Pharmaceutical Chemistry Journal, Vol. 27, No. 12, 1993

SYNTHESIS AND BIOLOGICAL ACTIVITY OF FUROBENZAZOCINE DERIVATIVES

G. A. Tolstikov, É. É. Shul'ts, T. Sh. Mukhametyanova, T. G. Tolstikova, V. G. Popov, A. F. Ismagilova, D. N. Lazareva, and F. S. Zarudin

UDC 547.655:547.673.5:609.6

The observation in the 6,14-endo-ethenotetrahydrothebaines series of substances with a clear effect on the central nervous system [8], the vegetotropic activity of narcotine [9], the familiar antidepressant properties of morphanthridine [3], Altinil (benzthiazepine derivatives), and other compounds with a tricyclic structure containing 1 or 2 heteroatoms were the basis for our work on the synthesis and study of the biological activity of furobenzazocine (I) derivatives. We obtained compound I by thermal rearrangement of 6,14-endo-etheno-7α,8α-(thiolan-4'-one-1',1'-dioxido)-6,7,8,14-tetrahydrothebaine; this compound is described in [16].

The synthetic transformations of 6-(2',3'-dihydrobenzo[b]thiophene-3'-one-1,1-dioxido)-3,4,6,7-tetrahydro-5H-furo-4.3.3-f,g) [3] benzazocine (I) are based on the presence in the structure of an active methylene group on the thiolene-1,1-dioxide ring. Boiling I with aromatic aldehydes for 8 h in acetic acid in the presence of NH_4Cl under the conditions in [5] leads to formation of the corresponding benzylidene derivatives (IIa, e, f). Combined condensation of I, an ortho ester, and aniline [18] in acetic acid led to formation of the corresponding 2-anilinomethylene derivative (III) in 68% yield. The structure of the compounds obtained was established on the basis of spectral data. The IR spectra of the compounds contain strong absorption bands from the sulfonyl group (ν_{as} 1300-1320 cm^{-1}, ν_s 1110-1140 cm^{-1}) and the conjugated benzylidene group (ν 1690-1695, 1660 cm^{-1}) (Table 1). In the PMR spectrum of compound III there are signals corresponding to the presence of an aniline moiety. Based on the upfield shift of the NH signal (δ 8.65 ppm, J = 11.7 Hz), we can conclude that the double bond has a (Z) configuration [15, 18]. Compound IIa easily reacts with 2-chlorobenzimidazole at 20°C in the presence of Et_3N with formation of a pure 1,4-addition product (IV). In the IR spectrum of IV, we see stretching vibrations of the SO_2, the enalized carbonyl, and the C=N groups (see Table 1). The ^{13}C NMR spectrum contains a set of signals from the α-chlorobenzimidazole residue, the phenyl group, and the enalized carbonyl carbon (Table 2). Analysis of the NMR spectra of compound IV suggests stereohomogeneity; we did not carry out studies to determine whether to classify it within the threo or erythro series.

By condensation of I with anilines or phenylhydrazine, we obtained anilino- and phenylhydrazino derivatives (Va-e, VI). By azo coupling of I with $ArN_2^+Cl^-$ generated in situ we obtained the corresponding azo derivatives (VIIa-e). The UV spectra of VII are characterized by absorption maxima corresponding to the presence of a benzothiophene dioxidoaza aromatic chromophore [for VIIc, λ 246 (ε 37,040), 280 (27,320), 368 (17,220), 406 (9025) nm]. Making the alcoholic solution basic with KOH leads to lengthening of the conjugation chain [λ_{max} (ε) 246 (38,275), 287 (18,780), 282 (20,285), 336 (16,080), 425 (12,520) nm], which probably promotes stabilization of the hydrazone form.

By condensation of I with $CH_2(CN)_2$ under the conditions in [4], we obtained the dicyanomethylene derivative (VIII) in 87% yield. In the IR spectrum of the compound, there are stretching vibration bands for SO_2 (ν 1120, 1140, 1310 cm^{-1}), the nitrile (ν 2190, 2220 cm^{-1}) groups (see Table 1). In the ^{13}C NMR spectrum, the signal from the C^3 carbon atom is shifted upfield to 176.0 ppm, the signals from the nitrile groups are located at 111.58 and 111.35 ppm (see Table 2). We found that compound I easily enters into the Gewald reaction [7, 15] in the presence of Et_3N, and without separation of the intermediate VIII gives a furobenzazocine containing a 2-aminobenzo[b]thiophene moiety (IX). The presence of a thiophene moiety is confirmed by the spectral data. In the ^{13}C NMR spectrum, there are signals from $C^{3'}$, $C^{3'a}$, $C^{8'a}$, located in the 87, 70, 112, 51, 110, and 80 ppm region respectively.

