SYNTHESIS AND DRUGLIKENESS ESTIMATION OF AMIDE DERIVATIVES OF 1-BENZYLTHEOBROMINE-8-THIOGLYCOLIC ACID

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ABSTRACT

Five-stage synthetic scheme for obtaining of N-substituted 1-benzyltheobromine-8-thioglicolacetamides was described. The intermediate compound 1-benzyl-8-bromotheobromine was synthesized using aliquat 336 as phase transfer catalyst in very good yield. Five amide derivatives of 1-benzyltheobromine-8-thioglycolic acid were obtained in yields of 61 to 81%. The structures of the studied compounds were established by FTIR, ¹H NMR spectral data. In order to estimate the drug-likeness of compounds 7a-e, a theoretical calculation of some molecular descriptors was made using two approaches: the Lipinski's Rule of Five limitations and the OSIRIS Property Explorer evaluation score. The comparison of the calculated results indicate that only one compound violates the Lipinski's Rule of Five parameters – 7c, which makes it unsuitable for further structural optimizations. On the other hand compound 7e shows the highest drug like properties with Fragment Based Druglikeness score of 2.58 and total Drug score of 0.43 which are better than the same scores of parent compound theobromine.

Keywords: 1-benzyltheobromine-8-thioglycolic acid, 1-benzyltheobromine-8-thioglicolacetamides, drug-likeness, Lipinski's Rule of Five

INTRODUCTION

Theobromine, formerly known as a bitter alkaloid of the cacao plant (3,29), is a caffeine derivative and metabolite found primarily in chocolate. It may occur in the body as it is a product of the human metabolism of caffeine, which is metabolised in the liver into 10% theobromine, 4% theophylline, and 80% paraxanthine (27). In the liver, theobromine is metabolized into xanthine and subsequently into meth-

yluric acid (10). Theobromine is highly fat soluble with peaking in the plasma 1–2 h after ingestion (21).

Like other methylated xanthine derivatives, theobromine is both a competitive nonselective phosphodiesterase inhibitor (13), which raises intracellular cAMP, activates PKA, inhibits TNF- α (11,19) and leukotriene synthesis (22), and reduces inflammation and innate immunity (22) and nonselective adenosine receptor antagonist (12). As a phosphodiesterase inhibitor, theobromine helps prevent the phosphodiesterase enzymes from converting the active cAMP to an inactive form (24).

As an adenosine receptor antagonist, theobromine appears to have equal affinity for A₁ compared to A_{2A} receptors, while caffeine shows a slightly lower affinity for A₁ receptors (25). Theobromine has one fifth the stimulant effect of caffeine, but with a longer half-life in the body (21).

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As a phosphodiesterase inhibitor, theobromine inhibits phosphodiesterase (PDE) non-selectively and also shows adverse effects on the cardiovascular and central nervous systems (1,5,8,15). It is of interest to investigate the structure–activity relationships of alkylxanthines. During this investigation has been found that the alkyl substitution at N1 leads to increased selectivity to PDE4 inhibition. In addition, introduction of a benzyl group at the N1 position results in a potent and selective PDE4 inhibitor, with the most potent PDE4 inhibitory activity among xanthine derivatives known to be PDE4 inhibitors (26).

These results determined the purpose of our work to obtain amide derivatives of 1-benzyltheobromine-8-thioglycolic acid and to determine their drug-like properties as preliminary information for their further application as potential PDE inhibitors.

MATERIAL AND METHODS

Apparatuses and devices

The used chromatographic system for TLC control and purity elucidation is based on an aluminium sheets Silica gel F254 (Merck, Darmstadt, Germany), using the following mobile phases: *Phase 1*: 25% NH_4OH /Acetone/ CHCl_3 / $\text{CH}_3\text{CH}_2\text{OH}$ (1/3/3/4) and *Phase 2*: H_2O /n-butanol/ CH_3COOH (5/4/1), with detection at UV 254 nm. Yields were calculated for purified products. The IR spectra $400 - 4000\text{cm}^{-1}$ were recorded on a Shimadzu FT-IR Spectrometer in KBr pellets. The ^1H -NMR spectra were registered at 100 MHz on spectrometer Bruker 100 (Faenlanden, Switzerland) as δ (ppm) relative to TMS as internal standard and the coupling constants (J) are expressed in Hertz (Hz). All NH protons were D_2O exchangeable. All names were generated by using ACD/Name Version 2.51 (9).

