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Research Article

COMPUTER PROGNOSIS OF BIOLOGICAL ACTIVITY FOR A NUMBER OF NEW 7-R-8-SUBSTITUTED-1,3-DIMETHYLXANTHINE

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ABSTRACT

Objectives: Creation of new potential active pharmaceutical ingredients of synthetic origin is an urgent problem of modern medical chemistry. With this purpose was obtained a number of original 7,8-disubstituted theophylline, and some molecular and pharmacological descriptors are calculated using public Web-resource Chemicalize.org. There was shown the influence of respective substituents in 7 and 8 positions of molecules of synthesized substances on druglike and was confirmed the prospects of chosen area of study.

Methods: Among drug like characteristics to identify compound's leads, the following parameters were selected and analyzed (tautomerism, molecular refraction, distribution factor in the system octanol-water [log P], polar surface area [PSA], "druglike" filters).

Results: Monitoring of obtained data confirmed the prospects for further pharmacological investigations for the original derivatives 1,3-dimethylxanthine with appropriate substituents on 7 and 8 positions of the molecule. So, for five of tested substances the total number of possible stereoisomers and tautomers ≥4. According to indicators of molecular refraction only seven compounds do not meet the Ghosh filter (X, XII, XIII, XVIII-XXI). The meaning of distribution factors in the system octanol-water for all tested substances is lower than the maximum possible. Indicators PSA compounds I-XXI correlate with Maggie and Weber filters (excluding III), providing their possible passive molecular transportaion through cell membranes. Substances II, IX, XI correspond to requirements of all "druglike" filters. Interesting is the fact that the common structural element of these substances is residue of hydrazine. When negative leaderlike, to requirements of other "druglike" filters correspond 9 of 21 obtained compounds (I, IV, VI-VIII, XIV-XVII). The structural similarity of tested substances with already known methylated xanthine derivatives ranges from 63.9% to 88.8%.

Conclusion: Finally it should be noted that the results of the initial pharmacological screening in experiments *in vitro* and *in vivo* confirmed the studied theoretical calculations of virtual analysis and allowed to identify promising substances with antioxidant, antiradical, anti-hypoxic and other profiles of action. Some common factors were established in a series "chemical structure – biological activity." Subsequent publications will report about continued study in this area.

Keywords: Virtual analysis, 7,8-disubstituted 1,3-dimethylxanthine, Druglike, Ghosh, Maggie and Weber filters.

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INTRODUCTION

Despite considerable progress in the creation of original medicines and further development of modern pharmaceutical technologies, various diseases continue to affect millions of people. In order to get new active pharmaceutical ingredients of synthetic origin is time-consuming; require the expenditure of much labor and quite expensive process. Scientists focus on task-oriented approach in order to search and create highly effective substances: Chemical compounds are tested only on a limited number of pharmacological actions, and properties of the basic structures are optimized by the way of synthesis and study of target products of reactions. The real possibility of a comprehensive study of biological activity may provide new technologies based on the latest achievements of molecular biology, bio-informatics, virtual screening, computer simulation, etc. [1-3].

METHODS

In order to find new potential candidates into the drug substances were synthesized 8-bromo-1,3-dimethyl-7-(phenethyl-3-phenylpropyl-3-phenylalyl- and 3-(4-(trifluoromethoxy)phenyl)prop-2-inyl)-1*H*-purine-2,6(3*H*,7*H*)-dione. The latter is utilized in reactions with appropriate nucleophilic reagents to give 7-R-8-thio-(hydrazine-)theophylline, further functionalization which led to the creation of large array of original 7,8-disubstituted 1,3-dimethylxanthine containing in its structure a series of pharmacophores. Structure and individuality of synthesized compounds are confirmed by the complex of modern spectral methods of analysis. For a series of the obtained substances we carried out virtual analysis using public Web-resource Chemicalize.org developed on the basis of ChemAxon [4]. Among drug like characteristics to identify compound's leads, the following parameters were selected and analyzed.

Tautomerism

A significant step towards understanding the properties of certain molecule is the study of its three-dimensional (3D) conformations. The study of configuration space of molecule and analysis of different isomers of the latter may be important. Atoms chirality plays a major role in various fields of chemistry as enantiomers often show quite different physical, chemical and biological properties. Most combinatorial libraries contain substances in the form of two-dimensional structures with incomplete guidance of stereochemical and tautomeric state. This inevitably leads to ambiguous stereochemistry or tautomerisation when converting structures into 3D format. The list of tautomers and stereoisomers of molecules is important for virtual applied screening programs such as doc-, 3D-search or 3D-quantitative structure-activity relationships, because it facilitates the discovery and development of new drug substances.

