

Synthesis and brain antihypoxic activity of some aliphatic and arylaliphatic amides of caffeine-8-thioglycolic acid

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Accepted April 27, 2007

The synthesis of some aliphatic and arylaliphatic amides of caffeine-8-thioglycolic acid was studied. The structures of synthesized compounds were proved by microanalyses, IR- and ¹H NMR data. Values of acute *p.o.* and *i.p.* toxicity in mice show lower toxicity compared to caffeine. Declines in spontaneous locomotor activity support the idea of depressive CNS activity of the compounds. Two compounds exhibited brain antihypoxic activity (**5a** and **5b** against haemic and circulatory hypoxia, respectively).

Keywords: caffeine-8-thioglycolic acid, aliphatic and arylaliphatic amides, acute toxicity, brain antihypoxic activity

Xanthine derivatives possess different pharmacological activity. Some of the asymmetrically substituted xanthines are useful for treating CNS diseases such as Alzheimer's type dementia (1). For example, a new xanthine derivative, propentophylline, was recently introduced as a drug with neuroprotective properties for treatment of brain dementia (2), boosting the search for new xanthine derivatives with neuroprotective activity. Introduction of different substituents on the 8th position in caffeine structure is of great importance for extending the biological activity spectrum of its derivatives (3).

The synthesis of five new 1,3,7-trimethylxanthine derivatives is reported. Acute intraperitoneal and peroral toxicity, effect on the locomotor activity and brain asphyctic, haemic and circulatory antihypoxic activity of compounds are described.

EXPERIMENTAL

Analytical methods

Melting points were determined on an electrothermal apparatus (Büchi 535, Switzerland) in an open capillary tube and are uncorrected. The IR spectra were recorded on a Shimadzu FTIR 8101M spectrophotometer (Shimadzu, Japan) in nujol. The ¹H NMR

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spectra were measured on a Bruker 100 WP (100-MHz) spectrometer (Germany) using DMSO- d_6 as solvent and chemical shifts were expressed as δ values in ppm against TMS as an internal standard. TLC was performed on DC-Alufolien Kieselgel 60 F₂₅₄, 0.20 mm (Merck, Germany) sheets with the mobile phase: chloroform/acetone/ethanol (3:3:4, V/V). The spots were detected at UV 254 nm. All names were generated by using AutoNom 2000 Add-in for MDL ISIS/Draw (4).

Syntheses

Synthesis of 8-bromocaffeine **2** was performed from caffeine and hydrobromic acid in the presence of hydrogen peroxyde (5).

General method for preparation of (1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-ylsulfanyl)-acetamides (5a–e)

Method A. – (1,3,7-Trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-ylsulfanyl)-acetic acid methyl ester **4** (2.99 g, 0.01 mol) and a corresponding amine (0.02 mol) were mixed. The mixture was heated at 120 °C until **4** melted. Thereafter it was heated at the same temperature for 45–60 minutes. A minimal quantity of ethanol was added to the reaction mixture after cooling to room temperature. The product crystallized after cooling. The separated crystals were recrystallized from ethanol.

Method B. – Caffeine-8-thioglycolic acid **3** (3.13 g, 0.011 mol), the corresponding amine (0.01 mol) and 4-dimethylaminopyridine (DMAP, 0.3 g, 0.0025 mol) were dissolved in 100 mL of anhydrous dimethylformamide at 60 °C. After complete dissolution, dicyclohexylcarbodiimide (DCC, 2.7 g, 0.013 mol) dissolved in 15 mL of anhydrous dimethylformamide was added. The reaction mixture was stirred at room temperature for 24 h and the white precipitate of *N,N*-dicyclohexylurea (DCU) was filtered off. After concentrating to 1/3 volume of the filtrate on the rotary evaporator, cooled anhydrous ethanol was added and the solution was kept for about 24 h at –5 °C. The crystals of DCU were filtered off and the filtrate was evaporated. The residue was crystallized from ethanol. The separated crystals were washed with petroleum ether and recrystallized from ethanol.