The starting materials were of commercially available research – grade chemicals. (Merck, Darmstadt, Germany). Commercial aliquat 336 was used as catalysts.

Synthesis of 8-bromotheobromine (2)

The bromination of theobromine was carried out in a four-neck round bottom flask (total volume 1000 ml) placed in a heating mantle with a mechanical stirrer and temperature controller. The centre neck was fitted with mechanical stirrer whose speed

was maintained at 700 rpm. A thermometer for temperature control and a Liebig condenser for reflux were inserted into two of the side necks. The other side neck allowed sampling of the reaction mixture. A 0.1 mol of theobromine were dissolved in 200 ml acetic acid. 29 ml of 62% HBr were added to the solution. The temperature was raised up to $80^\circ - 85^\circ\text{C}$. After complete homogenization of the reaction mixture 25 ml 30% hydrogen peroxide were added dropwise. The reaction mixture was left under the same conditions for 4 hours, then cooled to room temperature and decolourized with sodium sulphite. The colorless solution was poured into 400 ml ice water and kept for 12 hours at 4°C . The separated precipitate of 8-bromotheobromine was filtered under reduced pressure and recrystallised from ethanol. Yield – 23.2g (85%), m.p. – above 300°C . The structure of the compound was confirmed by IR spectral analysis.

Synthesis of 1-benzyl-8-bromotheobromine (3)

In a round bottom flask 0.04 mol of 8-bromotheobromine and 0.06 mol of finely powdered KOH were suspended in 50 ml benzyl chloride. A half milliliter of the catalyst aliquot 336 was added and the temperature was raised under a glycerin bath up to 150°C for one hour. The reaction was controlled by TLC and stopped after exhaustion of the starting compounds. After cooling a volumetric precipitate of 1-benzyl-8-bromotheobromine was formed. The obtained crystals were filtered and washed with petroleum ether. After drying out the crystals were processed with 50 ml of water and filtered again. The filtrate was evaporated and the benzyl chloride residue was regenerated. The yield after purification was 98%, m.p. – $185 - 187^\circ\text{C}$. The structure of the compound was confirmed by IR spectral analysis.

Synthesis of 1-benzyltheobromine-8-thioglycolic acid (4)

The reaction was carried out in reactor of 500 ml capacity which was equipped with mechanical stirrer (speed was maintained at 700 rpm) and a reflux condenser was placed on top of the reactor in order to prevent the escape of volatile compounds. The reaction mixture is water: ethanol = 40:60. 0.06 mol sodium hydroxide was preliminary solved in the water phase. Afterwards 0.03 mol of thioglycolic acid were added. The ethanol and the 0.029 mol of 1-benzyl-8-bromotheobromine were added and the re-

action mixture was heated under reflux for 1 and a half hour. The reaction mixture is filtered when hot and acidified with previously prepared solution of 1 part acetic acid and 4 parts water, with pH about 2. A white precipitate was obtained, which was filtered and dissolved in 5% sodium hydrogen carbonate. The insoluble sodium salt of the unreacted 1-benzyl-8-bromotheobromine was formed. The mixture was filtered and the filtrate was acidified with c. HCl to pH about 3. The separated precipitate was filtered under vacuum and dried. Yield –81%, m.p. – 193 – 194°C. The structure of the compound was confirmed by IR spectral analysis and its purity was elucidated by TLC.

Synthesis of methyl ester of 1-benzyltheobromine-8-thioglycolic acid (5)

Esterification of 1-benzyltheobromine-8-thioglycolic acid was performed according to the classical esterification (23) by interaction of the corresponding acid and alcohol in presence of sulfuric acid. The reaction was carried out in a round bottom flask in excess of anhydrous methanol (300 ml). The flask was placed in a cooling bath and 30 ml of H₂SO₄ were added in aliquots. After its full addition 17g of 1-benzyltheobromine-8-thioglycolic acid were added and the mixture was boiled under reflux for 4 hours. The process was monitored by TLC until exhaustion of the initial thioglycolic acid. After the end of the reaction the mixture was filtered and a triple amount of water was added to the filtrate. The mixture was kept for 24 hours at 12°C until formation of a volumetric precipitate, which was filtered and purified by re-crystallization from ethanol. Yield –86.1%, m.p. – 143 – 144°C. The structure of the compound was confirmed by IR spectral analysis and its purity was elucidated by TLC.

