Pharmaceutical Chemistry Journal, Vol. 28, No. 7, 1994

SYNTHETIC ANTICONVULSANTS, ANTIHYPOXICS, AND INDUCERS OF THE LIVER MONOOXYGENASE SYSTEM BASED ON AMIDES AND UREA. XV. SYNTHESIS AND BIOLOGICAL ACTIVITY OF NEW *ORTHO*-SUBSTITUTED BENZHYDRYLUREAS: POTENTIAL SYNTHONES OF QUINAZOLINES AND BENZODIAZEPINES

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UDC 547.495.2:615.213:616-0.01.8

Our earlier studies of the anticonvulsive [2, 3] and antihypoxic [4] activities of a large number of benzhydrylureas revealed several highly active agents.

With the aim of looking for new biologically active compounds, we have synthesized two previously unstudied *ortho*-hydroxy-substituted benzhydrylureas (compounds I and II), and have studied their anticonvulsive and antihypoxic activities. In addition, compounds I and II were found to be synthones of many classes of heterocyclic compounds, such as the quinazolines and benzodiazepines, which are known for their high and multifarious pharmacological activities [5, 6].

2-Hydroxyl-5-chlorobenzhydrylurea (I) was synthesized by condensation of the appropriate benzhydrylamine with nitrourea, and the compound was isolated and purified as described in [3].

$$RR^1CHNH_2 \rightarrow \underset{\text{I}}{RR^1CHNHCONH_2} \rightarrow \underset{\text{II}}{RR^1CHNHCONHCOCF_3}$$

I, II: $R = Ph$, $R^1 = C_6H_3OH\text{-}2\text{-}Cl\text{-}5$

Since introduction of a trifluoroacetyl group frequently increases the pharmacological effect of a basal substance [7, 8], we prepared N-(2-hydroxyl-5-chlorobenzhydryl)-N'-(trifluoroacetyl)urea (II) by reacting benzhydrylurea I with trifluoroacetic anhydride in the presence of catalytic quantities of sulfuric acid. Reaction of trifluoroacetic anhydride with I could involve attachment of the trifluoroacetyl group to the primary (NH_2) or secondary (NH) amino groups or to the hydroxyl groups.

The PMR spectrum of compound I contained duplet signals at 6.04 ppm (CH) and 6.88 ppm (NH), along with a singlet signal at 5.95 ppm (NH_2) and multiplets from aromatic protons (7.66-8.22 ppm); the PMR spectrum of compound II contained duplet signals at 6.08 ppm (CH) and 8.72 ppm (NH) and a singlet weak-field signal at 10.75 ppm, which is characteristic for the $CONHCOCF_3$ group, while the singlet signal at 5.95 ppm (NH_2) was absent. In addition, the infrared spectrum of benzhydrylurea II lacked absorption bands at 3420 and 3460 cm^{-1} (NH_2), but contained an additional intense band at 1710 cm^{-1} ($NHCOCF_3$). The infrared spectra of both benzhydrylureas I and II contained an absorption band at 3580 cm^{-1} (OH). Thus, the IR and PMR spectrum data of compounds I and II, combined with elemental analysis and TLC analysis, unambiguously show them to have the structures shown above.

The anticonvulsive activities of benzhydrylureas I and II were determined in maximum electric shock and corazol titration tests (Table 1), and antihypoxic properties were studied in models of acute hemic, histotoxic, and hypoxic hypoxia with hypercapnia (Table 2). Both compounds had low acute toxicity (LD_{50} values were greater than 2000 mg/kg).

Tomsk Polytechnical University. Scientific-Research Institute of Pharmacology, Tomsk Scientific Center, Russian Academy of Medical Sciences. Translated from Khimiko-farmatsevticheskii Zhurnal, No. 7, pp. 11-12, July 1994. Original article submitted February 25, 1993.

