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SEARCH FOR NEW DRUGS

SYNTHESIS AND ANTIDIABETIC ACTIVITY OF THIAZOLO[2,3-*f*]PURINE DERIVATIVES AND THEIR ANALOGS

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Thiazolo[2, 3-*f*]purine derivatives and their analogs – dihydrothiazolo[2, 3-*f*]purine, 7-(thietan-3-yl)purine, and 8-(2-hydroxypropylthio)purine derivatives – were synthesized. The compounds synthesized here had no effects on protein glycation reactions using glucose; they gave weak inhibition of glycogen phosphorylase; they had no hemorheological activity. Substances with hypotensive activity greater than that of Dibazol were found. A number of substances had hypoglycemic effects greater than those of chlorpropamide and Adebit. Two compounds inhibited dipeptidylpeptidase-4, but were less active than reference agent vildagliptin.

Keywords: thietanes, purine, antidiabetic activity.

Data from the International Diabetes Federation (IDF) indicate that there are now around 415 million patients with diabetes mellitus and that by 2040 the number may reach 642 million [1]. The current arsenal of agents for the pharmacological correction of metabolic anomalies in diabetes mellitus generally do not allow adequate glycemic control to be attained or the development of micro- and macrovascular complications to be prevented [2 – 4]. Thus, the development of novel antidiabetic substances is a relevant and necessary objective.

Type 2 diabetes mellitus is generally a manifestation of metabolic syndrome, which along with impaired glucose tolerance and dysfunction of the islet apparatus of the pancreas includes the following main components: arterial hypertension, abdominal-type obesity, hyperlipidemia, and hypercholesterolemia. The combination of these factors increases the probability of developing serious cardiovascular complications – atherosclerosis, myocardial infarction, cerebral stroke, and sudden death [5].

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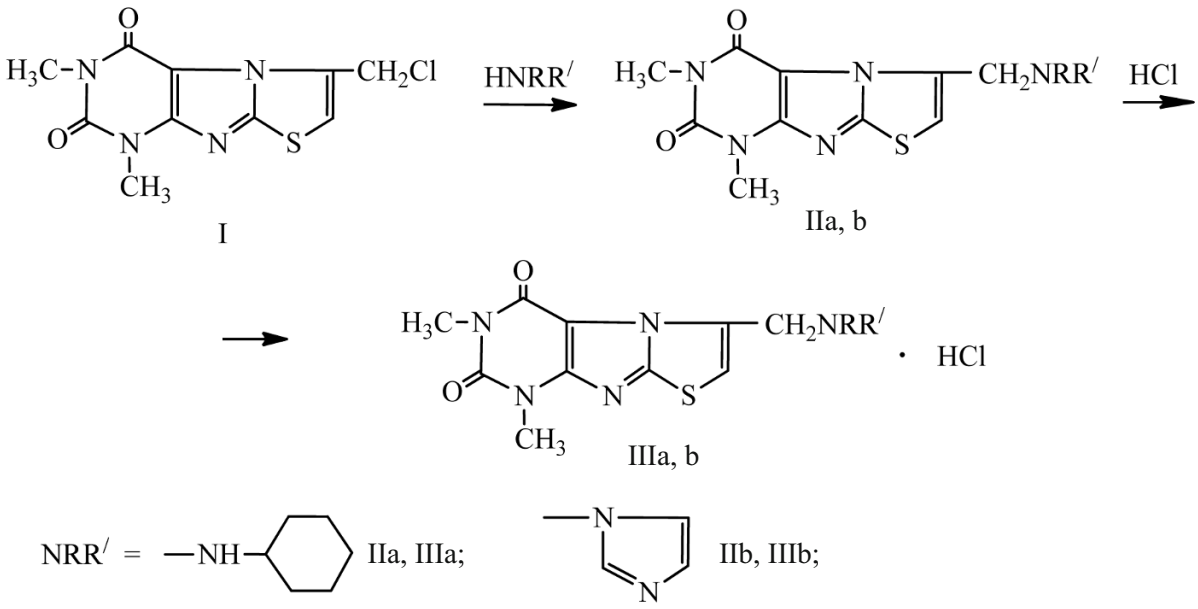
In our previous work [6] we demonstrated the hypoglycemic activity of dihydrothiazolo[2, 3-*f*]purine derivatives. The aims of the present work were to study the biological activity of thiazolo[2,3-*f*]purine derivatives and their structural analogs in relation to a series of antidiabetic targets - type 4 dipeptidylpeptidase, glycogen phosphorylase, and the formation of glycation end products - and to evaluate their effects on arterial blood pressure and the rheological properties of the blood.