General procedure for the synthesis of amides of 1-benzyltheobromine-8-thioglycolic acid (7a-e)

In a conical flask 0.005 mol of methyl ester of 1-benzyltheobromine-8-thioglycolic acid and 0.01 mol of the corresponding amine (6a-e) was mixed and placed in glycerin bath at 115° – 130°C respectively. The process was monitored by TLC until exhaustion of the initial compounds. The obtained crystals were purified accordingly by re-crystallization from ethanol and/or ether.

The IUPAC names of the newly synthesized compounds together with the interpretation of their IR and ¹H NMR spectra are presented below; the chemical structures are presented in Fig. 3, the relevant melting points and the individual yields are presented in Table 1.

2-(1-benzyl-3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-ylthio)-N-cyclohexylacetamide (7a): IR (KBr): ν 1725, 1705, 1685, 1605, 1558; ¹H NMR (100 MHz, DMSO-d₆) δ , ppm: 9.40 (s, 1H, NH), 7.24-7.36 (m, 5H, C₆H₅), 4.80 (s, 2H, N1-CH₂), 3.48 (s, 3H, N3-CH₃), 3.70 (s, 2H, S-CH₂), 3.82 (s, 3H, N7-CH₃), 1.36-3.85 (m, 11H, C₆H₁₁).

2-(1-benzyl-3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-ylthio)-N-cyclohexyl-N-ethylacetamide (7b): IR (KBr): ν 1720, 1702, 1680, 1552; ¹H NMR (100 MHz, DMSO-d₆) δ , ppm: 7.24-7.36 (m, 5H, C₆H₅), 4.80 (s, 2H, N1-CH₂), 3.45 (s, 3H, N3-CH₃), 3.70 (s, 2H, S-CH₂), 3.80 (s, 3H, N7-CH₃), 1.40-3.80 (m, 22H, 2xC₆H₁₁).

2-(1-benzyl-3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-ylthio)-N,N-dicyclohexylacetamide (7c): IR (KBr): ν 1715, 1702, 1684, 1554; ¹H NMR (100 MHz, DMSO-d₆) δ , ppm: 7.24-7.36 (m, 5H, C₆H₅), 4.80 (s, 2H, N1-CH₂), 3.46 (s, 3H, N3-CH₃), 3.70 (s, 2H, S-CH₂), 3.80 (s, 3H, N7-CH₃), 3.26 (m, 2H, N-CH₂CH₃), 1.36-3.88 (m, 11H, C₆H₁₁), 1.22 (t, 3H, N-CH₂CH₃).

2-(1-benzyl-3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-ylthio)-N-cyclohexyl-N-methylacetamide (7d): IR (KBr): ν 1716, 1702, 1680, 1555; ¹H NMR (100 MHz, DMSO-d₆) δ , ppm: 7.24-7.36 (m, 5H, C₆H₅), 4.80 (s, 2H, N1-CH₂), 3.45 (s, 3H, N3-CH₃), 3.70 (s, 2H, S-CH₂), 3.80 (s, 3H, N7-CH₃), 3.26 (s, 2H, N-CH₂CH₃), 1.38-3.80 (m, 11H, C₆H₁₁), 3.72 (s, 3H, N-CH₃).

2-(1-benzyl-3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-ylthio)-N-((tetrahydrofuran-2-yl)methyl)acetamide (7e): IR (KBr): ν 1720, 1701, 1684, 1595, 1552; ¹H NMR (100 MHz, DMSO-d₆) δ , ppm: 9.40 (s, 1H, NH), 7.24-7.36 (m, 5H, C₆H₅), 4.80 (s, 2H, N1-CH₂), 3.40 (s, 3H, N3-CH₃), 3.70 (s, 2H,

S-CH₂), 3.81 (s, 3H, N7-CH₃), 3.13 (s, 2H, NH-CH₂), 1.86-4.23 (m, 7H, furan).

RESULTS AND DISCUSSION

The synthesis of amide derivatives of 1-benzyltheobromine-8-thioglicolic acid consists of brominating of theobromine (1) to obtain 8-bromotheobromine (2). Its further interaction with benzyl chloride resulted in synthesis of 1-benzyl-8-bromotheobromine (3). The next stage is the formation of the corresponding 1-benzyltheobromine-8-thioglicolic acid (4) by interaction of (3) with thioglycolic acid. The necessary for the aminolysis ester derivative (5) was obtained by esterification. The targeted structures were synthesized by classical aminolysis. The total synthetic scheme for the preparation of the initial methyl ester of 1-benzyltheobromine-8-thioglicolic acid is presented on Fig. 1.

thesis was performed under phase-transfer catalysis conditions, whereat aliquat 336 was used as catalyst. The corresponding reaction is presented on Fig. 2.