Molecular refraction

Its calculation is based on atomic method proposed by Viswanadhan *et al*. [5]. Molecular refraction quantitatively correlates with the volume of molecule and its polarization, so this indicator is also associated with London dispersion forces, which play an important role in the interaction "drug-receptor."

Distribution factor in the system octanol-water (log P)

It is a ratio of concentration non-ionized substance in both phases of solvents that are immiscible with each other. This indicator shows lipophilicity of tested compound. For substances, containing groups that are capable to ionize and can exist in solution in ionized form, can be calculated log D, which additionally considers solubility of ionized form of the sample in aqueous solution.

Polar surface area (PSA)

Necessary to demonstrate the degree of correlation with passive molecular transfer through membranes and, therefore, allows to evaluate transport properties of potential drugs. This descriptor is formed by polar atoms of molecule. For this is counted topological PSA, which almost coincides with 3D PSA.

"Druglike" filters

Based on studies of the characteristics of compounds that affect their biological action, Lipinski formulated empirical Lipinski's rule of five [6], also known as Pfizer's rule of five – a practical method for "druglike" assessing, that is definition in the chemical substance of properties, which make it conditionally active drugs in the body. The rule describes molecular properties that are important to the pharmacokinetics of substance, including its absorption, distribution, metabolism and excretion. Like many other empirical rules, there are many exceptions to the Lipinski's rule. To determine other "druglike" indicators of newly created substances, there was analyzed a number of options of studied molecules. Bioavailability: Molecular weight ≤500; distribution factor in the system octanol-water ≤5; number of donors of hydrogen bonds ≤5; number of hydrogen bond acceptors ≤10; number of links where is possible rotation ≤10; PSA ≤200; number of condensed aromatic rings ≤5≥6. Ghosh filter [7]: Molecular weight ≥160≤480; number of atoms ≥20≤70; distribution factor in the system octanol-water ≥−0.4≤5.6; refractivity ≥40≤130. Leaderlike: Molecular weight ≤450; number of rings ≤4; number of links where is possible rotation ≤10; number of donors of hydrogen bonds ≤5; the number of hydrogen bond acceptors ≤8. Maggie filter: Molecular weight ≥200≤600; number of rings ≤7; number of links where is possible around ≤15; number of donors of hydrogen bonds ≤5; number of hydrogen bond acceptors ≤10; distribution factor in the system octanol-water ≥−2≤5; PSA ≤150. Weber filter: Number of connections around which is possible rotation ≤10; PSA ≤140.

Structural similarity

Determined to tested substances by calculating their similarities to already known substances listed in the appropriate database, and is expressed as a percentage.

RESULTS

Results of virtual analysis of compounds, in chemical structure of which are found potential pharmacophore clusters, are available in Table 1.

Table 1: Formula of structure of a number of synthesized compounds and molecular descriptors value calculated using appropriate software

