ANTIDEPRESSANT BENZAMIDES

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UDC 615.214.32.038

Recent decades have seen substantial advances in the development of new antidepressants [4, 5, 23]. The need has, however, become apparent for drugs which have adequately large therapeutic indices and show a minimum of undesirable side effects for the treatment of depressive states of differing origins (in this connection, see [7, 12, 15, 17-19, 22]). Theoretical studies are proceeding in parallel. Attempts have been made to classify antidepressants according to their chemical structure or pharmacological effects [4], resulting in the identification of "antidepressants of various groups" in respect of chemical structure, as opposed to the tricyclic (classical) antidepressants and MAO inhibitors, and also according to their biochemical behavior as "typical" or "atypical" antidepressants. Difficulties were however encountered in the development of these classifications, and ambiguities in the resolution of questions arising in this area. Classification of antidepressants in respect of chemical nomenclature or formal and restrictive chemical features is not really rational. Structure-activity relationships, including conformational features of the compounds and molecular aspects of the functions of the appropriate bioreceptors, have been considered for the most part in respect of the tricyclic antidepressants (for recent reports, see [10, 16]). In this connection, the identification in the chemical structure of the greatest variety of similar fragments (pharmacophoric or auxiliary groups) should assist in the establishment of relationships between structure and activity, and consequently in a more rational approach to the design of novel drugs. For example, it is easy to see that nearly all types of antidepressant contain an aromatic 6-π, 6-π + 6-π, or 10-π electron system (the last being for example noncharacteristic of neuroleptics). The side chain contains between two and four units between the aromatic nucleus and the basic nitrogen (a primary, secondary, or tertiary amino-group), and the framework of the side chain can include, in addition to carbon, heteroatoms (oxygen or nitrogen). Diphenylmethane or diphenylamine fragments are frequently present, as are electron-donor or weakly electron-acceptor substituents. Also included is the drug moclobemide, 4-chloro-N-(2-morpholinoethyl)benzamide (I), which is indicated for use as a short-acting antidepressant, and is a type A MAO inhibitor with respect to 5-HY and NA [11, 13, 14, 21]. This compound has satisfactory activity in vivo (its in vitro activity is considerably lower), but it has some deficiencies. In particular, when given in man it causes sleepiness, tremor, and other side effects [13]. The side chain in (I) contains four units between the aromatic ring and the basic nitrogen, which is typical of sedative drugs such as neuroleptics [20]. Bearing in mind, however, that extending the four-unit chain in the neuroleptic molecule results in loss of activity, the question arises as to the desirability of replacing the dimethylene moiety in (I) by the trimethylene moiety. The same conclusion is suggested by literature reports that MAO inhibitors can undergo considerable structural modifications without loss of their inherent activity.

With these considerations in mind, we have synthesized some N-(3-aminopropyl)benzamides (IIa-m) (Table 1). These compounds were obtained by the general methods A and B:

A: $ArCOCl + NH_2(CH_2)_3NR_2 \longrightarrow ArCONH(CH_2)_3NR_2 \cdot X$ IIa-j

B: $ArCOCl + NH_2(CH_2)_3Hal \xrightarrow{HNR_2} ArCONH(CH_2)_3Hal \longrightarrow$ II k-m

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Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 23, No. 11, pp. 1304-1309, November, 1989. Original article submitted March 20, 1989.

0091-150X/89/2311-0873$12.50

TABLE 1. N-(3-Aminopropyl)benzamides (IIa-m)

Compound	Yield, %	mp, °C	Empirical formula
IIa	67	250	$C_{14}H_{20}N_2O_2 \cdot C_2H_2O_4$
IIb	73	171—172	$C_{14}H_{19}FN_2O_2 \cdot HCl$
IIc	86	107—108	$C_{14}H_{19}ClN_2O_2 \cdot C_4H_4O_4$
IId	72	189,5—191	$C_{14}H_{19}ClN_2O_2 \cdot HCl$
IIe	91	182—182,5	$C_{14}H_{19}BrN_2O_2 \cdot HCl$
IIf	50	146—147	$C_{15}H_{22}N_2O_3 \cdot C_2H_2O_4$
IIg	84	73—73,5	$C_{15}H_{22}N_2O_3$
IIh	48	150	$C_{16}H_{24}N_2O_4 \cdot C_2H_2O_4$
IIi	60	135,5—136	$C_{17}H_{26}N_2O_3 \cdot HCl$
IIj	90	205	$C_{14}H_{19}N_3O_4 \cdot HCl$
IIk	66	89—90	$C_{14}H_{21}ClN_2O \cdot HCl$
IIℓ	27	190	$C_{22}H_{29}N_3O \cdot 2HCl \cdot H_2O$
IIm	39	185—186	$C_{21}H_{27}N_3O \cdot 3HCl$

Note. Compounds (IIa, h, j, ℓ) melted with decomposition, (IId, e, f, j, ℓ) were recrystallized from alcohol, (IIb) from butanol, (IIc, m) from acetone, (IIa, i) from propan-2-ol, (IIg) from hexane—benzene; (IIc) was the maleate, and (IIg) the hydrochloride, mp 95-96°C.