Based on previous experiments improving the reaction conditions (20) we led the reaction in water/ethanol media, in the presence of sodium hydroxide. At these conditions no side reaction was observed and the reaction time was shortened up to 1 and a half hour with yield of 81%. The next stage is formation of the corresponding 1-benzyltheobromine-8-thioglicolic acid (4) by interaction of (3) with thioglycolic acid. The necessary for the aminolysis, ester derivative (5), was obtained by classical esterification (23).

The targeted amide derivatives were synthesized by interaction of the corresponding amine and the methyl ester of 1-benzyltheobromine-8-thioglicolic acid.

Fig. 1. General scheme of synthesis of methyl ester of 1-benzyltheobromine-8-thioglicolic acid

The synthesis of 8-bromotheobromine (2) was carried out via oxidative bromination of theobromine (1) according to the literary method (14), based on application of HBr and H₂O₂ in glacial acetic acid. Under these conditions the reaction due 4 hours and the corresponding yield of re-crystallized 8-bromotheobromine was 80 -85%.

The next stage of our synthetic sequence is obtaining 1-benzyl-8-bromotheobromine (3). The syn-

colic acid, according to Fig. 3.

The aminolysis of the compounds was performed in melt, with 2:1 correlation of the reactants for the selected amine. For all the synthesis the reaction mixture was heated in glycerin bath until the methyl ester of 1-benzyltheobromine-8-thioglicolic acid was melted, which formed melt with the applied amine, and this temperature is maintained until the

Fig. 2. Synthesis of 1-benzyl-8-bromotheobromine

Fig. 3. General scheme for synthesis of the targeted amide derivatives of 1-benzyltheobromine-8-thioglycolic acid

end of the reaction. The reaction times are between 20 min to one hour, the temperature vary from 110 to 130°C and the yields are in range of 61 to 81,2%.

Using the above described methods five amide derivatives of 1-benzyltheobromine-8-thioglycolic acid were synthesized. The reaction conditions and the corresponding reaction time and yield for each of the targeted products are given in Table 1.

It is clearly seen in Table 1 that target products **7a-e** are obtained with good yields and purity, whereas **7a** is obtained with highest yield. The structure of the newly synthesized compounds was proven by elemental analysis, IR and ^1H -NMR spectroscopy.

The obtained structures are white crystalline powders, soluble in organic solvents (chloroform,

benzene, dimethylformamide) and practically insoluble in water. The obtained amides are stable to hydrolysis under acidic or alkali conditions, close to physiological pH and temperatures about 40°C. Under these conditions no hydrolysis is observed for a period of more than 20 hours.

The FT-IR spectra of the studied N-substituted 1-benzyltheobromine-8-thioglycolacetamides **7a-e** in the region of the 4000 – 400 cm^{-1} exhibit several characteristic bands. The two strong bands at about 1680 to 1702 cm^{-1} are ascribable to the stretching vibration of two carbonyl groups in the xanthine ring. The vibrational band recorded at 1716 – 1725 cm^{-1} belongs to the carbonyl in the amide moiety in the side chain (amide I), while the band at 1595 – 1605

Table 1. Reaction conditions and the corresponding reaction time and yield and melting points for the synthesis of each of the targeted products

compound	temperature °C	reaction time min.	Yield %	Melting point °C
7a	120°	20	81,2	180-183
7b	130°	60	62	149-151
7c	130°	40	64	130-134
7d	115°	60	61	157-160
7e	110°	60	66	160-161

cm⁻¹ in the spectra of **7a,e** corresponds to stretching vibration N-H from the same residue (amide II). This band do not present in the spectra of the other compounds since they are tertiary amides. The band at about 1550 cm⁻¹ belongs to the stretching vibration of C=C bonds in xanthine ring.