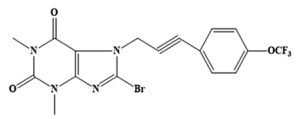
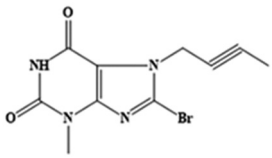
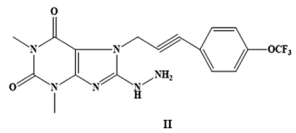
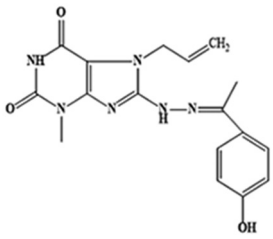
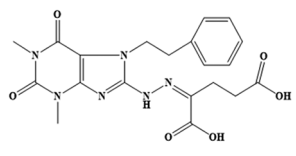
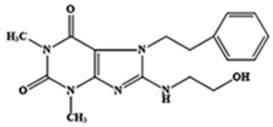
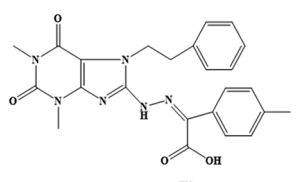
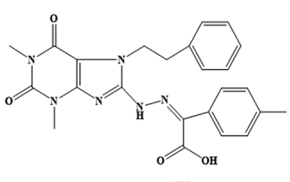
S. No.	Compound	The number of possible stereoisomers and tautomers	Molecular refraction	Log P	PSA	"Druglike" filters	Structure similarity
1.	 I	1 (1)	90.771	4.15	67.67	Lipinski's rule of five: Yes Bioavailability: Yes Ghosh filter: Yes Leaderlike: No Maggie filter: Yes Weber filter: Yes	 80.3%
2.	 II	1 (3)	92.326	3.16	105.72	Lipinski's rule of five: Yes Bioavailability: Yes Ghosh filter: Yes Leaderlike: Yes Maggie filter: Yes Weber filter: Yes	 74.5%
3.	 III	2 (4)	113.235	2.18	157.43	Lipinski's rule of five: Yes Bioavailability: Yes Ghosh filter: Yes Leaderlike: No Maggie filter: No Weber filter: No	 76.2%
4.	 IV	2 (4)	127.649	4.30	120.13	Lipinski's rule of five: Yes Bioavailability: Yes Ghosh filter: Yes Leaderlike: No Maggie filter: Yes Weber filter: Yes	 81.7%

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Table 1: ***(Continued)***

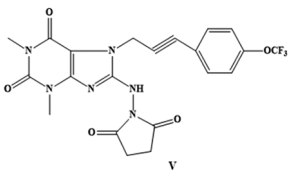
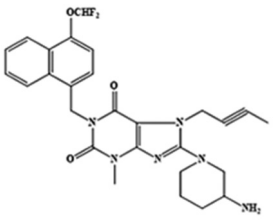
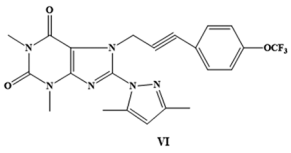
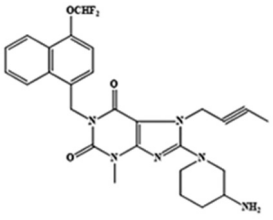
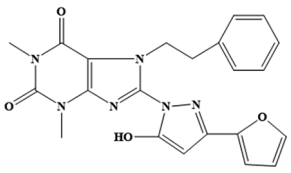
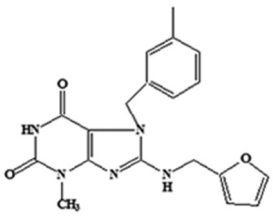
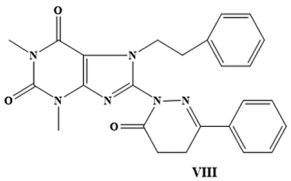
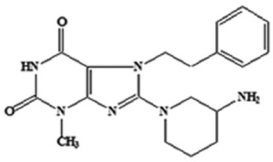
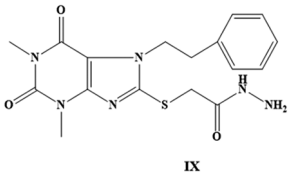
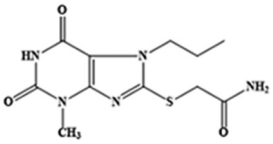
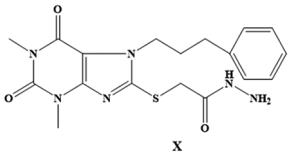
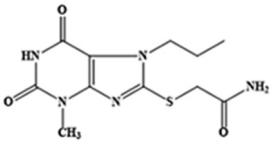
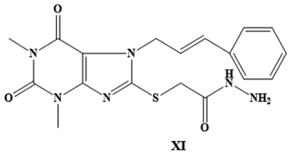
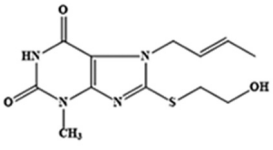
S. No.	Compound	The number of possible stereoisomers and tautomers	Molecular refraction	Log P	PSA	"Druglike" filters	Structure similarity
5.	 V	1 (3)	108.523	2.90	117.08	Lipinski's rule of five: Yes Bioavailability: Yes Ghosh filter: No Leaderlike: No Maggie filter: Yes Weber filter: Yes	 68.9%
6.	 VI	1 (1)	110.722	4.18	85.49	Lipinski's rule of five: Yes Bioavailability: Yes Ghosh filter: Yes Leaderlike: No Maggie filter: Yes Weber filter: Yes	 68.3%
7.	 VII	1 (1)	119.339	3.53	89.40	Lipinski's rule of five: Yes Bioavailability: Yes Ghosh filter: Yes Leaderlike: No Maggie filter: Yes Weber filter: Yes	 63.9%
8.	 VIII	1 (1)	126.922	3.06	91.11	Lipinski's rule of five: Yes Bioavailability: Yes Ghosh filter: Yes Leaderlike: No Maggie filter: Yes Weber filter: Yes	 73.9%
9.	 IX	1 (1)	103.970	0.84	113.56	Lipinski's rule of five: Yes Bioavailability: Yes Ghosh filter: Yes Leaderlike: Yes Maggie filter: Yes Weber filter: Yes	 88.8%
10.	 X	1 (1)	136.017	2.64	107.85	Lipinski's rule of five: No Bioavailability: Yes Ghosh filter: No Leaderlike: No Maggie filter: Yes Weber filter: Yes	 72.0%
11.	 XI	2 (1)	109.533	1.16	113.56	Lipinski's rule of five: Yes Bioavailability: Yes Ghosh filter: Yes Leaderlike: Yes Maggie filter: Yes Weber filter: Yes	 82.5%