0091-150X/94/2807-0452$12.50

TABLE 1. The Anticonvulsive Activity of Compounds I and II

Compound	LD_{50}, mg/kg	Therapeutic ratio (LD_{50}/ED_{50})	Dose, mg/kg	Maximum electric shock test			Convulsive threshold of Corazol, mg/kg	
				prevention of convulsions, %	surviving animals, %	ED_{50}, mg/kg	$M \pm m$, p	ACI
I	2000	22,2	200	50,0	100	90	112,9±3,5	1,10
			100	50,0	100		0,192	
			50	16,7	100			
II	2000	22,2	200	80,0	100	90	135,0±7,8	1,30
			100	50,0	66,7		0,008	
			50	16,7	100			
Chloracon	1368	5,7	200	50,0	83,3	240	132,4±11,4	1,30
			400	66,7	100		0,025	
			100	16,7	83,3			

Notes: ACI = anti-Corazol index

TABLE 2. The Antihypoxic Activity of Compounds I and II

Compound	Dose, mg/kg	Sodium nitrite, 300 mg/kg			Sodium nitroprusside, 25 mg/kg			Barochamber		
		control	experiment	AHI	control	experiment	AHI	control	experiment	AHI
I	200	18,2±0,9	18,5±1,7	1,0	13,8±1,2	16,0±0,9	1,2	33,0±2,2	41,0±2,3	1,3
			0,845			0,141			0,034	
II	200	18,2±0,9	17,0±0,9	0,9	13,8±1,2	13,7±1,2	0,99	35,5±2,1	40,5±2,4	1,14
			0,389			0,922			0,141	

Notes: AHI = antihypoxic index

In the Corazol titration test, benzhydrylureas I and II had weak anticonvulsive activity, though the trifluoroacetyl derivative II significantly increased the convulsive threshold of Corazol. However, in the maximum electric shock test, compounds I and II had similar high levels of anticonvulsive activity, with ED_{50} = 90 mg/kg; activity was almost three times greater than that of the reference agent Chloracon (ED_{50} = 240 mg/kg). Therapeutic ratios were correspondingly wider than that of the reference compound (see Table 1). In addition, it must be mentioned that benzhydrylureas I and II were significantly less active than the unsubstituted benzhydrylurea, which had EC_{50} = 47 mg/kg and an anti-Corazol index of 3.7 [2]. Both compounds had weak antihypoxic activity in models of acute hypoxia (see Table 2), and were less active than the unsubstituted benzhydrylurea [3].

Thus, the new benzhydrylureas I and II had pronounced anticonvulsive activity in the maximum electric shock test, but had low activity as antihypoxic agents.

EXPERIMENTAL (CHEMICAL)

IR spectra were recorded using a UR-20 apparatus. PMR spectra were taken on a Tesla BS-497 spectrometer (using HMDE as the internal standard, at 100 MHz). Reactions were followed and product purity was confirmed by TLC analysis on Silufol UV-254 plates, eluted with benzene:ethanol (8:2), and spots were detected in UV light. Elemental analyses agreed with expected values.

2-Hydroxyl-5-chlorobenzhydrylurea (I). 2-Hydroxyl-5-chlorobenzhydrylurea (0.01 mol) was heated with nitrourea (0.015 mol) in 100 ml of water for 5 h at 70°C. The reaction mix was cooled, and the resulting precipitate was washed with warm water and recrystallized from ethanol; this produced the desired product, compound I, with a yield of 72%. The melting temperature was 203-205°C and the formula was $C_{14}H_{13}ClN_2O_2$. The IR spectrum (vaseline, ν_{max}, cm^{-1}) was: 1670 (CO), 3343 (NH), 3460, 3420 (NH_2), 3580 (OH). The PMR spectrum (δ, DMSO-d_6, ppm) was: 5.95 s (NH_2), 6.04 (1H, CH), 6.88 (1H, NH), 7.66-8.22 m (8H, aromatic).

N-(2-Hydroxyl-5-chlorobenzhydryl)-N'-(trifluoroacetyl)urea (II). 2-Hydroxyl-5-chlorobenzhydrylurea I (0.01 mol) was mixed with 0.02 mol of freshly prepared trifluoroacetic anhydride in 20 ml of anhydrous benzene in the presence of 2 drops of sulfuric acid (d = 1.84) for 1 h. The solvent was then evaporated, and the resulting precipitate was recrystallized from

hexane, to produce compound II with a yield of 80%. The melting temperature was 313-314°C, and the formula was $C_{16}H_{12}ClN_2O_3F_3$. The IR spectrum (vaseline, ν_{max}, cm^{-1}) was: 1685 (C=O), 1710 ($COCF_3$), 3350 (NH), 3215 (CONHCO). The PMR spectrum (δ, DMSO-d_6, ppm) was: 6.08 (1H, CH), 8.72 (1H, NH), 7.68-8.35 m (8H, aromatic), 10.75 s (1H, NH).

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