TABLE 2. Physicochemical Properties of (I), (IId), (III), and (IV)

Compound	medium	Frequencies, cm^{-1}				pK_a (20 °C)
		ν_{NH} free	ν_{NH} bonded	$\nu_{C=O}$ (amide I)	amide II	
IId	Vaseline grease	—	3339	1629	1533	5,75
	CCl_4	3463	3293	1675	1517	(6,81)
I	Vaseline grease	—	3275	1638	1540	5,25
	CCl_4	3425	—	1670	1510	(6,31)
III	Vaseline grease	—	3322	1632	1531	6,40
	CCl_4	3460	—	1676	1516	
IV	KBr	—	3307 3341	1640	1539	—
	CCl_4	3458	—	—	—	

Note. pK_a values were obtained for solutions in 50% alcohol. Values for aqueous solutions are given in brackets. The spectra in CCl_4 were obtained at $c = 1 \cdot 10^{-3}$ M.

Here, Ar = C_6H_5 (IIa), 4-FC_6H_4 (IIb), 2-ClC_6H_4 (IIc), 4-ClC_6H_4 (Id, k), 4-BrC_6H_4 (IIe), 2-anisyl (IIf), 4-anisyl (IIg), 3,4-$(CH_3O)_2C_6H_3$ (IIh), 4-$C_3H_7OC_6H_4$ (IIi), 2-$NO_2C_6H_4$ (IIj), 4-tosyl (IIℓ, m); NR_2 = morpholino (IIa-ℓ), diethylamino (IIk), 4-benzylpiperazino (IIℓ) 4-phenylpiperazino (IIm); Hal = Cl or Br. X = hydrogen chloride or an organic acid.

In order to assess further the effects of the side chain in 4-chlor-N-(ω-morpholinoalkyl)-benzamides on pharmacological activity and physicochemical properties, the homolog of (IId), namely 4-chloro-N-(4-morpholinobutyl)benzamide (III), and the model compound 4-chloro-N-propylbenzamide (IV) were synthesized. Compound (III) was found to be virtually devoid of the useful pharmacological properties possessed by both (I) and (IId). Examination of the IR spectra of (I), (IId), and (III) as the free bases showed several interesting features both in respect of similarities and differences (Table 2).

As will be seen from Table 2, the carbonyl group in these compounds is conjugated with the benzene ring ($\nu_{C=O}$) at 1675-1680 cm^{-1}, which is also evident from UV spectra (λ_{max} 240 nm, ε 11,900). The relatively high value of ν_{NH} for bonded and free groups, together with the presence of strong amide II absorption indicates that the amide groups have the trans-configuration (relative to the hydrogen and oxygen atoms) in the associated and nonassociated molecules [1]. In the case of the model compound (IV) in CCl_4 solution, one absorption band in present for the unbonded NH group; similarly with (I) under these conditions there are neither intermolecular nor intramolecular hydrogen bonds (IHB). The spectrum of (III) in CCl_4 shows vibrations for the free NH group, the intensity of the band characteristic of the bonded NH group being negligibly small. The presence of IHB in CCl_4 solutions of (IId), and the absence of such bonding in (I) and (III) may be attributed to the relatively favored six-

TABLE 3. Energetic Properties of IHB in (IId)

T	S_1	S_2	$-\Delta H$, kJ/mole
287	25,2949	1,2981	
292	24,2155	1,3195	
318	19,1165	1,4528	11,087
341	16,0406	1,4528	
350	15,4870	1,7168	

Note. The linear plot parameters were found by least squares, correlation coefficient 0.999.

membered pseudoring involving IHB in the case of (IId) as compared with the possible five- or seven-membered rings for (I) and (III). In this respect, it is noteworthy that the basicity of the morpholine residue (Table 2) clearly has no controlling effect on the formation of IHB, since (III) is more basic than (IId).