The dicyanobenzothiophene dioxide derivative VIII contains in its structure an active methylene group, capable of being coupled with diazonium salts, reacting with compounds with cumulative bonds. As a result of the reactions, additional heterocyclic

Institute of Organic Chemistry, Ufa Science Center, Russian Academy of Sciences, Ufa. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 27, No. 12, pp. 20-26, December, 1993. Original article submitted March 25, 1992.

0091-150X/93/2712-0834$12.50

TABLE 1. Properties of Synthesized Compounds

Compound	Yield, %	Empirical formula	m.p. °C (solvent for crystallization)	IR spectrum, ν_{max}, cm^{-1}	PMR spectrum, δ, ppm, in $CDCl_3$	UV spectrum λ_{max}, nm (ε)
IIf	89	$C_{31}H_{28}NO_7S$	210—5 (AcOH)	1110, 1135, 1295, 1660, 1690 (C=O); 1510, 1520, 1590, 1610, (C=C)		245, 280, 335, 368, 428
IIe	79	$C_{36}H_{30}NO_7S$	202—5 (AcOH)	1110, 1135, 1295, (SO_2); 1695 (C=O); 1500, 1520, 1590, 1620 (C=C)		220, 250, 285, 290, 392, 435
III	68	$C_{30}H_{28}N_2O_6S$	195—7 (AcOH)	1110, 1115, 1300, 1315 (SO_2); 1510, 1610, 1640, 1560, 1670 (C=C, C=N), 3060, 3400 (NH)	2,12 s (CH_3), 2,60 m (5H, $H^{6,4,7}$), 3,20 m (2H, H^3), 3,89 s, 3,95 s (OCH_3), 6,70 dd (2H, $H^{8,9}$), 6,90 d, 7,52 d (2H, $H^{5',6'}$), 7,30 dd (2H, Ar), 8,25 d (1H, CH, J=11,7 Hz), 8,65 d (1H, NH)	246 (34782) 280 (12500) 320 (4210)
IV	65	$C_{36}H_{32}N_3O_6SCl$	260—2 (ethyl-acetate)	1110, 1130, 1295, 1310 (SO_2); 750, 1510, 1530, 1570, 1590, 1615, 1630 (C=C, C=N); 3360 (OH)	2,10 s (CH_3), 2,50 m, 2,87 m, 3,05 m, (5H, $H^{4,6,7}$), 3,32 m (2H, H^3), 3,58 d (1H, CH), 3,92, 3,98 s (OMe), 6,62 d, 6,70 d (2H, $H^{8,9}$), J=8,1 Hz), 7,01 d, 7,30 d (2H, $H^{5',6'}$), 7.30 m (2H, 7,30 m (2H, Ph), 7,50 (2H, Ph), 7,90 s (OH)	248, 250, 290 300, 320, 365
Va	72	$C_{29}H_{28}N_2O_5S$	210—3 (ether)	1105, 1140, 1295, 1310 (SO_2); 740, 1520, 1605, 1640 (C=C); 3340 (NH)		
Vb	89	$C_{29}H_{27}N_2O_5SCl$	152—5 (ethyl acetate)	1110, 1120, 1165, 1295, 1330 (SO_2); 1505, 1580, 1620, 1670 (C=C); 320 (NH)	2,43 s (NMe), 2,80 m, (4H, $H^{4,7}$), 3,20 dd (1H, H^6), 3,70 m (2H, H^3), 3,93 s, 3,98 s (CH_3), 6,70 d (2H, $H^{8,9}$), 7,0 m (6H, $H^{2,4}$ Ar), 7,33 dd (2H, $H^{5',6'}$), 7,82 s (1H, H^2)	
Vc	62	$C_{29}H_{27}N_2O_5FS$	128—30 (ether)	1105, 1140, 1295 (SO_2); 750, 810, 840, 930, 1505, 1560, 1610, 1660 (C=C); 3360 (NH)		246 (18518), 280 (8930), 366 (3523); (alc. + +KOH): 240 (18750), 277 (10000) 287 (8784) 366 (6081), 405 (4522)
Vd	78	$C_{29}H_{26}N_2O_5F_2S$	115—20 (ether)	1110, 1140, 1300 (SO_2); 750, 820, 840, 1530, 1610, 1640 (C=C); 3380 (NH)		
Ve	75	$C_{35}H_{32}N_2O_6S$	163—7	1105, 1130, 1300 (SO_2); 810, 840, 1520, 1610, 1640 (C=C); 3400 (NH);		
VI	82	$C_{29}H_{26}N_3O_5S$	212—5	1105, 1140, 1295 (SO_2); 720, 760, 775, 1505, 1605, 1640, 1670		
VIIa	75	$C_{29}H_{29}N_3O_6S$	170—3 (*i*=PrOH)	1120, 1140, 1310 (SO_2); 720, 750, 780, 820, 1510, 1595, 1610, 1640, 1660		280 (31240), 288 (30360), 308 (25860), 396 (10960)
VIIb	88	$C_{29}H_{28}N_3O_6SCl$	205—8 (ethyl-acetate)	1120, 1145, 1295, 1330 (SO_2); 720, 780, 1510, 1580, 1600, 1620, 1670 (C=C)	2,25 s (NMe), 2,85 m (4H, $H^{4,6,7}$), 350 (2H, H^3), 3,94 s, 3,97 s (OMe), 6,77 dd (2H, $H^{8,9}$), 7,05 (4H, $H^{5',6'}$, Ar), 7,98 s (1H, OH)	
VIIc	68	$C_{29}H_{28}N_3O_6SF$	207—10 (ethyl-acetate)	1110, 1130, 1295, 1330 (SO_2); 1510, 1550, 1660 (C=C)	2,10 s (NMe), 2,55, 2,90 (5H, $H^{4,6,7}$), 3,38 (2H, H^3), 3,90, 3,96 s (OMe), 6,72 dd ($H^{8,9}$), 7,08 dd (2H, $H^{5',6'}$), 7,40 dd (2H, Ar), 7,28 (1H, Ar), 7,43 s (1H, H^2), 8,70 s (OH)	246 (37040), 280 (27320), 368 (17200), 406 (9025)

