LITERATURE CITED

1. A. A. Bakibaev, L. G. Tignibidina, V. D. Filimonov, et al., Khim. Farm. Zh., No. 5, 31-35 (1991).
2. A. A. Bakibaev, V. D. Filimonov, V. K. Gorshkova, et al., Khim. Farm. Zh., No. 4, 34-36 (1993).
3. E. V. Montsevichyute-Éringene, Pat. Fixiol., No. 4, 71-78 (1964).
4. A. G. Pechenkin, L. G. Tingibidina, V. K. Gorshkova, et al., Khim. Farm. Zh., No. 5, 57-59 (1979).
5. V. D. Filimonov, A. A. Bakibaev, A. V. Pustovoitov, et al., Khim. Farm. Zh., No. 5, 540-545 (1988).
6. M. J. Orloff, H. L. Williams, and C. C. Pfeifer, Proc. Soc. Exp. Biol. (N.Y.), 70, 254-257 (1949).
7. E. A. Swinyard, W. C. Brown, and L. S. Goodman, J. Pharmacol. Exp. Ther., 106, 319-330 (1952).

SYNTHETIC ANTICONVULSANTS, ANTIHYPOXICS, AND LIVER MONOOXYGENASE SYSTEM INDUCERS BASED ON AMIDES AND UREA.

VI*. SYNTHESIS AND SEARCH FOR LIVER MONOOXYGENASE SYSTEM INDUCERS AMONG COMPOUNDS CONTAINING THE BENZHYDRYL GROUP

A. A. Bakibaev, R. R. Akhmedzhanov,
T. P. Novozheeva, L. G. Tignibidina,
V. D. Filimonov, A. S. Saratikov,
and V. V. Shtrykova

UDC 547.883:615.355.591.436

The idea of the pharmacological utilization of compounds which induce liver cytochrome P-450-dependent monooxygenase system enzymes by dosage with hydrophobic xenobiotics was proposed by A. Conney [10] more than 20 years ago. Later studies [4] supported this concept in clinical practice, using zixorin (3-trifluoromethyl-α-ethylbenhydrol; Gideon Richter, Hungary), which was recommended for the treatment of liver and bile tract disease.

The benzhydryl group is a key pharmacological fragment for many biologically active compounds with a wide spectrum of pharmacological activities [1, 8, 9].

There has thus far been no systematic analysis of the liver monooxygenase enzyme system-inducing activity among compounds containing the benzhydryl group.

The aim of the present work was to synthesize different benzhydryl compounds, to screen them for enzyme-inducing activity, and to identify potential classes of organic compounds as inducers of the liver monooxygenase system. We synthesized a series of compounds (I-XII) containing the benzhydryl group, and studied their effects on the liver monooxygenase system using the hexobarbital sleep test in experimental animals. The yields and physicochemical properties of compounds I-XII are shown in Table 1, and their effects on the liver monooxygenase system are shown in Table 2.

Ph_2CHR,
I—XII

where R=H (I), OH (II), NH_2 (III), NH_2·HCl (IV), NHCHO (V), $NHCOCF_3$ (VI), $NHCONH_2$ (VII), NHCONHAC (VIII), $NHCONHCONH_2$ (IX), $NHCONHCHPh_2$ (X), $N{=}CHSO_3Na$ (XI), N=CHCH=CHPh (XII).

Diphenylmethane I and benzhydrol II were obtained in pure form by standard methods [3]. Benzhydrylformamide V was synthesized by our modification of the Leickhardt reaction [2];

*See [2] for Communication V.

Polytechnical University, Tomsk. Siberian Medical University, Tomsk. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 27, No. 4, pp. 39-41, April, 1993. Original article submitted July 8, 1992.

 0091-150X/93/2704-0260$12.50