N-[2-(3,4-dimethoxyphenyl)-ethyl]-2-(1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-ylsulfanyl)-acetamide (**5a**). – *Method A*: from **4** and 0.02 mol 2-(3,4-dimethoxyphenyl)-ethylamine (3.62 g, 3.30 mL); reaction time 1 h. *Method B*: from **3** and 0.01 mol 2-(3,4-dimethoxyphenyl)-ethylamine (1.81 g, 1.70 mL); reaction time 20 h.

N-phenethyl-2-(1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-ylsulfanyl)-acetamide (**5b**). – *Method A*: from **4** and 0.02 mol phenylethylamine (1.21 g, 2.60 mL); reaction time 1 h. *Method B*: from **3** and 0.01 mol phenylethylamine (0.61 g, 1.30 mL); reaction time 24 h.

N-(1-methyl-2-phenylethyl)-2-(1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-ylsulfanyl)-acetamide (**5c**). – *Method A*: from **4** and 0.02 mol 1-methyl-2-phenylethylamine (1.35 g, 2.50 mL); reaction time 1 h. A minimal quantity of ether was added to the reaction mixture after cooling to room temperature. The separated crystals were recrystallized from ethanol. *Method B*: from **3** and 0.01 mol 1-methyl-2-phenylethylamine (0.68 g, 1.20 mL); reaction time 24 h.

N-[2-(4-hydroxyphenyl)-ethyl]-2-(1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl-sulfanyl)-acetamide (5d). – *Method A*: from 4 and 0.02 mol 4-(2-aminoethyl)-phenol (1.37 g, 2.74 mL); reaction time 45 min. The separated crystals were recrystallized from ethanol/water 1:1. The free base of 4-(2-aminoethyl)-phenol was obtained as follows: 4-(2-aminoethyl)-phenol hydrochloride (0.029 mol, 5.04 g) was dissolved in 10 mL of water under heating and stirring. Sodium carbonate (1.54 g, 0.0145 mol) in 5 mL of water was added to the hot solution and 4-(2-aminoethyl)-phenol base crystallized after cooling. *Method B*: from 3 and 0.01 mol 4-(2-aminoethyl)-phenol (0.70 g, 1.4 mL); reaction time 24 min.

N-(tetrahydrofuran-2-ylmethyl)-2-(1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-ylsulfanyl)-acetamide (5e). – *Method A*: from 4 and 0.02 mol 1-(tetrahydrofuran-2-yl)-methylamine (2.02 g, 2.1 mL); reaction time 1 h. *Method B*: from 3 and 0.01 mol 1-(tetrahydrofuran-2-yl)-methylamine (1.01 g, 1.0 mL); reaction time 22 h.

Table I. Physico-chemical data for the synthesized compounds

| Compd. No. | Yield (%) | Method | M.p. (C) | Mol. formula (M_r) | Found/calcd. (%) | | | |
|------------|-----------|--------|----------|-----------------------------------|------------------|------|-------|------|
| | | | | | C | H | N | S |
| 5a | 72 | A | 180–182 | $C_{20}H_{25}N_5O_2S$ (447.51) | 53.55 | 5.59 | 15.62 | 7.06 |
| | 52 | B | | | 53.68 | 5.63 | 15.65 | 7.16 |
| 5b | 78 | A | 182–184 | $C_{18}H_{21}N_5O_3S$ (387.46) | 55.31 | 5.25 | 17.94 | 8.07 |
| | 67 | B | | | 55.80 | 5.46 | 18.08 | 8.27 |
| 5c | 75 | A | 164–165 | $C_{19}H_{23}N_5O_3S$ (401.48) | 56.31 | 5.15 | 17.34 | 7.87 |
| | 55 | B | | | 56.84 | 5.77 | 17.44 | 7.99 |
| 5d | 84 | A | 211–213 | $C_{18}H_{21}N_5O_4S$ (403.46) | 53.35 | 5.10 | 17.22 | 7.75 |
| | 64 | B | | | 53.59 | 5.25 | 17.36 | 7.95 |
| 5e | 69 | A | 172–183 | $C_{15}H_{21}N_5O_4S$ (367.42) | 48.75 | 5.45 | 18.98 | 8.57 |
| | 48 | B | | | 49.03 | 5.76 | 19.06 | 8.73 |

Structures 5a–e were established by elemental analysis, FTIR and 1H NMR spectral data (Tables I and II). The results were consistent with the assigned structures.