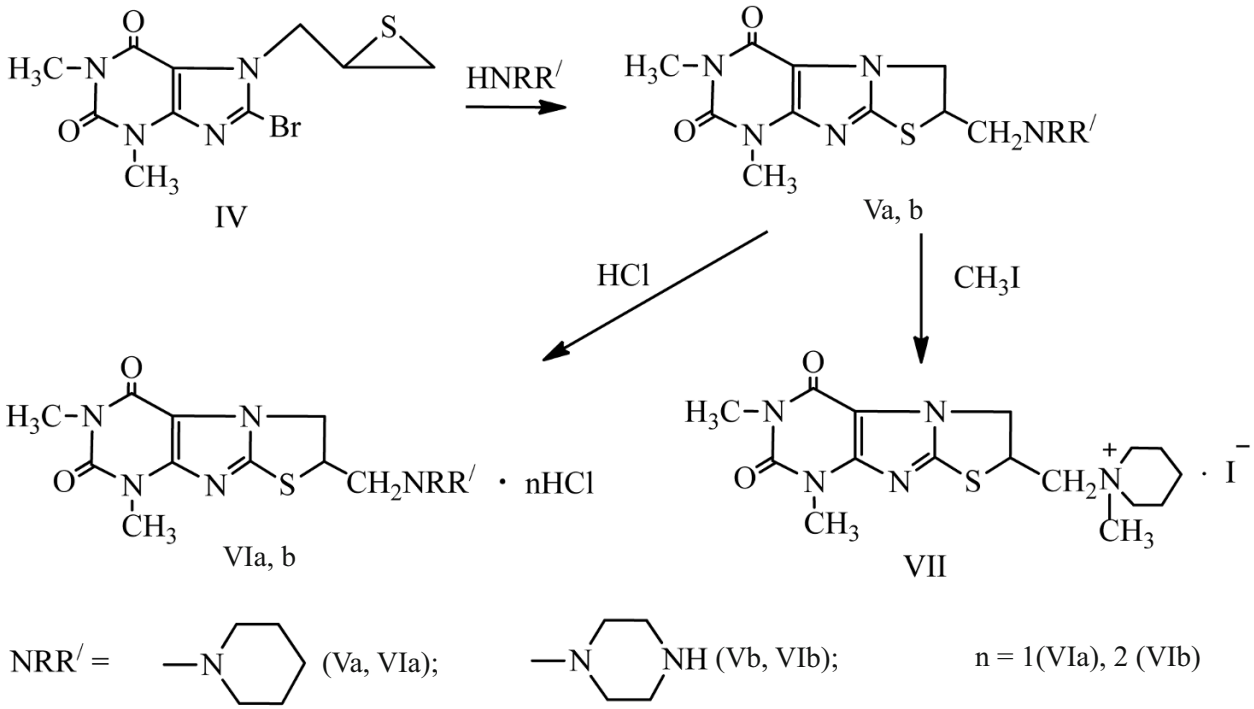
Reaction of 1,3-dimethyl-6-chloromethylthiazolo[2,3-*f*]-purin-2,4-(1*H*,3*H*)-dione (I) with cyclohexylamine or imidazole in ethanol was used to synthesize 6-substituted 1,3-dimethylthiazolo[2,3-*f*]purin-2,4-(1*H*,3*H*)-diones (IIa, b). Gaseous hydrogen chloride was passed through chloroform solutions of compounds IIa, b to obtain the hydrochlorides (IIIa, b) (scheme 1). The structure of compound IIb was confirmed by ^{1}H NMR spectroscopy, where signals from NCH_3, NCH_2, and SCH group protons was accompanied by singlets from protons in the imidazole ring at 7.3, 7.5, and 7.9 ppm.