More detailed information about the structure of compounds **7a-e** was provided by the ¹H NMR spectra. Thus, the strong singlets at 3.45÷3.48 and 3.80÷3.82 ppm in the spectrum of the studied compounds correspond to N-methyl protons at position 3 and 7. The signal of the N-methylene group from 1-benzyltheobromine-8-thioglycolic acid at position 8 appears at 3.70 ppm as broad singlet. The signals of methylene protons from the benzyl side chain at position 1 form strong singlet at 4.80 ppm. The signals of the aromatic protons from benzyl side chain at position 1 in the spectra of **7a-e** correspond to complicated multiplets between 7.24 and 7.36 ppm, but the integral curves correspond to the exact number of the protons. The signals of methylene protons from the cyclohexyl residue of **7a-d** form broad multiplet between 1.68 and 1.39 ppm. The methyne proton from the cyclohexyl residue forms a multiplet with weak intensity between 3.85 and 3.80 ppm. In the spectrum of **7d** there is a strong singlet at 3.75 ppm that corresponds to N-methyl protons in the side chain. The ethyl group in the spectrum of **7b** appears as multiplet at 3.26 ppm and strong triplet at 1.22 ppm. There are some differences between spectrum of **7e** and these of **7a-d** where protons of tetrahydrofurylmethyl residue form broad complex multiplets between 1.86 and 4.23 ppm. The values of the chemical shifts of the protons registered by ¹H NMR spectra were compared with simulated values (2,4, 6,7). We observed only small deviations of computed from experimental values, due to an impossibility

to render an account of influence of the solvent. Regardless, the simulated ¹H NMR spectra are in good correlation with the experimental ones.

Druglikeness prediction

There are many approaches that assess a compound's "druglikeness", partially based on topological descriptors, fingerprints of MDL structure keys or other properties. In addition the biological activity is also usually a function of the complex influence of a number of molecular descriptors. In some cases, an underlayment of a certain parameter is possible, whereas the hydrophobicity of the compounds, usually expressed as LogP, appears to be a key parameter for determination of compounds druglikeness.

In the present work we have applied two approaches in an attempt to evaluate the drug-like properties of the newly synthesized by us amide derivatives of 1-benzyltheobromine-8-thioglycolic acid: the Lipinski's Rule of Five limitations and the OSIRIS Property Explorer evaluation score.

Determination of Lipinski's Rule of Five parameters

Lipinski's rule of five also known as the Rule of five (RO5) is a rule of thumb to evaluate druglikeness or determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans. The rule was formulated by Christopher A. Lipinski in 1997, based on the observation that most medication drugs are relatively small and lipophilic molecules (16, 17). The rule describes molecular properties important for a drug's pharmacokinetics in the human body, including their absorption, distribution, metabolism, and excretion ("ADME"). However, the rule does not predict if a compound is pharmacologically active. Candidate drugs that confirm to the RO5 tend to have lower attrition rates

Table 2. Structure and some molecular parameters of the newly synthesized amide derivatives of 1-benzyltheobromine-8-thioglycolic acid

ID	Structure	Lipinski's Rule of Five Parameters					%ABS
		Log P	MW	n (O, N)	n (OH,NH)	TPSA	
7a		3.587	441.557	8	1	90.93	77.63
7b		4.208	469.611	8	0	82.14	80.66
7c		5.737	523.703	8	0	82.14	80.66
7d		3.832	455.584	8	0	82.14	80.66
7e		2.056	443.529	9	1	100.16	74.44
TB		-0.951	180.167	6	1	72.69	83.92

during clinical trials and hence have an increased chance of reaching the market (17,18). Lipinski's rule states that, in general, an orally active drug has no more than one violation of the following criteria: 1) no more than 5 hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms); 2) not more than 10 hydrogen bond acceptors (nitrogen or oxygen atoms); 3) a molecular mass less than 500 daltons and 4) an octanol-water partition coefficient $\log P$ not greater than 5.

In the present work, the Lipinski's parameters were calculated with the help of the web based server Molinspiration Cheminformatics (31). This software offers broad range of cheminformatics software tools supporting molecule manipulation and processing, including SMILES and SDfile conversion, normalization of molecules, generation of tautomers, molecule fragmentation, calculation of various molecular properties needed in QSAR, molecular modeling and drug design, high quality molecule depiction, molecular database tools supporting substructure and similarity searches (31).

Using this software we calculated the values of the Lipinski's Rule of Five parameters and the obtained results are presented in Table 2.

From the performed calculation is obvious, that only one structure violates the Lipinski's Rule of Five parameters – **7c**, which makes it unsuitable for further structural optimizations.

In addition we determined the extension of absorption, expressed by the percentage of absorption. The absorption percent was calculated (30) using the expression: $\%ABS = 109 - 0.345PSA$.

Evaluation of drug-like properties of the new synthesized compounds, using the OSIRIS Property Explorer tool.