To calculate the energy of the IHB in (IId), the temperature dependence of the integral intensities of the absorption bands in the region of stretching vibrations of the NH groups were examined. The calculations were carried out using the observed temperature changes in the areas of the peaks, which were proportional to the integral intensities [9], using the equation:

$$\ln \frac{S_1}{S_2} = \frac{-\Delta H}{1.98 \cdot T} + a,$$

where S_1 and S_2 are the areas of the peaks for the bonded and free NH groups respectively, ΔH is the energy of the IHB, and a is the linear dependence coefficient, equal to 1.3728. The results of the calculations of the areas of these absorption bands are given in Table 3.

The interactions of (IId) with model lipid membranes (liposomes of phosphatidylcholine) were assessed by their effects on the fluorescence of a surface probe (1,8-anilinonaphthalenesulfonic acid). The base value of the fluorescence of the probe-membrane complex was 32 arb. units. Compound (I) had no effect on the fluorescence of the probe-membrane complex, but (IId) increased it, providing indirect confirmation of its interaction with lipid membranes. Titration of the probe-membrane complex with (IId) enabled its overall affinity for the model lipid membranes to be found (1.125 arb. units), this being somewhat lower than for imipramine (9.068), pyrazidol (4.641), or befuralin (6.182). It follows that (IId) has a clear affinity for the lipid phase of the membrane, while (I) does not have such an affinity.

A possibly important difference of (IId) from (I) is therefore its ability to form quasi cycles in hydrophobic solvents as a result of IHB, and generally speaking the physicochemical characteristics of (IId) and related compounds given above probably correspond to some extent to the spectra of their pharmacological activity.

EXPERIMENTAL (CHEMISTRY)

UV spectra were obtained on a Specord M-40 (East Germany), and IR spectra on a Perkin-Elmer 580B instrument (Sweden). The peak areas were calculated using the QUANT program on a Perkin-Elmer IR DATA STATION-3600 (Sweden). Ionization constants were obtained by potentiometry on a Digisence pH meter (USA). The elemental analyses were in agreement with the calculated values.

4-Chloro-N-(3-morpholinopropyl)benzamide Hydrochloride (IId). To a solution of 17.5 g (0.1 mole) of 4-chlorobenzoyl chloride in 60 ml of dry chloroform was added dropwise with stirring and external water cooling (10-20°C) over 10-12 min 14.42 g (0.1 mole) of N-(3-aminopropyl)morpholine, and the mixture heated at 40-50°C for 20 min. It was then cooled to 18-23°C, and the solid which separated was filtered off, washed with chloroform, and recrystallized from abs. alcohol to give 22.9 g of (IId).

The other hydrochlorides (Table 1) were obtained similarly. If the hydrochloride did not separate as a solid under these conditions, the mixture was basified, the aqueous layer

TABLE 4. Effects of Benzamides (II) on the Duration of Immobilization of Animals (Porsolt Method [24])

Compound	LD_{50}, mg/kg	Dose, mg/kg	Duration of immobilization	
			sec	% of control
IId	450	PS	281±1,7	
		1	205±7,0	−28*
		PS	276±4,4	
		5	144±5,3	−48*
		PS	245±13	
		10	302±4,4	+23
IIf	100	PS	263±9,7	
		10	220±8,8	−17
		PS	264±6,1	
		20	229±12	−14
IIg	350	PS	260±6,1	
		10	193±12	−26*
		PS	281±10	
		35	271±17	−4
IIk	300	PS	262±10	
		10	260±8,8	−1
		PS	259±15	
		30	239±5,3	−8
IIℓ	100	PS	269±9,7	
		10	235±9,7	−13*
		PS	268±10	
		20	270±8,8	+0,7
IIm	100	PS	225±9,7	
		10	273±9,7	+21*
		PS	237±5,8	
		20	240±15	+1

Note. Each dose was used in six mice, strain CBWA. The behavior of the animals was assessed 20 min after intraperitoneal administration of the compound in a volume of 0.2 ml. Observations were continued for six minutes. An asterisk indicates $P < 0.05$. PS denotes physiological saline.

separated, the chloroform layer extracted with dilute hydrochloric acid, and the acid solution basified, extracted with an organic solvent (ether or benzene), and the solvent distilled off. The residue was dissolved in dry ether, and an ether solution of either hydrogen chloride, oxalic acid, or maleic acid added to precipitate the base salt, which was recrystallized if necessary (Table 1). Compound (IIg) was also characterized as the free base.