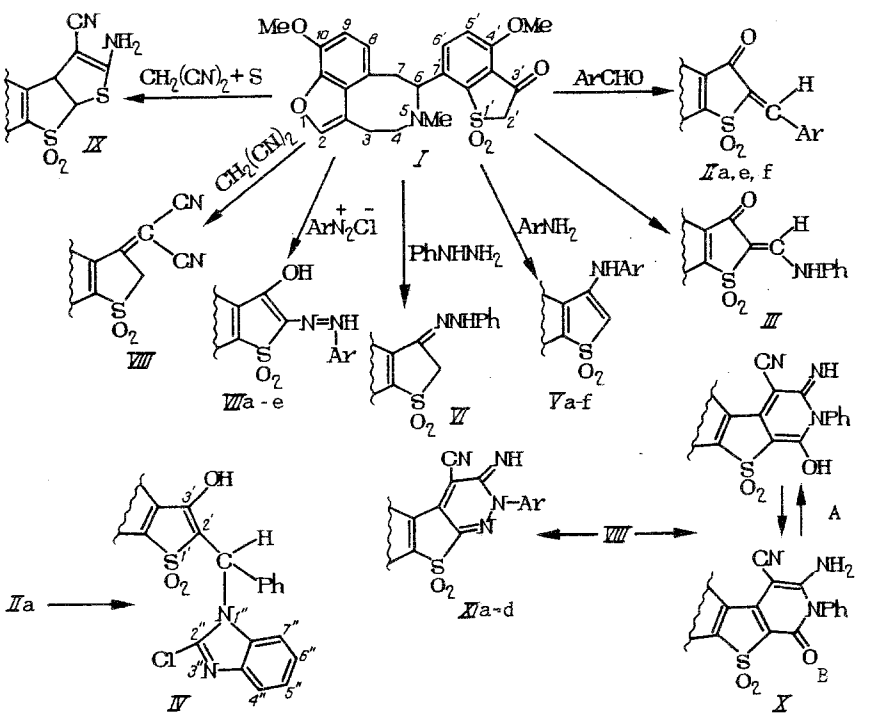
TABLE 1 (continued)