The OSIRIS Property Explorer used in this publication for druglikeness prediction tool is an integral part of Actelion's inhouse substance registration system (28). The prediction process relies on a pre-computed set of structural fragment that gives preliminary information on a number of drug-relevant properties, like druglikeness and/or toxicity alerts.

Evaluation of druglikeness

The synthesized by us new amide derivatives of 1-benzyltheobromine-8-thioglicolic acid were evaluated for druglikeness, using the web based serv-

er OSIRIS Property Explorer (32). The corresponding molecule's druglikeness was assessed by two parameters: **Fragment Based Druglikeness** and **Drug Score**.

Fragment Based Druglikeness

This parameter is calculated with the following equation summing up score values of those fragments that are present in the molecule under investigation:

$$d = \frac{\sum v_i}{\sqrt{n}}$$

A positive value states that the analyzed molecule contains predominately fragments which are frequently present in commercial drugs (33).

Drug Score

The drug score combines druglikeness, cLogP, logS, molecular weight and toxicity risks in one handy value that may be used to judge the compound's overall potential to qualify for a drug. This value is calculated by multiplying contributions of the individual properties with the first equation:

$$ds = \Pi \left(\frac{1}{2} + \frac{1}{2} S_i \right) \cdot \Pi t_i$$

where: ds is the drug score. s_i are the contributions calculated directly from cLogP, logS, molweight and druglikeness (p_i) via the second equation which describes a spline curve.

$$S_i = \frac{1}{1 + e^{ap_i + b}}$$

Parameters a and b are (1, -5), (1, 5), (0.012, -6) and (1, 0) for cLogP, logS, molweight and druglikeness, respectively. t_i are the contributions taken from the 4 toxicity risk types. The t_i values are 1.0, 0.8 and 0.6 for *no risk*, *medium risk* and *high risk*, respectively (34).

The corresponding values of the computational analysis are presented in Table 3.

From the performed evaluation was established, that compound **7e** shows a highest drug like properties with **Fragment Based Druglikeness score** of 2.58 and total **Drug score** of 0.43.

Evaluation of toxicity risks

The fragment lists, necessary for evaluation of toxicity risks, were created by rigorously shredding all compounds of the RTECS database known to be active in a certain toxicity class (e.g. mutagen-

Table 3. Druglikeness and drug score values for newly synthesized compounds

Compound	Druglikeness score	Drug score
7a	-1.05	0.24
7b	-0.68	0.24
7c	-6.11	0.12
7d	-1.16	0.20
7e	2.58	0.43
Theobromine	1.65	0.19

icity). During the shredding any molecule was first cut at every rotatable bonds leading to a set of core fragments. These in turn were used to reconstruct all possible bigger fragments being a substructure of the original molecule. Afterwards, a substructure search process determined the occurrence frequency of any fragment (core and constructed fragments) within all compounds of that toxicity class (35).

Due to the high structural similarity in the evaluated group of compounds it was determined, that for all the compounds a high risk of tumorigenic toxicity may be predicted, which is result from the presence of the corresponding group in all the target structures:

In addition the presence of the presented below structural fragment

may be a reason for the expected performance from structure **7d** of medium risk of mutagenicity.

CONCLUSION

The synthesis of 1-benzyltheobromine-8-thioglycolacetamides consists of bromination of theobromine to obtain the corresponding 8-bromotheobromine, its benzylation at position 1 in the presence of aliquat 366 as phase transfer catalyst and further interaction with thioglycolic acid with subsequent esterification with methanol. The corresponding amide derivatives are further obtained by aminolysis of

the methyl ester with the desired amine. The newly synthesized **7a-e** are crystal compounds with white to very pale-yellow colour, soluble in DMF, sparingly soluble in alcohol and insoluble in water. The structures of the studied compounds were established by FTIR, ¹H NMR spectral data. In order to estimate the drug-likeness of compounds **7a-e**, a theoretical calculation of some molecular descriptors was made using two approaches: the Lipinski's Rule of Five and the OSIRIS Property Explorer evaluation score. The comparison of the calculated results indicate that only one compound violates the Lipinski's Rule of Five parameters – **7c**, which makes it unsuitable for further structural optimizations. On the other hand compound **7e** shows a highest drug like properties with **Fragment Based Druglikeness score** of 2.58 and total **Drug score** of 0.43 which are better than the same scores of parent compound theobromine. For all of the compounds a good oral bioavailability manifestation may be expected. The possible pharmacological effects and clarification of their potential as prodrugs will be further estimated.

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