4-Methyl-N-[3-(4-phenylpiperazino)propyl]benzamide Trihydrochloride (IIm). To 7.8 g (0.04 mole) of 3-bromopropylamine hydrobromide, 20 ml of dichloroethane, and 30 ml of water was added a saturated solution of 12.7 g (0.12 mole) of sodium carbonate in water, and the mixture stirred for 30 min. A solution of 6.2 g (0.04 mole) of 4-methylbenzoyl chloride in 10 ml of dichloroethane was then added with external cooling (5-10°C), the mixture stirred at 20°C for 2 h, and the solid filtered off and washed with chloroform. The aqueous layer was extracted with chloroform, and the combined organic solutions evaporated to give 10.1 g of 4-methyl-N-(3-bromopropyl)benzamide as an oil. This (5 g, 0.0195) and 6.3 g (0.039 mole) of 4-phenylpiperazine in 20 ml of toluene were boiled for 9 h, the precipitated phenylpiperazine hydrobromide filtered off, and the toluene filtrate washed with water and evaporated. The residual base (IIm) was converted into its hydrochloride in solution in abs. alcohol and ether.

Compounds (IIk, ℓ) were obtained similarly, except that in the case of (IIk) the reaction was carried out with an excess of diethylamine in the absence of a solvent. Data for (IIa-m) are given in Table 1.

TABLE 5. Effects of Some Benzamides on MAO Activity in Vitro Substrate Serotonin

Compound	Concentration, μM	MAO activity, %
Control	—	100±12
IId	10	63±6*
	100	31±7*
IIf	100	86±8
IIk	100	102±7
IIℓ	100	82±4
IIm	100	73±7

Note. 100% MAO activity = 4.8 ± 0.52 nmole serotonin per 1 mg of protein per minute. MAO activity was measured by the isothermal diffusion of ammonia followed by Nesslerization in 25% rat brain homogenate [2]. The final saturating concentration of serotonin was 6.6 mM. The average values of MAO activity are given for 4-8 determinations. An asterisk indicates $p \leq 0.02$.

4-Chloro-N-(4-morpholinobutyl)benzamide (III). To a solution of 2.1 g (0.013 mole) of N-(4-aminobutyl)morpholine in 10 ml of pyridine was added gradually 2.6 g (0.015 mole) of 4-chlorobenzoyl chloride with stirring and cooling (at around 0°C). The mixture was kept for 3 h at 20°C, evaporated under reduced pressure, toluene added, and again evaporated. To the residue was added 60 ml of chloroform, followed with ice-water cooling by the addition of 30 ml of 15% sodium hydroxide solution. The organic layer was separated, dried over potassium carbonate, the solvent removed, and the residue crystallized from alcohol, then from acetone to give 2.9 g (65.6%) of (III), mp 105-106°C. This was then converted into its hydrochloride by treatment of its acetone solution with ethereal hydrogen chloride, mp 239-240°C. $C_{15}H_{21}\cdot ClN_2O_2\cdot HCl$.

EXPERIMENTAL (PHARMACOLOGY)

The compounds were first tested in the Porsolt model swimming test [24] in order to identify potential antidepressant properties. The more interesting results are given in Table 4.

All the test compounds except (IIm) shortened to varying degrees the period of immobilization, which is generally accepted as providing an indication of antidepressant properties. Comparison of the severity of the toxic effects of the compounds (LD_{50} values) with their activity showed that the most interesting compound was (IId), which was then subjected to extensive pharmacological examination.

In a learning disability model, following chronic administration of the compound (this model better reflects antidepressant activity [8]), (IId) eliminated symptoms of depressive behavior after 3-7 days' treatment, which is a shorter period than with standard antidepressants (desmethylimipramine, amitryptiline, and chlormipramine).

In model prolonged depressive behavior in cats induced by administration of reserpine, or arising from repeated psychoemotional stress (reactive depression [7]), in doses of 0.5-1.0 mg/kg the compound eliminated pathological symptoms by the 2nd-3rd day of chronic treatment. The spectrum of psychotropic activity of (IId), as found using model depressive behavior in cats, differed favorably from those of the usual tricyclic antidepressants and MAO inhibitors [3].

No side effects were shown by (IId) over a wide range of "therapeutic" doses. Unlike the tricyclic antidepressants, it showed no cholinolytic activity, did not raise the arterial pressure, and had no effects on the cardiovascular system (in contrast to irreversible MAO inhibitors). Side effects in the experimental studies were only seen as doses 100 times greater than the therapeutic levels.