Compound	Yield, %	Empirical formula	m.p. °C (solvent for crystallization)	IR spectrum ν_{max}, cm^{-1}	PMR spectrum, δ, ppm, in $CDCl_3$	UV spectrum λ_{max}, nm (ε)
VIId	82	$C_{29}H_{27}N_3O_6SF_2$	190—5 (ethyl-acetate)	1140, 1305, 1330, (SO_2), 710, 740, 1530, 1610, 1640, 1660 (C=C)	2,12 s (NMe), 2,70 (5H, $H^{4,6,7}$), 3,50 (2H, H^3), 3,90 s, 3,96 s (OCH_3), 6,72 d, 6,80 d (2H, $H^{8,9}$, J=9,6 Hz), 7,35 d, 750 (3H, Ph), 7,80 dd (2H, Ph), 8,65 s (OH)	246 (46304), 282 (15430), 285 (18950), 427 (11500)
VIIe	87	$C_{35}H_{33}N_3O_7S$	145—7 (*i*=PrOH)	1110, 1140, 1305, 1320 (SO_2), 710, 750, 810, 840, 930, 1520, 1590, 1610, 1640 (C=C)		
VIII	87	$C_{26}H_{26}N_3O_5S$	167—71 (ethyl-acetate)	1120, 1140, 1295, 1310, (SO_2), 1515, 1590, 1610, 1640 (C=C), 2190, 2220 (C≡N)		248 (8893), 287 (4720), 310 (4450), 356 (2780) 425 (610), 460 (828)
IX	75	$C_{26}H_{26}N_3O_5S_2$	162—5 (ethyl-acetate)	1120, 1140, 1300 (SO_2); 750, 810, 830, 930, 1510, 1580, 1610, 1640 (C=C); 2220 (C≡N)		218, 248, 280, 285, 315, 480
X	78	$C_{33}H_{28}O_6N_4S$	195—7 (ethyl-acetate)	1120, 1130, 1300, 1330 (SO_2); 710, 750, 780, 1510, 1560, 1605 (C=C); 1660, 1680 (C=O, C=N); 3380, 3420 (OH, NH); 2195, 2210 (C≡N)		220 (50000), 255 (95166), 340 (3364), 415 (582)
XIa	72	$C_{32}H_{27}N_5O_5S$	170—4 (ethyl-acetate)	1105, 1140, 1300, 1315 (SO_2); 740, 795, 900, 1510, 1600 (C=C, C=N); 2230 (C≡N); 3360 (NH)	2,10 s (NMe), 250, 2,98 (5H, $H^{4,6,7}$), 3,55 dd (2H, H^3), 3,86 s, 3,88 s (6H, OMe), 6,70 d (2H, $H^{8,9}$), 6,95 dd (2H, $H^{6',5'}$), 7,42 s (1H, H^2), 8,82 s (1H, NH)	215 (32420), 246 (25250), 280 (10250), 308 (8220), 430 (1260)
XIb	68	$C_{36}H_{26}N_5O_5SCl$	190—3	1125, 1140, 1310 (SO_2); 750, 780, 820, 905, 1510, 1590, 1610, 1660 (C=C, (C=N); 2230 (C≡N); 3380	2,10 s (NMe), 2,50 (2H, $H^{4,7}$), 3,05 (3H, $H^{4,7,5}$), 3,55 dd (2H, H^3), 3,82 s, 3,88 s (OMe), 6,72 dd (2H, $H^{8,9}$), 7,02 (2H, $H^{6',5'}$), 7,48 s (1H, H^2), 9,02 s (1H, NH)	246 (25280, 282 (15910), 302 (10250), 420 (980)
XIc	69	$C_{32}H_{26}N_5O_5SF$	176—80 ?	1140, 1300, 1315 (SO_2); 750, 780, 810, 900, 1515, 1590, 1610, 1660 (C=C, C=N); 2245 (C≡N); 3350 (NH)	2,08 s (Me), 2,62, 3,05 (5H, $H^{4,6,7}$), 3,38 dd (2H, H^3), 3,86 s, 3,88 s (6H, OMe), 6,78 dd (2H, $H^{8,9}$), 7,08 dd (2H, $H^{6',5'}$), 7,52 s (1H, H^2), 8,78 s (1H, NH)	215 (55995), 246 (28090), 280 (12660), 295 (9850), 315 (6930), 430 (1613)
XId	75	$C_{32}H_{25}N_5O_5SF_2$	100—3 (ethyl-acetate)	1140, 1300 (SO_2); 750, 870, 1510, 1600, 1620, 1640 (C=C, C=N); 2240 (C≡N); 3350 (NH)		246 (22648), 280 (14542), 375 (6060), 390 (6818), 415 (1020)