Pharmacology

Animals. – Male mice, strain H, mass 22–25 g, kept under standard conditions in animal house (water and food *ad libitum*, 12 h dark and light cycle) were used throughout the experiment. Controls were treated with the vehicle only (0.2% Tween 80 in saline), in the same volume as treated animals (0.1 mL per 10 g b.m.). No effects were observed in separate experiments to rule out the *per se* effect of the vehicle.

All experimental procedures described herein were in accordance with the NIH guidelines of the Care and Use of Laboratory animals.

Acute toxicity. – LD_{50} of the studied compounds was assessed by per oral and intraperitoneal route of administration. The tests were conducted according to the OECD TG 425 Up-And-Down Procedure (6).

Table II. Spectral data of the synthesized compounds

| Compd. No. | IR (cm ⁻¹) (Nujol) | ¹ H NMR (δ, ppm) (DMSO-d ₆) |
|------------|---|--|
| 5a | 3226 (NH), 3070 (CH – aromatic), 1704 (CO – xanthine), 1664 (CO – xanthine), 1645 with shoulders at 1608 and 1637 (CO – amide I, C=N, C=C – aromatic), 1558 and 1539 (C=C – xanthine, C=C – aromatic), 755 and 746 (δCH – aromatic) | 9.40 (s, 1H, NH), 7.18–6.98 (m, 3H, aromatic ring), 3.78 (s, 6H, 2xOCH ₃), 3.60 (s, 2H, CH ₂), 3.55–3.50 (m, 2H, CH ₂), 3.81, 3.61 and 3.31 (s, 3H, CH ₃), 2.80–2.76 (m, 2H, CH ₂) |
| 5b | 3274 (NH), 3100 (CH – aromatic), 1699 (CO – xanthine), 1661 with shoulders at 1605 and 1647 (CO – amide I, C=N, C=C – aromatic), 1558 and 1539 (C=C – xanthine, C=C – aromatic, δNH – amide II), 754 and 746 (δCH – aromatic) | 9.40 (s, 1H, NH), 7.08–6.95 (m, 5H, aromatic ring), 3.65 (s, 2H, CH ₂), 3.55–3.50 (m, 2H, CH ₂), 3.78, 3.59 and 3.29 (s, 3H, CH ₃), 2.79–2.69 (m, 2H, CH ₂) |
| 5c | 3271 (NH), 3063 (CH – aromatic), 1703 (CO – xanthine), 1699 (CO – xanthine), 1668 with shoulders at 1605 and 1634 (CO – amide I, C=C – aromatic), 1584 with shoulders at 1557 and 1538 (C=C – aromatic, C=C – xanthine, δNH – amide II), 755 and 744 (δCH – aromatic) | 9.40 (s, 1H, NH), 7.05–7.01 (m, 5H, aromatic ring), 4.05–4.07 (m, 1H, CH), 3.90 (s, 2H, CH ₂), 3.79, 3.59 and 3.33 (s, 3H, CH ₃), 2.82–2.65 (m, 2H, CH ₂ Ph), 1.30–1.20 (d, 3H, CH ₃) |
| 5d | 3348 (OH), 3279 (NH), 3086 (CH – aromatic), 1699 with shoulder at 1703 (CO – xanthine), 1653, 1626 with shoulder at 1605 (CO – amide I, C=C – aromatic), 1562, 1537 and 1514 (C=C – aromatic, C=C – xanthine, δNH – amide II), 748 (δCH – aromatic) | 9.40 (s, 1H, NH), 7.11–6.95 (m, 4H, aromatic ring), 3.77 (s, 2H, CH ₂), 3.66–3.46 (m, 2H, CH ₂), 3.65, 3.55 and 3.31 (s, 3H, CH ₃), 2.85–2.69 (m, 2H, CH ₂) |
| 5e | 3262 (NH), 1701 (CO – xanthine), 1689 (CO – xanthine), 1665 with shoulders at 1605 and 1635 (CO – amide I, C=C – aromatic), 1590 with shoulders at 1560 and 1542 (C=C – aromatic, C=C – xanthine, δNH – amide II), 762 and 748 (skeletal vibrations) | 9.40 (s, 1H, NH), 3.75 (s, 2H, CH ₂), 3.73–3.40 (m, 5H, 2xCH ₂ , CH), 3.73, 3.52 and 3.29 (s, 3H, CH ₃), 1.95–1.20 (m, 6H, 3xCH ₂) |