A study of the mode of action of (IId) and its analogs [2] has shown (IId) to be a selective, reversible type A MAO inhibitor in rat brain with respect to substrate serotonin both in vitro (Table 5) and in vivo (50% inhibition in an intraperitoneal dose of 1 mg/kg), in accordance with the high serotonin potentiating activity of (IId). Modification of the (IId) molecule (Table 5) resulted in a decrease in activity and (or) loss of selectivity with respect to serotonin deamination.

In contrast to (I), (IId) interacted directly with tyrosine hydroxylase (TH), the limiting enzyme in the biosynthesis of dopamine: when (IId) was added in a concentration of 10^{-7} M to a homogenate of the highly purified enzyme isolated from rat brain [6], 100% suppression of the reaction rate was observed. Over the concentration range 10^{-8}-10^{-3} M, (I) had no effect on the rate of the TH reaction under the same conditions. These findings show that (IId) has a considerable effect on dopaminergic processes in the brain. The suppressive effects of (IId) on TH are expressed kinetically as a noncompetitive process.

The effects of (IIℓ) and (IIm) on the rate of the TH reaction differ qualitatively in respect of their kinetic mechanisms from that of (IId), the two former compounds showing a mixed effect, increasing the Michaelis constant for tyrosine (interaction with the active site of the enzyme) while simultaneously removing substrate inhibition of TH (interaction with the allosteric site).

The results of extensive preclinical trials of (IId), which have demonstrated it to have potential antidepressant activity, novel features of psychotropic activity, special features of its action, and high bioavailability in conjuction with the originality of its chemical structure, confirm that (IId) is a promising antidepressant drug, and information was submitted to the Pharmacological Committee of the Ministry of Health of the USSR for clinical trials.

On the basis of the results of clinical trials, (IId) has been included in the Register of New Drugs ('Befol') by order No. 994 of the Ministry of Health of the USSR (31.08.87), and has been authorized for extensive clinical use.

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MUTUAL INFLUENCE OF ASCORBIC AND γ-AMINOBUTYRIC ACIDS ON THEIR BIOLOGICAL PROPERTIES DURING COMPLEXATION

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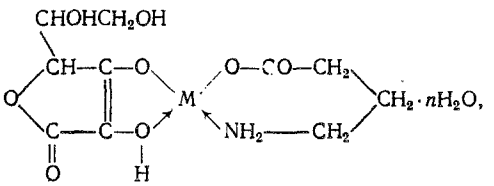
UDC 615.272.014.425:547.475.2.07

The authors of [4] studied the influence of complexation on the anti-oxidant and antihypoxic activity of ascorbic acid. It was thereby found that during a simultaneous coordination of ascorbic acid and S-methylmethionine by Fe^{2+} and Co^{2+} ions, the reduction potential and the antihypoxic activity of ascorbic acid increases.

The changes in the chemical and biological properties of ascorbic acid during a simultaneous coordination with amino acids are due to the mutual influence of different ligands, as a result of which their degree of polarization and electronic state are changing. The properties of the amino acids may thus also change. It was of interest to study the influence of ascorbic acid on the properties of amino acids jointly coordinated with it. Mixed-ligand compounds of cobalt and iron with ascorbic acid and γ-aminobutyric (GABA) acids were selected as the subjects of the investigation. As known, GABA participates in inhibition processes in the CNS, in metabolic and energetic processes in brain tissue. GABA and its analogs are widely used as effective neurotropic medicinal preparations (Aminalon, sodium hydroxybutyrate, Phenibut, etc.).

The influence of a mixed-ligand complexation on the neurotropic activity of GABA was studied using the examples of cobalt and iron γ-aminobutyrato-ascorbates having the following structure:



where M = Co, Fe; $n = 1,2$,

and also of an analogous compound of cobalt with ascorbic and acetyl-γ-aminobutyric acid. The synthesis and properties of these compounds are not described in the literature.

The mixed-ligand compounds of cobalt and iron with ascorbic and γ-aminobutyric acids were obtained by the action of barium hydroxide on solutions of metal sulfates containing equivalent amounts of pharmacopoeia-grade ascorbic and γ-aminobutyric acids according to the reaction

$$MSO_4 + H_2C_6H_6O_6 + \dot{N}H_3(CH_2)_3COO^- \longrightarrow M[(HC_6H_6O_6)(NH_2(CH_2)_3COO^-)]$$

followed by the isolation of the desired end products by precipitation with acetone from the filtrate after the separation of the barium sulfate precipitate. A compound with acetyl-γ-

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0091-150X/89/2311-0879$12.50