moieties are formed [7, 12]. The reaction of VIII with PhNCO in the presence of Et_3N, according to data in [13], led to formation of the benzothienopyridine dioxide derivative X. Upon azo coupling of VIII with diazonium salts, we isolate thieno[2,3-c]pyridazines (XIa-d). The spectral data of the compounds obtained (X, XI) are consistent with the data in work characterizing the presence of a pyridazine or pyridine ring [12]. The UV spectra of compounds XIa-d are characterized by a bathochromic shift of the absorption maxima and a reduction of the extinction coefficient for the absorption maximum in the 415-430 nm region. For

TABLE 2. ^{13}C NMR Spectra of Synthesized Compounds

No. of atom	Compound				
	I	III	IV	VIII	IX
2	140,05	142,03	140,12	140,65	140,94
3	37,23	38,94	37,75	37,58	37,32
4	45,77	43,03	45,05	44,68	44,85
5 (Me)	46,15	44,93	46,38	46,18	45,53
6	68,92	68,03	69,35	69,38	69,49
7	23,64	24,57	24,05	24,43	23,00
8	111,09	114,41	111,34	111,15	111,80
9	122,93	120,51	120,00	120,48	120,37
10	144,17	145,30	144,50	144,75	144,61
2a	131,40	130,79	130,69	130,35	132,71
7a	125,17	124,67	125,95	124,27	124,16
7b	127,24	125,35	127,50	127,42	127,64
10a	143,59	142,81	143,82	143,10	144,19
2′	52,40	118,37	120,53	51,99	118,95
3′	199,82	162,11	159,43	176,00	112,51
4′	158,02	159,42	155,09	155,09	158,67
5′	130,03	130,79	129,95	130,36	130,41
6′	105,54	106,96	106,05	106,52	105,89
7′	119,88	118,37	118,55	115,86	119,05
3′a	122,13	123,58	122,95	123,69	87,70
7′a	116,18	115,57	119,50	114,89	114,02
=CHN	—	159,42	—	—	125,50 (3′b)
CH	—	—	52,52	—	110,80 (8′a)
Ar	—	128,06, 128,97, 129,62, 132,79	121,54 127,47, 128,34, 129,0, 131,69	—	—



Ar=Ph (a), 3-ClC_6H_4 (b), 4-FC_6H_4 (c), 3-F-4-F-C_6H_3(d), 3-$PhOC_6H_4$ (e), 4-$MeOC_6H_4$ (f).

compound X, we observe a hypsochromic shift of the absorption maximum (λ_{max} 255, 340, 415 nm) upon acidification of the alcoholic solution (λ_{max} 252, 300, 400 nm), which obviously is connected with stabilization of the ketone form B.

EXPERIMENTAL (CHEMICAL)

The NMR spectra were obtained on a Bruker AM 300 MHz spectrometer, internal standard TMS. The IR spectra were recorded on the UR-20 spectrophotometer in Vaseline oil. The UV absorption spectra were taken on the Specord M-400. We followed the course of the reactions using TLC data on Silufol UV-254 plates, eluting agents 10:1 and 20:1 chloroform—methanol. The properties of the compounds obtained are given in Tables 1 and 2. The elemental analysis data corresponds to the calculated values.

10-Methoxy-6-[7′-(4′-methoxy-2′-benzylidenebenzothiophen-3′-one-1′,1′-dioxido)]-5-methyl-3,4,6,7-tetrahydro-5H-furo[4,3,2-f,g] [3]Benzazocine (IIa). A mixture of 0.5 g compound I, 2 ml benzaldehyde, and 0.2 g NH_4Cl was boiled in 5 ml acetic acid for 8 h. The salt was filtered, the reaction mass was poured onto a watch glass for evaporation, the residue was treated with ether, and the precipitate was filtered. Obtained: 0.48 g (78%) compound IIa, which according to spectral data is identical to that described in [16]. Compounds IIe, f were synthesized according to this technique.