Spontaneous locomotor activity. – Spontaneous locomotor activity was measured in an actometer (Activity Cage Ugo Basile, Italy). The animals ($n = 6$ per group) were introduced into a chamber and their movements were quantified for 120 min at intervals of 20 min. The tested compounds were administered at a dose of $1/20$ part of LD_{50} , *i.p.*, 30 min prior to the experiment. The results were compared to vehicle-treated animals.

Antihypoxic activity. – The tested compounds were administered at a dose of $1/20$ part of LD_{50} , *i.p.*, 30 min prior to the experiment. Three models of provoked brain hypoxia were used. For asphyctic hypoxia 30 minutes after intraperitoneal administration, mice ($n = 8$ per group) were placed into hermetic bottles of 200 cm³. Latency of hypoxic

time (in min) was determined and compared with the control, vehicle-treated group (7). For haemic hypoxia, 30 minutes after intraperitoneal administration of a compound, mice ($n = 8$ per group) were intraperitoneally treated with NaNO_2 (360 mg per kg^{-1} b.m.) and antihypoxic activity was estimated in minutes as latent time evidencing hypoxia according to the method of Roshtina and Ostrovskaya (8). For circulatory hypoxia, 30 minutes after intraperitoneal administration of compounds, mice ($n = 8$ per group) were intraperitoneally treated with NaF (150 mg per kg^{-1} b.m.) and antihypoxic activity was estimated in minutes as latent time of evidencing hypoxia (9).

Data analysis

The LD_{50} data were assessed by the AOT 425 statistical program (6). Locomotor activity and antihypoxic activity were expressed as % of the control (vehicle treated) and were compared by Student's *t*-test.