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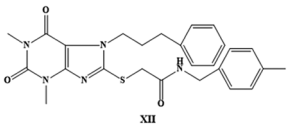
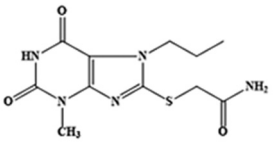
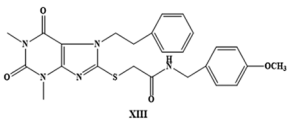
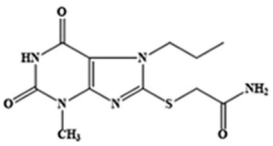
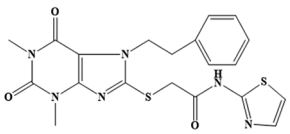
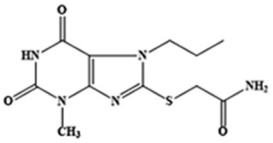
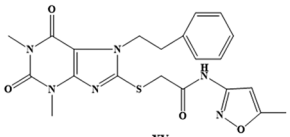
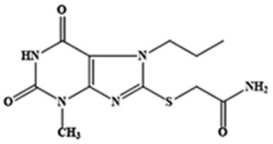
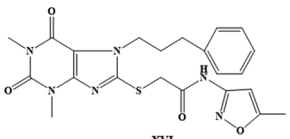
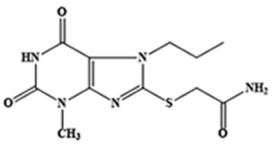
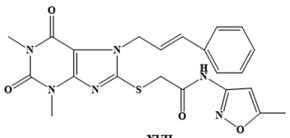
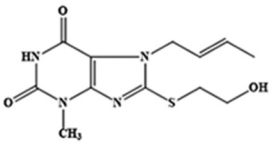
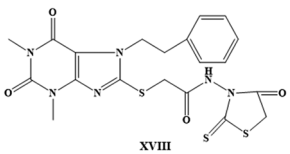
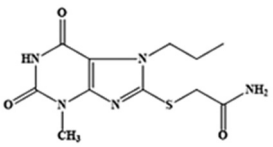
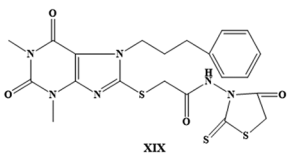
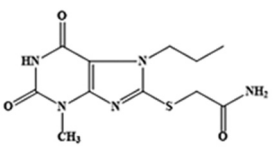
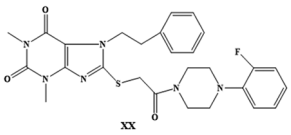
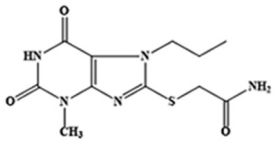
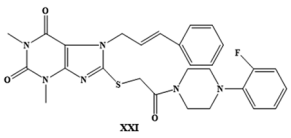
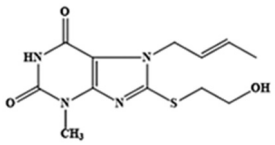
Table 1: ***(Continued)***