Dihydrogenated thiazolopurine derivatives were synthesized from 8-bromo-1,3-dimethyl-7-(thiiran-2-ylmethyl)-1*H*-purin-2,6-(3*H*,7*H*)-dione (IV). Reaction of compound IV with piperidine or piperazine hexahydrate in ethanol yielded 7-substituted

Scheme 1

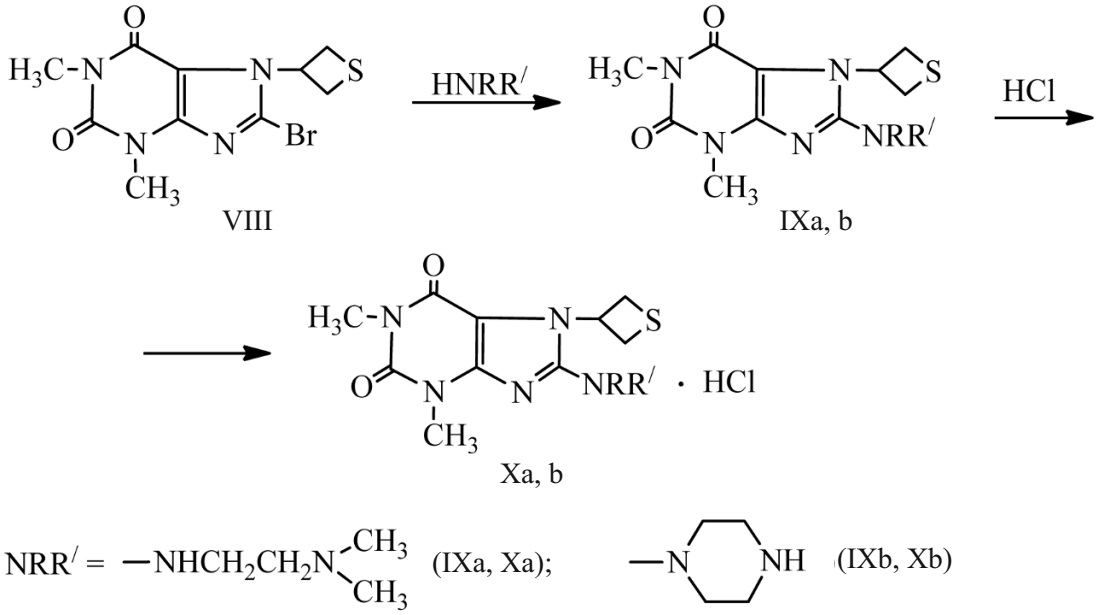


Scheme 2

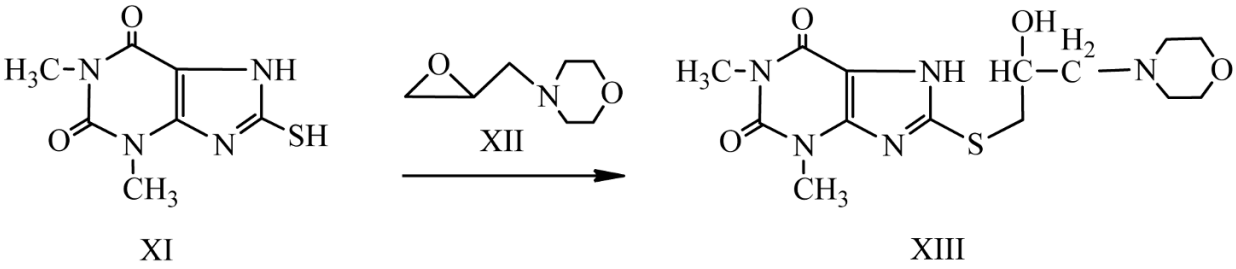


1,3-dimethyl-6,7-dihydrothiazolo[2,3-*f*]purin-2,4-(1*H*,3*H*)-diones (Va, b). Treatment of compounds Va, b with ethanolic hydrogen chloride in dioxane yielded the corresponding hydrochlorides (VIa, b). Reaction of compound Va with methyl iodide in dioxane yielded 1-[1,3-dimethyl-2,4-dioxo-1,2,3,4,6,7-hexahydrothiazolo[2,3-*f*]purin-7-yl)-methyl]methylpiperidin-1-ium iodide (VII) (scheme 2). The structure of compound Vb was confirmed by ^{1}H and ^{13}C NMR spectroscopy. Along with singlets from the two NCH_3 groups and multiplets from the piperazinomethyl residue, the ^{1}H NMR spectrum contained a multiplet from the dihydrothiazole ring at 4.17 – 4.77 ppm. Formation of the dihydrothiazole ring was also confirmed by carbon signals at 49.59 (C_3) and 51.54 (C_2) ppm in the ^{13}C NMR spectrum.