10-Methoxy-6-[7′-(4′-methoxy-2′-anilinomethylenebenzothiophen-3′-one-1′,1′-dioxido)]-5-methyl-3,4,6,7-tetrahydro-5H-furo[4,3,2-f,g] [3]Benzazocine (III). Compound I (0.3 g) was added to a mixture of 0.37 g triethylorthoformate and 0.6 g aniline in 10 ml AcOH, boiled for 2 h, and cooled. Compound III [0.18 g (68%)] was filtered off.

10-Methoxy-6-[7′-(3′-hydroxy-4′-methoxy-2′-(2″-chlorobenzimidazolylbenzyl)benzothiophene-1,1-dioxido)]-5-methyl-3,4,6,7-tetrahydro-5H-furo[4,3,2-f,g] [3]Benzazocine (IV). 2-Chlorobenzimidazole (0.1 g) in 5 ml benzene and 0.09 g Et_3N was added with stirring to a solution of 0.25 g compound IIa in 5 ml benzene. The reaction mass was stirred for 6 h at 20°C, 10 ml water was added, the substance was extracted with chloroform, the organic layer was washed with water and dried over $MgSO_4$, the solvent was evaporated, the residue (an oil) was purified by column chromatography on silica gel (Czechoslovakia) with particle size L 100/160 (eluting agent, chloroform). Obtained: 0.20 g (65%) compound IV.

10-Methoxy-6-[7′-(4′-methoxy-3′-anilinobenzothiophene-1′,1′-dioxido)-3,4,6,7-tetrahydro-5H-furo[4,3,2-f,g] [3]Benzazocine (Va). Aniline (0.15 g) was added to a solution of 0.25 g compound I in 15 ml AcOH and boiled for 2 h. The solvent was evaporated on a watch glass. Ether was added to the residue, the precipitate formed was filtered off, and it was recrystallized from ethylacetate. We analogously obtained compounds Vb-e and 10-methoxy-6-[7′-(4′-methoxy-3′-(3′-phenylhydrazino)-dihydrobenzothiophene-1′,1′-dioxido)]-3,4,6,7-tetrahydro-5H-furo[4,3,2-f,g] [3]benzazocine (VI).

10-Methoxy-6-[7′-(3′-hydroxy-4′-methoxy-2′-phenylazobenzothiophene-1′,1′-dioxido)]-3,4,6,7-tetrahydro-5H-furo[4,3,2-f,g] [3]Benzazocine (VIIa). Diazonium salt (10 ml) (obtained from 0.35 g aniline, 0.27 g $NaNO_2$, 5 ml water, and 2.5 ml 2 N HCl) was added dropwise to a solution of 0.3 g compound I in 10 ml pyridine at 0°C. Over the course of 30 min, the temperature was raised to room temperature, 10 ml water was added, the aqueous layer was extracted with chloroform, the chloroform extracts were washed with a large amount of water, dried over $MgSO_4$, evaporated, and the residue was dried by azeotropic distillation with benzene, and the oil obtained was crystallized from ethylacetate. Using this technique, in the reaction of compound I with diazonium salts obtained from 3-chloroaniline, 4-fluoroaniline, 3,4-difluoroaniline, or 4-phenoxyaniline respectively we synthesized compounds (VIIb-e).

10-Methoxy-6-[7′-(4′-methoxy-3′-dicyanomethylene-2′,3′-dihydrobenzothiophene-1′,1′-dioxido)]-3,4,6,7-tetrahydro-5H-furo[4,3,2-f,g] [3]Benzazocine (VIII). The dinitrile of malonic acid (0.05 g) was added to a solution of 0.88 g of compound I in 10 ml absolute alcohol, 0.05 ml piperidine, and 0.14 ml AcOH; after 6 h, another 0.06 g $CH_2(CN)_2$ was added, and the reaction mass was stirred on a magnetic stirrer for 17 h. Upon cooling down to 0°C, 0.82 g (87%) compound VIII was filtered off.

10-Methoxy-6-[7′-(4′-methoxy-2′-amino-3′-cyanobenzo[b]thieno[2,3-c]thiophene-8′,8′-dioxido)]-3,4,6,7-tetrahydro-5H-furo[4,3,2-f,g] [3]Benzazocine (IX). A mixture of 0.2 g $CH_2(CN)_2$, 0.4 g I, 0.1 g finely ground sulfur, and 0.12 g dimethylamine in 5 ml alcohol was stirred with a magnetic stirrer at 40°C for 5 h. The residue was filtered off, washed with ether, and dissolved in chloroform. The chloroform layer was washed with water, dried over $MgSO_4$, the solvent was evaporated, the residue was crystallized from ether, and 0.38 g (75%) of compound IX was isolated.