RESULTS AND DISCUSSION

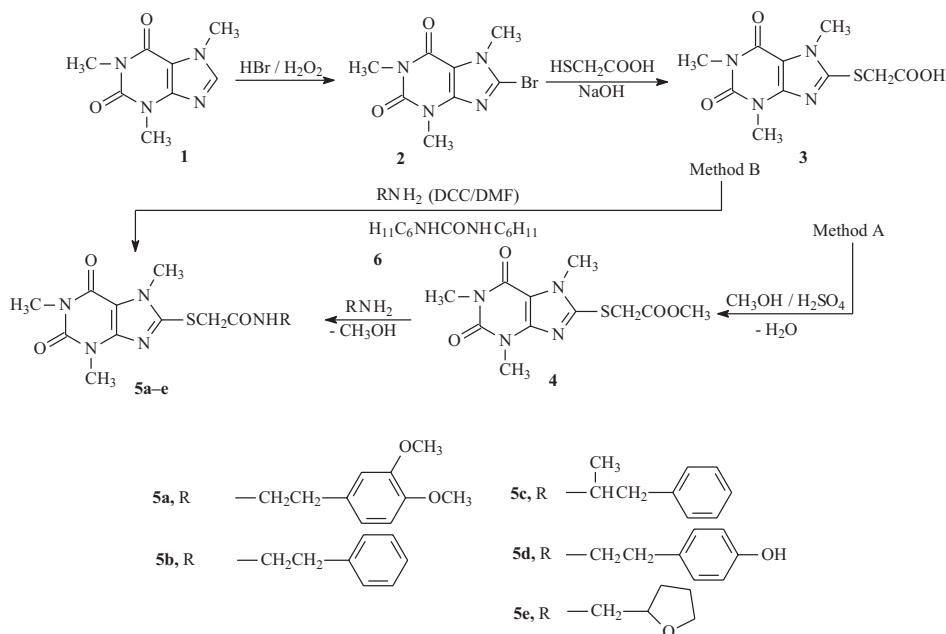
Chemistry

Caffeine-8-thioglycolamides were obtained from the corresponding amines by using two synthetic approaches: aminolysis of methyl caffeine-8-thioglycolate (4) with amines (Method A) and reaction with caffeine-8-thioglycolic acid (3) in the presence of carbodiimides (Method B).

The 8-substituted caffeine derivatives, described in this article, were synthesized as outlined in Scheme 1.

A modified method of Persch and Beyerle (10) was used to synthesize caffeine-8-thioglycolic acid (3). The reaction was carried out in 60% ethanol and the yield was 92%. Methyl caffeine-8-thioglycolate (4) was prepared by the method used for synthesizing ethyl esters of 7-alkylxanthinyl-8-thioglycolic acids (11). The reaction was carried out in anhydrous methanol in the presence of a catalytic amount of sulfuric or phosphoric acid and the yield was 95%. After aminolysis of methyl caffeine-8-thioglycolate (4), compounds 5a–e were obtained.

The second approach to obtaining the title compounds is also outlined in Scheme 1. The process was carried out at the molar ratio of reactants 1:1:1 (acid/DCC/amine) at room temperature in DMF. The reaction time varied between 20 and 24 h in dependence on arylaliphatic amine used as the starting compound. The yields were about 10–20%. The yields of 5a–e obtained by the carbodiimide method were lower than those obtained by aminolysis of methyl caffeine-8-thioglycolate (4). These results can be explained by the effects of the solvent on the reactivity of 3. It is known that in the carbodiimide method the increase in acid strength results in increased ester yield and shortening of the reaction time (12). Since acetic acid exists predominantly in the monomeric form in polar amphiprotic solvents (13, 14) it is assumed that in our case 3 in DMF manifests the same tendency. Thus, De Tar and Silverstein (13, 14) claim that the presence of acid monomer is responsible for the lower reactivity. On the other hand, DMF is a solvent with great solvation properties and the existing acid monomer will be more solvated. In this case, energy losses connected with acid desolvation must be of great importance.



The IR spectra of the synthesised caffeine-8-thioglycolamides in the region 4000 to 400 cm^{-1} exhibit several characteristic bands. Thus, the three strong bands at 1660–1703 cm^{-1} are ascribable to stretching vibrations of two carbonyl groups in the xanthine ring and to stretching vibration of the amide carbonyl group (amide I band) in the side chain. The band of bending vibration of the NH-group (amide II band) is in the 1590–1514 cm^{-1} region where stretching vibrations of $\text{C}^4=\text{C}^5$ and $\text{C}^8=\text{N}^9$ bands of the xanthine ring appear, but it is more intensive. The intensive absorption band at 3279–3262 cm^{-1} corresponds to stretching vibrations of the NH-group in the side chain. In the spectrum of **5d**, a strong absorption band at 3348 cm^{-1} is ascribable to stretching vibrations of the OH-group in the tyramine residue. Absorption bands at about 3100–3000 cm^{-1} are ascribable to stretching vibrations of C–H bonds in the aromatic ring, placed in the side chain as phenethyl group.