Scheme 3



Scheme 4



Thietane-containing analogs of dihydrothiazolopurines were synthesized from 8-bromo-1,3-dimethyl-7-(thietan-3-yl)-1*H*-purine-2,6-(3*H*,7*H*)-dione (VIII). Reaction of compound VIII with N,N-dimethylethylenediamine or piperazine in ethanol yielded 8-substituted 1,3-dimethyl-7-(thietan-3-yl)-purine-2,6-(3*H*,7*H*)-diones (IXa, b). Treatment of compounds IXa, b with ethanolic hydrochloride solution in dioxane was used to synthesize their hydrochlorides (Xa, b) (scheme 3). The ^{1}H NMR spectra of compounds IXa, b confirmed preservation of the thietane ring, for example the multiplet from the NCH group at 5.3 – 5.7 ppm. Spectra also contained signals from NCH_3 group protons and protons from the corresponding amine residues. The IR spectra of compound IXb contained an N-H bond stretch vibration absorption band at 3340 cm^{-1}.

Reaction of 8-mercapto-1,3-dimethyl-1*H*-purine-2,6-(3*H*,7*H*)-dione (XI) with 2-(morpholinomethyl)oxirane (XII) in *n*-propanol was used to synthesize the acyclic dihydrothiazolopurine analog 8-[2-hydroxy-3-morpholinopropyl)-thio]-1,3-dimethyl-1*H*-purine-2,6-(3*H*,7*H*)-dione (XIII) (scheme 4). The ^{1}H NMR spectrum of compound XIII confirmed the presence of a morpholine residue, for example the triplet from the $O(CH_2)_2$ group centered at 3.76 ppm. The spectrum also contained signals from the NCH_3 group and protons from the propyl residue as broad singlets at 4.16 and 7.86 ppm, from protons of the OH and NH groups respectively. The IR spectrum of compound XIII contained stretch vibration absorption bands from NH and OH bonds at 3090 – 3130 and 3415 cm^{-1} respectively.

EXPERIMENTAL CHEMICAL SECTION

^{1}H NMR spectra were recorded on a Tesla BS 567 instrument with a working frequency of 100 MHz in $CDCl_3$ (internal standard TMS, compounds Vb, IXb, and XIII) and trifluoroacetic acid (internal standard HMDS, compounds IIb, IXa. The ^{13}C NMR spectrum of compound Vb was recorded on a JEOL FX-90 Q instrument with a working fre-

quency of 22.5 MHz in $CDCl_3$ (internal standard TMS). IR spectra of compounds as suspensions in Vaseline grease were recorded on a UR-20 instrument. Melting temperatures were measured on an SMP 11 instrument. Elemental analysis results for C, H, and N were consistent with calculated values.

The yields and properties of the compounds synthesized here are presented in Table 1. Starting compounds were synthesized by known methods: compounds I [7], IV [8], VIII [9], XI [10], and XII [11]. We described the synthesis of compounds IIa and IIIa in [12] and that of compounds Va-c in [6].

6-[(1*H*-Imidazol-1-yl)methyl]-1,3-dimethylthiazolo[2,3-*f*]-purine-2,4-(1*H*,3*H*)-dione (IIb). Metallic sodium (0.28 g, 12 mmol) was carefully dissolved in 10 ml of absolute ethanol; when gas bubbles stopped forming, 0.82 g (12 mmol) of imidazole was added. The resulting solution was supplemented with 60 ml of dimethylformamide and ethanol was removed by evaporation using a water bath. Compounds I (2.85 g, 10 mmol) was added to the resulting solution and the mixture was boiled for 8 h. On cooling, the resulting precipitate was collected by filtration, washed with water, and dried. This yielded compound IIb. The ^{1}H NMR spectrum, δ, ppm, was: 3.1 (s, 3H, 3-CH_3); 3.3 (s, 3H, 1-CH_3); 4.3 (broad s, 2H, 6-CH_2); 7.1 (s, 1H, 7-H); 7.3 (broad s, 1H, 4'-H); 7.5 (broad s, 1H, 5'-H); 7.9 (s, 1H, 2'-H).

6-[(1*H*-Imidazol-1-yl)methyl]-1,3-dimethylthiazolo[2,3-*f*]-purine-2,4-(1*H*,3*H*)-dione hydrochloride (IIIb). Gaseous hydrochloride was passed through a solution of 1.58 g (5 mmol) of compound IIb in 20 ml of chloroform for 5 – 10 min to pH 2. The resulting precipitate was collected by filtration, washed with chloroform, and dried. This yielded compound IIIb.

