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 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 IXXI correlate with Maggie and Weber filters (excluding III), providing their possible passive molecular transportations 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.
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 rings 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 rotation ≤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.

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

(Contd...)
### Table 1: (Continued)

| S. No. | Compound | The number of possible stereoisomers and tautomers | Molecular refraction | Log P | PSA | 'Druglike' filters | Structure similarity |
|--------|----------|---------------------------------------------------|----------------------|-------|-----|-------------------|---------------------|
| 5.     | ![Image](image5.png) | 1 (3) | 108.523 | 2.90 | 117.08 | Lipinski's rule of five: Yes | ![Image](image5_structure.png) |
|        |          |         |          |      |      | Bioavailability: Yes | ![Image](image5_bioavailability.png) |
|        |          |         |          |      |      | Ghosh filter: No | ![Image](image5_ghosh_filter.png) |
|        |          |         |          |      |      | Leaderlike: No | ![Image](image5_leaderlike.png) |
|        |          |         |          |      |      | Maggie filter: Yes | ![Image](image5_maggie_filter.png) |
|        |          |         |          |      |      | Weber filter: Yes | ![Image](image5_weber_filter.png) |
| 6.     | ![Image](image6.png) | 1 (1) | 110.722 | 4.18 | 85.49 | Lipinski's rule of five: Yes | ![Image](image6_structure.png) |
|        |          |         |          |      |      | Bioavailability: Yes | ![Image](image6_bioavailability.png) |
|        |          |         |          |      |      | Ghosh filter: Yes | ![Image](image6_ghosh_filter.png) |
|        |          |         |          |      |      | Leaderlike: No | ![Image](image6_leaderlike.png) |
|        |          |         |          |      |      | Maggie filter: Yes | ![Image](image6_maggie_filter.png) |
|        |          |         |          |      |      | Weber filter: Yes | ![Image](image6_weber_filter.png) |
| 7.     | ![Image](image7.png) | 1 (1) | 119.339 | 3.53 | 89.40 | Lipinski's rule of five: Yes | ![Image](image7_structure.png) |
|        |          |         |          |      |      | Bioavailability: Yes | ![Image](image7_bioavailability.png) |
|        |          |         |          |      |      | Ghosh filter: Yes | ![Image](image7_ghosh_filter.png) |
|        |          |         |          |      |      | Leaderlike: No | ![Image](image7_leaderlike.png) |
|        |          |         |          |      |      | Maggie filter: Yes | ![Image](image7_maggie_filter.png) |
|        |          |         |          |      |      | Weber filter: Yes | ![Image](image7_weber_filter.png) |
| 8.     | ![Image](image8.png) | 1 (1) | 126.922 | 3.06 | 91.11 | Lipinski's rule of five: Yes | ![Image](image8_structure.png) |
|        |          |         |          |      |      | Bioavailability: Yes | ![Image](image8_bioavailability.png) |
|        |          |         |          |      |      | Ghosh filter: Yes | ![Image](image8_ghosh_filter.png) |
|        |          |         |          |      |      | Leaderlike: No | ![Image](image8_leaderlike.png) |
|        |          |         |          |      |      | Maggie filter: Yes | ![Image](image8_maggie_filter.png) |
|        |          |         |          |      |      | Weber filter: Yes | ![Image](image8_weber_filter.png) |
| 9.     | ![Image](image9.png) | 1 (1) | 103.970 | 0.84 | 113.56 | Lipinski's rule of five: Yes | ![Image](image9_structure.png) |
|        |          |         |          |      |      | Bioavailability: Yes | ![Image](image9_bioavailability.png) |
|        |          |         |          |      |      | Ghosh filter: Yes | ![Image](image9_ghosh_filter.png) |
|        |          |         |          |      |      | Leaderlike: Yes | ![Image](image9_leaderlike.png) |
|        |          |         |          |      |      | Maggie filter: Yes | ![Image](image9_maggie_filter.png) |
|        |          |         |          |      |      | Weber filter: Yes | ![Image](image9_weber_filter.png) |
| 10.    | ![Image](image10.png) | 1 (1) | 136.017 | 2.64 | 107.85 | Lipinski's rule of five: No | ![Image](image10_structure.png) |
|        |          |         |          |      |      | Bioavailability: Yes | ![Image](image10_bioavailability.png) |
|        |          |         |          |      |      | Ghosh filter: No | ![Image](image10_ghosh_filter.png) |
|        |          |         |          |      |      | Leaderlike: No | ![Image](image10_leaderlike.png) |
|        |          |         |          |      |      | Maggie filter: Yes | ![Image](image10_maggie_filter.png) |
|        |          |         |          |      |      | Weber filter: Yes | ![Image](image10_weber_filter.png) |
| 11.    | ![Image](image11.png) | 2 (1) | 109.533 | 1.16 | 113.56 | Lipinski's rule of five: Yes | ![Image](image11_structure.png) |
|        |          |         |          |      |      | Bioavailability: Yes | ![Image](image11_bioavailability.png) |
|        |          |         |          |      |      | Ghosh filter: Yes | ![Image](image11_ghosh_filter.png) |
|        |          |         |          |      |      | Leaderlike: Yes | ![Image](image11_leaderlike.png) |
|        |          |         |          |      |      | Maggie filter: Yes | ![Image](image11_maggie_filter.png) |
|        |          |         |          |      |      | Weber filter: Yes | ![Image](image11_weber_filter.png) |

(Contd...)
| S. No. | Compound | The number of possible stereoisomers and tautomers | Molecular refraction | Log P | PSA | "Druglike" filters | Structure similarity |
|-------|----------|-----------------------------------------------|---------------------|-------|-----|-------------------|---------------------|
| 12.   |          | 1 (1)                                          | 138.637             | 4.05  | 87.54 | Lipinski’s rule of five: Yes Bioavailability: Yes Ghosh filter: No Maggie filter: Yes Weber filter: Yes | 82.5% |
| 13.   |          | 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.   |          | 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.   |          | 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.   |          | 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.   |          | 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.   |          | 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.   |          | 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% |
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 transportation 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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