S. No.	Compound	The number of possible stereoisomers and tautomers	Molecular refraction	Log P	PSA	"Druglike" filters	Structure similarity
12.	 XII	1 (1)	138.637	4.05	87.54	Lipinski's rule of five: Yes Bioavailability: Yes Ghosh filter: No Leaderlike: No Maggie filter: Yes Weber filter: Yes	 82.5%
13.	 XIII	1 (1)	135.458	2.93	96.77	Lipinski's rule of five: Yes Bioavailability: Yes Ghosh filter: No Leaderlike: No Maggie filter: Yes Weber filter: Yes	 80.2%
14.	 XIV	1 (1)	120.622	2.72	100.43	Lipinski's rule of five: Yes Bioavailability: Yes Ghosh filter: Yes Leaderlike: No Maggie filter: Yes Weber filter: Yes	 78.0%
15.	 XV	1 (1)	122.846	2.54	113.57	Lipinski's rule of five: Yes Bioavailability: Yes Ghosh filter: Yes Leaderlike: No Maggie filter: Yes Weber filter: Yes	 76.2%
16.	 XVI	1 (1)	127.447	2.98	113.57	Lipinski's rule of five: Yes Bioavailability: Yes Ghosh filter: Yes Leaderlike: No Maggie filter: Yes Weber filter: Yes	 74.4%
17.	 XVII	2 (1)	128.409	2.86	113.57	Lipinski's rule of five: Yes Bioavailability: Yes Ghosh filter: Yes Leaderlike: No Maggie filter: Yes Weber filter: Yes	 72.4%
18.	 XVIII	2 (3)	132.642	2.35	104.61	Lipinski's rule of five: No Bioavailability: Yes Ghosh filter: No Leaderlike: No Maggie filter: Yes Weber filter: Yes	 72.5%
19.	 XIX	1 (1)	136.017	2.64	107.85	Lipinski's rule of five: No Bioavailability: Yes Ghosh filter: No Leaderlike: No Maggie filter: Yes Weber filter: Yes	 72.0%

(Contd...)

Table 1: ***(Continued)***

S. No.	Compound	The number of possible stereoisomers and tautomers	Molecular refraction	Log P	PSA	"Druglike" filters	Structure similarity
20.	 XX	1 (1)	146.044	3.47	81.99	Lipinski's rule of five: No Bioavailability: Yes Ghosh filter: No Leaderlike: No Maggie filter: Yes Weber filter: Yes	 76.4%
21.	 XXI	2 (1)	151.607	3.79	81.99	Lipinski's rule of five: No Bioavailability: Yes Ghosh filter: No Leaderlike: No Maggie filter: Yes Weber filter: Yes	 72.0%

DISCUSSION

Monitoring of obtained data confirmed the prospects for further pharmacological investigations for the original derivatives 1,3-dimethylxanthine with appropriate substituents on 7 and 8 positions of the molecule. So, for five of tested substances (II, III, IV, V, XVIII) the total number of possible stereoisomers and tautomers ≥4. According to indicators of molecular refraction only seven compounds do not meet the Ghosh filter (X, XII, XIII, XVIII-XXI). The meaning of distribution factors in the system octanol-water for all tested substances is lower than the maximum possible. Indicators PSA compounds I-XXI correlate with Maggie and Weber filters (excluding III), providing their possible passive molecular transportaion through cell membranes. Substances II, IX, XI correspond to requirements of all "druglike" filters. Interesting is the fact that the common structural element of these substances is residue of hydrazine. When negative leaderlike, to requirements of other "druglike" filters correspond 9 of 21 obtained compounds (I, IV, VI-VIII, XIV-XVII). The structural similarity of tested substances with already known methylated xanthine derivatives ranges from 63.9% to 88.8%.

CONCLUSION

Finally it should be noted that the results of the initial pharmacological screening in experiments *in vitro* and *in vivo* confirmed the studied theoretical calculations of virtual analysis and allowed to identify promising substances with antioxidant, antiradical, anti-hypoxic and other profiles of action. Some common factors were established in a series "chemical structure – biological activity." Subsequent publications will report about continued study in this area.

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