1,3-Dimethyl-7-(piperazin-1-ylmethyl)-6,7-dihydrothiazolo[2,3-*f*]purine-2,4-(1*H*,3*H*)-dione (Vb). A mixture of 3.31 g (10 mmol) of compound IV and 9.70 g (50 mmol) of piperazine hexahydrate in 100 ml of ethanol was boiled for 5 h. The mixture was cooled and the resulting precipitate was collected by filtration, washed with water, and dried. This yielded compound Vb. The ^{1}H NMR spectrum, δ, ppm, was: 2.47 – 2.65 (m, 4H, $N(CH_2)_2$); 2.75 – 3.00 (m, 6H, $N(CH_2)_3$); 3.35 (s, 3H, 3-CH_3); 3.51 (s, 3H, 1-CH_3); 4.17 – 4.77 (m, 3H, SCH-NCH_2). The ^{13}C NMR spectrum, δ, ppm, was: 27.91 (3-CH_3); 29.91 (1-CH_3); 45.86 ($HN(CH_2)_2$); 49.59 (C_6); 51.54 (C_7); 54.48 ($N(CH_2)_2$); 61.90 (7-CH_2); 106.98; 151.27; 152.35; 153.57; 156.60 (purine carbons).

1,3-Dimethyl-7-(piperidin-1-ylmethyl)-6,7-dihydrothiazolo[2,3-*f*]purine-2,4-(1*H*,3*H*)-dione hydrochloride (VIa). Hydrogen chloride solution (5%) in ethanol was added dropwise with mixing to compound Va (1.78 g, 5 mmol) in 50 ml of dioxane to pH 2. The resulting precipitate was collected by filtration, washed with dioxane, and dried. This produced compound VIa.

1,3-Dimethyl-7-(piperazin-1-ylmethyl)-6,7-dihydrothiazolo[2,3-*f*]purine-2,4-(1*H*,3*H*)-dione dihydrochloride (VIb). This was prepared in the same way as compound VIa.

1-[((1,3-Dimethyl-2,4-dioxo-1,2,3,4,6,7-hexahydrothiazolo[2,3-*f*]purine)-7-yl)methyl]-1-methylpiperidin-1-iumiodide (VII). A solution of 3.56 g (10 mmol) of compound Va and 4.26 g (30 mmol) of methyl iodide in 100 ml of dioxane was boiled for 3 h. The reaction was cooled and the resulting precipitate was collected by filtration, washed with dioxane, and dried. This yielded compound VII.

1,3-Dimethyl-8-[(2-dimethylaminoethyl)amino]-7-(thietan-3-yl)-1*H*-purine-2,6-(3*H*,7*H*)dione (IXa). A mixture of 3.31 g (10 mmol) of compound VIII and 1.68 g (20 mmol) of *N*,*N*-dimethylethylenediamine in 50 ml of ethanol was boiled for 5 h. The reaction was cooled and the resulting precipitate was collected by filtration, washed with water, and dried. This yielded compound IXa. The ^{1}H NMR spectrum, δ, ppm, was: 2.65 (d, 6H, J 5 Hz, $N(CH_3)_2$); 2.88 – 3.26 (m, 10H, 1- and 3-CH_3, $S(CH)_2$, NCH_2); 3.50 – 3.84 (m, 4H, $S(CH)_2$, 8-NCH_2); 5.30 – 5.68 (m, 1H, NCH).

1,3-Dimethyl-8-(piperazin-1-yl)-7-(thietan-3-yl)-1*H*-purine-2,6-(3*H*,7*H*)-dione (IXb). A mixture of 3.31 g (10 mmol) of compound VIII and 9.70 g (50 mmol) of piperazine hexahydrate in 50 ml of ethanol was boiled for 3 h. The reaction was filtered hot. The filtrate was cooled and the resulting precipitate was collected by filtration, washed with water, and dried. This yielded compound IXb. The IR spectrum, ν_{max}, cm^{-1}, was: 1610, 1655, 1690 (C=O, C=N, C=C); 3340 (N-H). The ^{1}H NMR spectrum, δ, ppm, was: 2.92 – 3.32 (m, 10H, $S(CH)_2$, 2 $N(CH_2)_2$); 3.40 (s, 3H, 1-CH_3); 3.48 (s, 3H, 3-CH_3); 4.20 – 4.44 (m, 2H, $S(CH)_2$); 5.26 – 5.70 (m, 1H, NCH).