10-Methoxy-6-[8′-(5′-methoxy-3′-amino-4′-cyano-1′,2′-dihydro-1′-oxo-2′-phenyl-1H-benzo[4,5]thienyl[2,3-c]pyridine-9′,9′-dioxido)]-3,4,6,7-tetrahydro-5H-furo[4,3,2-f,g] [3]Benzazocine (X). PhNCO (0.1 g) in 1 ml THF was added to a mixture of 0.2 g compound VIII and 0.1 g Et_3N in 5 ml anhydrous THF at 50°C. The reaction mass was boiled for 5 h and then poured over ice. The product was extracted with chloroform, then the organic layer was washed with water, dried over $MgSO_4$, and evaporated. The residue obtained was crystallized from ethylacetate. Compound X was filtered off.

10-Methoxy-6-{8′-(3′,4′-dihydro-5′-methoxy-4′-cyano-3′-imino-2′-phenylbenzo[4,5-c]thieno[2,3-c]pyridazine-9′,9′-dioxido)}-3,4,6,7-tetrahydro-5H-furo[4,3,2-f,g] [3]Benzazocine (XIa). Diazonium salt (10 ml) (from 0.3 g aniline, 0.22 g $NaNO_2$, 5 ml water, and 2.3 ml 2 N HCl) was added dropwise to a solution of 0.3 g dicyano derivative VIII in 10 ml pyridine

TABLE 3. Biological Activity of Synthesized Compounds (all the data are given in % relative to the parameters in the control group)

Compound	LD_{50}, mg/kg	Orientation responses				Duration of soporific effect		Duration of phenamine-induced stereotypy	Duration of apomorphine-induced hypothermia	Analgesic activity		
		horizontal test	vertical test	on background of clofelin		hexenal	chloral-hydrate			electroshock stimulation	hot plate	vinegar "cramps"
				horizontal test	vertical test							
I	450	97±17,9	202±29,1	13±5,6	81±28,6	132±3,7	270±8,9	54±0,1	87±0,2	80,7±0,7	174,6±17,3	113±4,0
IIa	2000	135±3,6	153±41,9	208±30,0	157±61,8	106±12,6	150±25,9	38±0,1	97±0,25	88,5±4,4	164±0,12	85,8±6,4
IIb	1000	204±16,2	322±40	78±12,0	205±57,2	125±0,3	165±17,2	130±0,4	100±0,2	98±4,0	192±10,6	119±4,0
IIc	2000	145±11,7	207±30,9	68±8,0	76±28,5	170±6,1	179±6,3	123±0,1	97±0,2	52±2,0	128±10,0	21±7,7
Va	310	107,1±7,1	101±13,6	—	—	81,8±9,3	50,0±2,3	125±0,3	100±0,7	107,8±2,2	73,2±7,7	65,4±11,7
Vb	1000	252±27,9	284±43,7	52,0±0,2	362±2,4	131±2,5	221±6,9	71,0±0,12	97±0,2	78,8±2,8	173,3±13,3	70,3±11,7
Vc	800	141,5±5,5	152,4±9,1	—	—	85,4±0,9	132,4±21,2	103±0,13	—	80±8,4	169,0±8,7	90,6±7,8
Vd	1300	80,3±9,9	115,4±9,8	—	—	71,4±7	182,1±26,8	125±0,13	—	139,2±1,8	99±9,6	52,4±1,8
Ve	650	86,9±4,9	84,4±14,3	—	—	96,9±14,0	150±0,75	150±0,75	98,8±0,9	93,4±4,9	79,3±4,3	83,3±10,5
VI	440	113±14,3	209±33,6	70,0±16,0	462±14,8	238±18,6	220,4±0,15	132±0,34	93,0±0,2	74,6±2,8	176±18,6	94,0±7,4
VIIa	1300	114±12,5	75,3±13,6	—	—	61,4±5,3	50,0±0,8	50±0,8	99,4±0,9	107±3,2	67,2±7,7	52±6,2
VIIb	2000	108,0±19,8	307±32,7	94±20,0	119±28,6	137±10,0	322±0,1	125±0,1	108±0,2	74,0±1,0	153±18,6	63,5±11,1
VIIc	1200	107,0±9,8	95,8±11,9	—	—	98,9±7,3	127±24,9	95,8±0,13	—	128±5,4	118,3±8,1	84,6±10,3
VIId	1000	91,5±5,9	66,4±15,4	—	—	70,8±3,6	152,1±13,7	88,5±0,13	—	100,9±5,9	96,0±3,8	79,3±5,8
VIIe	1120	86,9±12,5	82,5±13,6	—	—	36,7±10,8	25,0±1,2	25,0±1,2	101,8±1,0	98,9±6,5	121,4±10,3	80,2±19,1
IX	1600	211,0±19,8	305±34,5	65,0±18,0	143±47,7	106±4,2	197±13,3	44,0±0,1	112,0±0,2	138,3±3,3	174,6±21,3	114,2±2,3
Xc	1000	103,8±3,9	111±4,2	—	—	141,9±5,6	25,0±1,2	100±0,15	99,1±0,7	100±0,15	72,4±3,5	80,2±9,3
X	1300	79,9±6,5	177,9±8,4	—	—	69,4±8,4	50,0±0,75	125±0,4	102,4±1,2	114,2±1,6	68,1±3,4	83,9±10,4