The strong singlets at about 3.30, 3.60 and 3.80 ppm in the spectra (Table II) correspond to *N*-methyl protons at positions 1, 3 and 7. The signal of the *N*-methylene group from caffeine-8-thioglycolic acid at position 8 appears at 3.50–3.90 ppm as a broad singlet. The signals of the other methylene protons and aromatic protons were observed clearly in the spectra of **5a–d**. The signals of methylene protons from the side chain of **5a–d** form complicated multiplets at 1.20–2.85 and 3.40–3.73 ppm. The signals of methylene protons from the side chain of **5c** and **5e** and the side chain methyl protons of **5c** fall in this region, which made a precise interpretation of the spectra difficult. However, the integral curves correspond to the exact number of protons.

Compounds **5a–e** are white crystals, insoluble in water and sparingly soluble in alcohols, but soluble in organic solvents such as chloroform, benzene, dimethylformamide and dimethylsulfoxide.

Pharmacology

Tested compounds showed significantly ($p < 0.05$) lower toxicity than 1,3,7-trimethylxanthine (caffeine) (Table III). All compounds except **5c** have acute toxicity of 5 g kg⁻¹ b.m. or more. The toxicity of compound **5d** (> 5 g kg⁻¹ b.m.) could be due to tyramine substituent at position 8 in the side chain while the most toxic compound **5c** (LD_{50} 0.5–1 g kg⁻¹ b.m.) has an amphetamine residue.

Table III. Intraperitoneal and peroral acute toxicity data of compounds **5a–e** in mice

| Compd. No. | LD_{50} (i.p.) (mg kg ⁻¹ b.m.) | LD_{50} (p.o.) (mg kg ⁻¹ b.m.) | IA |
|------------|---|---|-------|
| 5a | 2750 ^a | > 5000 ^a | < 0.6 |
| 5b | 3000 ^a | > 5000 ^a | < 0.6 |
| 5c | 500 ^a | 1000 ^a | 0.5 |
| 5d | > 5000 ^a | > 5000 ^a | 1 |
| 5e | 1400 ^a | 4600 ^a | 0.3 |
| Caffeine | 369 | 527 | 0.7 |

^a Statistically significant difference in comparison with caffeine ($p = 0.05$).
IA (Index of Absorption) = LD_{50} (i.p.)/ LD_{50} (p.o.).

Compounds **5a,b,d,e** were found to significantly suppress spontaneous locomotor activity, while **5c** significantly increased locomotion (Table IV).

Statistically significant antihypoxic activity of compound **5a** was established in the experimental model of haemic hypoxia while for compound **5b** in the model of circulatory hypoxia (Table IV).

There are literature data that administration of sodium fluoride increases the blood histamine content and decreases the oxygen carrying capacity (15). As known, hypoxia causes significant changes in the activity of numerous intracellular enzymatic proteins. Under the conditions of haemic hypoxia, a functional deficiency of the antioxidant system and a high level of lipid peroxidation are observed, which contribute to maintaining a labile state of the lysosomal membranes and activation of hydrolytic enzymes (16). In our experiment, expressed antihypoxic activity of compound **5a** in the haemic hypoxia model could be partly explained by possible antioxidant properties of that compound. This hypothesis remains to be elucidated in future experiments.

Caffeine is the most commonly ingested alkylxanthine and is a recognized psychostimulant. This compound improves some aspects of cognitive performance, but reduces cerebral blood flow both in animals and humans. The decrease in cerebral blood flow is produced at doses that increase cerebral glucose consumption. This is unlikely to be a

Table IV. Locomotor activity and brain antihypoxic activity of compounds 5a–e in mice