1,3-Dimethyl-8-[(2-dimethylaminoethyl)amino]-7-(thietan-3-yl)-1*H*-purin-2,6-(3*H*,7*H*)-dione hydrochloride (Xa). This was prepared in the same way as compound VIa.

1,3-Dimethyl-8-(piperazin-1-yl)-7-(thietan-3-yl)-1*H*-purin-2,6-(3*H*,7*H*)-dione hydrochloride (Xb). This was prepared in the same way as compound VIa.

8-[(2-Hydroxy-3-morpholinopropyl)thio]-1,3-dimethyl-1*H*-purin-2,6-(3*H*,7*H*)-dione (XIII). A mixture of 2.12 g (10 mmol) of compounds XI and 1.72 g (12 mmol) of compound XII in 50 ml of *n*-propanol was boiled for 3 h. The reaction was cooled, and 150 ml of diethyl ether was added; the resulting precipitate was decrease collected by filtration, washed with diethyl ether, and dried. This produced compound XIII. The IR spectrum, ν_{max}, cm^{-1}, was: 1120 (C=O); 1610, 1650, 1715 (C=O, C=N, C=C); 3090 – 3130(N-H); 3415 (O-H). The ^{1}H NMR spectrum, δ, ppm, was: 2.33 – 2.78 (m, 8N, SCH_2, $N(CH_2)_3$); 3.06 – 3.60 (m, 7H, 1- and 3- CH_3, CH); 3.76 (4H, t, J 5 Hz, $O(CH_2)_2$); 4.16 (broad s, 1H, OH); 7.86 (broad s, 1H, NH).

EXPERIMENTAL BIOLOGICAL SECTION

In vitro dipeptidylpeptidase-4 activity. The inhibitory activity of compounds against plasma dipeptidylpeptidase-4 was assessed by adding 40 μl of plasma from healthy volunteers to 50 μl of 0.1 M tris-HCl buffer pH 8.0. The mixture

was supplemented with 10 μl of test substance solution at the required concentration in tris buffer and preincubated at 37°C for 5 min. Dipeptidylpeptidase-4 substrate gly-pro-*p*-nitroanilide (Sigma, USA) (1 mM, 100 μl) was then added to the reaction mix. Reactions were incubated at 37°C for 15 min and the formation of *p*-nitroanilide was measured in terms of optical density at 405 nm [13] using an Infinite M200 PRO microplate reader (Tecan, Austria). Vildagliptin (Sigma, USA) was used as positive control [14].

***In vitro* glycogen phosphorylase activity.** The inhibitory activity of compounds against glycogen phosphorylase was assessed in reactions consisting of 100 μl of 50 mM HEPES buffer pH 7.2 containing 100 mM KCl, 2.5 mM $MgCl_2$, 0.5 mM glucose-1-phosphate (Sigma #G6875, USA), and 1 mg/ml glycogen; reactions were incubated with 0.2 U/ml rabbit muscle glycogen phosphorylase (Sigma #P1261, USA) and 5 μl of test substance solution at the required concentration at 30°C for 30 min. Reactions were then supplemented with 150 μl of a solution containing 1.05% $(NH_4)_2MoO_4$ and 0.034% malachite green. The quantity of phosphate anion released in 20 min at 30°C was assessed in terms of optical density at 620 nm [15] using an Infinite M200 PRO microplate reader (Tecan, Austria). Positive controls consisted of the experimental glycogen phosphorylase inhibitor CP-316819 (Sigma #PZ0189, USA) [16].

The protein glycation reaction with glucose was modeled in a reaction mix containing glucose (500 mM) and bovine serum albumin (BSA) (1 mg/ml) dissolved in phosphate buffer pH 7.4 and 0.02% sodium azide to prevent bacterial growth [17]. All substances were dissolved in DMSO. Experimental samples were supplemented with test substances at final concentrations of 10^{-3} and 10^{-4} M; control samples were supplemented with the same volume of solvent. All experimental samples were incubated for 24 h at 60°C. At the end of the incubation period, the specific fluorescence of glycated BSA was measured using an F-7000 spectrofluorimeter (Hitachi, Japan) at λ_{ex} = 370 nM and λ_{em} = 440 nm. Antiglycation activity was recorded as the ratio with fluorescence in control samples. The reference substance was the known inhibitor of the nonenzymatic glycosylation aminoguanidine [18].