at 0°C. Over the course of 1 h, the temperature was raised to room temperature, 10 ml water was added, the aqueous layer was extracted with chloroform, the chloroform extracts were washed with water and dried over $MgSO_4$, the solvent was evaporated, and the oil obtained was crystallized from ethylacetate. Obtained: 0.31 g (72%) compound XIa. The reaction of compound VIII with the diazonium salts of 3-chloroaniline, 4-fluoroaniline, and 3,4-difluoroaniline leads to formation of compounds XIb-d.

EXPERIMENTAL (BIOLOGICAL)

The acute toxicity and antidepressant activity of the compounds were determined on white nonpedigree mice of mass 18-20 g. The compounds were injected into the stomach in a dose of 5 mg/kg. The action of the compounds on the central nervous system was studied in tests of motor activity [10], the duration of action of sporifics (hexenal 75 mg/kg, chloralhydrate 300 mg/kg) and apomorphine- [11] and phenamine-induced stereotypy. The analgesic activity was studied using electroshock [14] and thermal [19] stimulation and "vinegar cramps" [17]. The test results are shown in Table 3. The toxicity was determined by the Kerber method [1].

From the data in Table 3, we see that the new furobenzazocine derivatives are moderately hazardous compounds: the LD_{50} is 310-2000 mg/kg. Splitting the morphinane skeleton and rearranging it into the furobenzazocine derivative led to loss of the analgesic activity characteristic of 6,14-endo-ethenotetrahydrothebaine sulfones [6]. Introduction of an additional pyridazine moiety at the $C^{2',3'}$ position (XIc, d) leads to enhancement of the pain-relieving effect in the visceral pain model. All the compounds containing the 2-aza aromatic moiety or the 3-anilino substituent, independently of the aryl substituent (Va-e, VIIa-e) increased the pain sensitivity threshold by 30-50% in the visceral pain model. Moreover, the $C^{2',3'}$-pyridazine-substituted (XIb, c), 2′-arylaza- (VIIa, e), 3′-anilino- (Va, e) derivatives of furobenzazocine depress chloralhydrate-induced sleep by 50-70%. Introduction of chlorine atoms into the aromatic substituent of the indicated compounds (Vb, VIIb) leads to an increase in motor activity and the duration of phenamine-induced stereotypy, and potentiation of the soporific effect of chloralhydrate, which is probably connected with the stimulating effect on the D_2 receptors [2].

An analogous effect is observed for the 3′-hydrazine derivative VI. The compound containing an additional aminothiophene moiety (IX) increased the pain sensitivity threshold by 38-70% in tactile pain tests, potentiated the action of chloralhydrate, and increased the motor activity of the animals (by a factor of 2-3 compared with the control). The benzylidene derivatives IIa-c and also compound I (not containing additional nitrogen-containing moieties) did not give an analgesic effect, did not potentiate the soporific effect of barbiturates, increased the orientation responses, and eliminated the effect of clofelin. With an increase in the length of the conjugation chain, we observed an increase in the sedative activity.

Thus the new furobenzazocine derivatives display antidepressant activity; some of them have a pronounced sedative effect (arylidene, phenylaza substituents); others have a stimulating effect (arylaza-, pyridazino, anilino derivatives). Introduction of additional nitrogen-containing chromophores leads to an increase in analgesic activity.

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