| Compd. No. | Dose (mg kg ⁻¹ b.m.) | Locomotor activity (%) | | Antihypoxic activity | | | | | | | | | |
|------------|---------------------------------|------------------------|----------------|----------------------|-----|------------------|------|--------------------|------------------|------------------|------------------|---------------------|--|
| | | | | Asphyctic hypoxia | | | | Haemic hypoxia | | | | Circulatory hypoxia | |
| | | | | (min) ^b | | (%) ^a | | (min) ^b | | (%) ^a | | (min) ^b | |
| Control | | 100 | 8 | 17.8 | 2.0 | 100 | 12.6 | 1.2 | 100 | 9.9 | 1.4 | 100 | |
| 5a | 137 | 33 | 7 ^c | 19.5 | 4.1 | 110 | 15.4 | 1.5 ^c | 123 ^c | 11.6 | 2.9 | 118 | |
| 5b | 150 | 14 | 2 ^c | 17.4 | 2.1 | 98 | 14.0 | 1.8 | 112 | 12.2 | 1.5 ^c | 124 ^c | |
| 5c | 25 | 117 | 7 ^c | 16.7 | 1.6 | 94 | 14.5 | 2.2 | 116 | 10.5 | 1.4 | 106 | |
| 5d | 250 | 39 | 4 ^c | 17.2 | 3.1 | 97 | 13.0 | 1.5 | 104 | 10.5 | 2.7 | 106 | |
| 5e | 70 | 47 | 5 ^c | 15.2 | 2.6 | 85 | 14.6 | 1.4 | 116 | 9.7 | 1.6 | 98 | |
| Caffeine | 18 | 128 | 6 ^c | 17.7 | 4.2 | 99 | 13.2 | 1.4 | 95 | 9.1 | 1.4 | 94 | |

^a In comparison with control (vehicle only).

^b Mean ± SD, *n* = 8.

^c Statistically significant difference in comparison with control (*p* < 0.05).

beneficial profile of a drug to be used for the treatment of dementia of either neurodegenerative or vascular origin (16). In the model of circulatory hypoxia in our experiments, caffeine expresses a slightly pro-hypoxia properties.

The study of Eun *et al.* (17) showed that preliminary acute treatment of mice with the xanthine derivative pentoxifylline increased cerebral blood flow and attenuated hypoxic-ischemic brain injury in immature rats. The mechanism of this action is probably due to the relaxation of brain blood vessels *via* the Ca²⁺ channel blocking activity and some rheological properties.

Compounds 5a–d used in the study contain phenylethylamine residues. The presence of substituents in the carbohydrate side chain in compound 5c increases acute toxicity without alteration in antihypoxic activity. Antihypoxic activity is expressed in compounds 5a (unsubstituted phenylethylamine fragment) and 5b (with two methoxy groups in benzene ring). It seems that methoxy groups in the benzene ring do not influence acute toxicity. Compound 5d is devoid of antihypoxic activity and is practically nontoxic. Structurally, it contains phenolic group in the benzene ring. More compounds with different substituents on position 8 should be synthesized to determine the structure/activity relationship; as evident from our experiments, only compound 5b exhibits a pronounced circulatory antihypoxic activity.

CONCLUSIONS

The most promising compounds are 5a (*N*-[2-(3,4-dimethoxyphenyl)-ethyl]-2-(1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-ylsulfanyl)-acetamide) and 5b (*N*-phenethyl-2-(1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-ylsulfanyl)-acetamide). They are practically non-toxic, impaired spontaneous locomotor activity and exhibited a

brain antihypoxic activity in models of haemic hypoxia (compound **5a**) and circulatory hypoxia (compound **5b**). Further experiments will be done to assess the exact antihypoxic mechanism of action of compounds **5a** and **5b**.

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S A Ž E T A K

Sinteza i antihipoksično djelovanje alifatskih i arilalifatskih amida kofein-8-tioglikolne kiseline

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U radu je opisana sinteza alifatskih i arilalifatskih amida kofein-8-tioglikolne kiseline i njihova karakterizacija elementarnom analizom, IR- i ^1H NMR spektroskopijom. Testiranja na miševima pokazuju da su sintetizirani spojevi primijenjeni *p.o.* i *i.p.* manje toksični od kofeina. Smanjenje lokomotoričke aktivnosti podupire ideju o njihovom depresivnom djelovanju na SŽS. Spojevi **5a** i **5b** djeluju antihipoksički u uvjetima krvne i cirkulacijske hipoksije u mozgu.

Ključne riječi: kofein-8-tioglikolna kiselina, alifatski i arilalifatski amidi, antihipoksično djelovanje u mozgu, akutna toksičnost

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