Hemorheological activity was assessed in terms of changes in blood viscosity in rabbits in an in vitro model of altered blood rheological properties – blood was incubated at 42.5°C for 60 min. Blood samples were standardized to a hematocrit of 45 U. Test substances were added to blood samples to a final concentration of 10 μM. The reference agent was pentoxifylline (Aventis, Germany). Blood viscosity was measured on an AKR-2 viscometer (Russia). The effects of substances on measures of blood viscosity were evaluated in terms of changes in the index of erythrocyte aggregation, which was calculated as the ratio of blood viscosity at a shear rate of 3 sec^{-1} to blood viscosity at 100 sec^{-1}.

Hypoglycemic Activity was assessed by i.p. administration of test substances to adult male albino rats at a dose of 50 mg/kg. Samples of venous blood were collected from the tail vein and the glucose concentration was measured using a Biosen C Line analyzer (EKF Diagnostics, Germany) at 0.2 and 4 h. Reference agents were chlorpropamide and Adebit.

Hypotensive activity was studied in acute experiments in white rats anesthetized with ethaminal sodium (50 mg/kg, i.p.) with i.v. administration of test substances. Arterial blood pressure was measured in the carotid artery with a mercury manometer over 1 h. The measure of hypotensive activity was expressed as the ED_{20} – the dose of compound decreasing arterial blood pressure by 20% at 30 – 60 min. The reference agent was Dibazol.

TABLE 1. Yields and Properties of Compounds Synthesized Here

Compound	Yield, %	T_m, °C (solvent)	Atomic formula
IIb	33	237 – 239 (isopropanol)	$C_{13}H_{12}N_6O_2S$
IIIb	42	283 – 285 (ethanol)	$C_{13}H_{13}ClN_6O_2S$
Vb	79	218 – 220 (ethanol)	$C_{14}H_{20}N_6O_2S$
VIa	88	252 – 254 (ethanol)	$C_{15}H_{22}ClN_5O_2S$
VIb	98	246 – 248 (ethanol)	$C_{14}H_{22}Cl_2N_6O_2S$
VII	88	253 – 254 (ethanol)	$C_{16}H_{24}JN_5O_2S$
IXa	57	199 – 200 (ethanol)	$C_{14}H_{22}N_6O_2S$
IXb	70	223 – 224 (ethanol)	$C_{14}H_{20}N_6O_2S$
Xa	91	263 – 264 (ethanol)	$C_{14}H_{23}ClN_6O_2S$
Xb	91	239 – 241 (ethanol)	$C_{14}H_{21}ClN_6O_2S$
XIII	96	170 – 171*	$C_{14}H_{21}N_5O_4S$

* Ethanol/diethyl ether, ratio 1:3

RESULTS AND DISCUSSION

The thiazolo[2,3-*f*]purine derivatives and their structural analogs prepared here were tested for hypotensive, hemorheological, and antidiabetic activities. The results are presented in Table 2. In particular, studies of activity in whole animals showed that the substances of this series had marked hypotensive properties. Compounds VIa, Xa, Xb, and XIII had greater activity than Dibazol in terms of the ED_{20} value. Imidazole-substituted derivative IIIb and compound VII, containing a quaternary nitrogen atom in the side chain, had levels of activity which were 10 – 15 times lower than the most active compound of the series, VIa. This leads to the conclusion that the hypotensive activity is associated with the lipophilic radical in the side chain (the piperidine, piperazine, morpholine, or akylamine residues) and decreases in the presence of an aromatic substituent or quaternary nitrogen atom.

In terms of effects on erythrocyte aggregation, virtually all test purine derivatives were inactive and even had proaggregant properties, as in the case of imidazolylmethyl derivative IIIb. The exception was compound IIIa, characterized by having a cyclohexylaminomethyl radical, though this substance was also less active than pentoxifylline in terms of the absolute value of the erythrocyte aggregation index. Overall, the absence of any change in the erythrocyte aggregation index is evidence that compounds of this series had no effect on erythrocyte deformability or blood viscosity.

The antidiabetic properties of the thiazolo[2,3-*f*]purine derivatives and their structural analogs synthesized here were studied in vitro. Their influences on dipeptidylpeptidase type 4 (DPP4) and glycogen phosphorylase (GP) activities and on the formation of glycation end products were determined. Test compounds at concentrations of 0.1 – 1.0 mM had no statistically significant antiglycation activity. Weak glycogen phosphorylase-inhibiting properties were noted with compounds VIa and XIII, containing piperidine and morpholine radicals in the side chain respectively, though their activity levels were significantly lower than that of reference agent CP-316819. At the same time, two compounds (IIIa and VII, containing a cyclohexylamine and an *N*-methylpiperidine residue respectively) were dipeptidylpeptidase type 4 inhibitors, but were less active than reference agent vildagliptin at a concentration of 100 μM. The most active compound, IIIa, had an IC_{50} of 39.14 μM (the IC_{50} for vildagliptin was 0.034 μM in a parallel experiment). Among purine analogs, structurally similar nanomolar inhibitors of

TABLE 2. Biological Activities of Test Compounds

Compound	Hypotensive, ED_{20}, mg/kg	Change in erythrocyte aggregation index, Δ% ($m \pm SEM$)	Antiglycation activity, % ($m \pm SEM$)		DPP4-inhibiting activity (10^{-4} M), % ($m \pm SEM$)	GP inhibiting activity (10^{-4} M), % ($m \pm SEM$)	Hypoglycemic properties (50 mg/kg, i.p.), blood glucose compared with baseline, Δ% ($m \pm SEM$)	
			10^{-3} M	10^{-4} M			at 2 h	at 4 h
IIIa	– [1]	– 12.2 ± 0.9*	14.54 ± 9.19	– 12.43 ± 4.10	83.32 ± 1.93*	8.84 ± 10.88	– 38.76 ± 4.7*	– 32.40 ± 5.7*
IIIb	31.6	30.0 ± 6.3*	– 3.79 ± 3.72	– 0.18 ± 1.89	-5.78 ± 1.68	2.72 ± 3.24	– 9.98 ± 4.8	0 ± 5
VIa	3.1	4.19 ± 0.3*	15.59 ± 6.29	– 0.83 ± 7.16	4.36 ± 2.17	17.32 ± 2.65*	– 22.80 ± 3.36*	– 18.69 ± 5.30
VIb	– [2]	9.0 ± 1.2	11.80 ± 5.91	0.75 ± 6.70	7.95 ± 2.09	12.29 ± 10.52	– 34.79 ± 5.1*	– 22.30 ± 2.8*
VII	46.8	3.1 ± 0.2	– 0.50 ± 2.39	– 16.98 ± 1.60	67.11 ± 3.12*	12.92 ± 5.75	– 35.04 ± 16.2	– 33.7 ± 3.1*
Xa	3.5	– 0.7 ± 0.9	16.98 ± 4.41	5.07 ± 4.39	6.38 ± 0.98	7.91 ± 9.02	– 27.16 ± 7.6	– 22.98 ± 2.1*
Xb	7.1	5.69 ± 1.0	3.87 ± 3.79	– 3.30 ± 5.11	9.3 ± 0.84*	9.51 ± 6.85	– [3]	– [3]
XIII	7.1	5.8 ± 0.2	– 20.33 ± 11.72	– 0.72 ± 6.92	5.50 ± 0.36*	23.09 ± 1.71*	– 8.61 ± 1.09*	– 15.41 ± 9.31
Dibazol	22.1							
Pentoxifylline		– 18.6 ± 2.5*						
Aminoguanidine			57.83 ± 0.58*	6.01 ± 2.12				
Vildagliptin					99.65 ± 1.16*			
CP-316819						94.54 ± 1.52*		
Chlorpropamide							– 11.0 ± 0.01*	– 12.0 ± 0.015*
Adebit							– 24.0 ± 2.01*	– 23.0 ± 0.1*

* Data statistically significant compared with controls (Mann-Whitney U test, $p < 0.05$)
[1] Insoluble in water
[2] Dose of 5 mg – death.
[3] Not studied

DPP4 containing a 3-aminopiperidine fragment have been described [19]. This suggests that administration of an amino group at position 3 of the cyclohexylamine residue of compound IIIa increases its affinity for the active center of the enzyme and strengthens its inhibitory activity.

The hypoglycemic activity of the derivatives was then studied by single-dose administration to experimental animals. Compounds IIIa, VIb, and VII were found to be more active than reference agents chlorpropamide and Adebit, while compounds VIa and Xa had activity comparable with these agents. Thus, hypoglycemic activity was greater for derivatives containing an aminomethyl group in an aliphatic or alicyclic fragment in the side chain. While the likely target of the hypoglycemic action of compound IIIa is dipeptidylpeptidase type 4, identification of the mechanism of the hypoglycemic actions of the other compounds requires further study.

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