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QSAR models for inhibitors of physiological impact of *Escherichia coli* that leads to diarrhea

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ABSTRACTS

Quantitative structure – activity relationships (QSARs) developed to evaluate percentage of inhibition of STa-stimulated (*Escherichia coli*) cGMP accumulation in T84 cells are calculated by the Monte Carlo method. This endpoint represents a measure of biological activity of a substance against diarrhea. Statistical quality of the developed models is quite good. The approach is tested using three random splits of data into the training and test sets. The statistical characteristics for three splits are the following: (1) $n = 20$, $r^2 = 0.7208$, $q^2 = 0.6583$, $s = 16.9$, $F = 46$ (training set); $n = 11$, $r^2 = 0.8986$, $s = 14.6$ (test set); (2) $n = 19$, $r^2 = 0.6689$, $q^2 = 0.5683$, $s = 17.6$, $F = 34$ (training set); $n = 12$, $r^2 = 0.8998$, $s = 12.1$ (test set); and (3) $n = 20$, $r^2 = 0.7141$, $q^2 = 0.6525$, $s = 14.7$, $F = 45$ (training set); $n = 11$, $r^2 = 0.8858$, $s = 19.5$ (test set). Based on the proposed here models hypothetical compounds which can be useful agents against diarrhea are suggested.

1. Introduction

Quantitative structure – activity relationships (QSARs) based on the molecular descriptors [1–3] are widely used as a tool to predict biochemical and medicinal characteristics of various compounds [4–10]. Such approaches are successfully applied not only in research but have been also broadly adopted by industry.

Diarrhea is a major health problem throughout the world. Only 12 years ago, in 2000 about 22% of all deaths of children in sub-Saharan Africa, and 23% in South Asia, were attributed to diarrhea diseases in 20 [11].

There is the compound that is a consider to be a starting substance for search of new effective inhibitors of physiological impact of *Escherichia coli* (STa) that leads to diarrhea: 5-(3-bromophenyl)-1,3-dimethyl-5,11-dihydro-1H indeno – [20,10,5,6] pyrido[2,3-d] pyrimidine-2,3,6-trione (BPIPP) [11]. *E. coli* induces diarrhea when it binds to intestinal epithelial cell membrane receptor, guanylyl cyclase type C (GC-C). This process activates the enzyme to convert guanosine triphosphate (GTP) to cyclic guanosine 30,50-monophosphate (cGMP). In turn, such reaction induces activation of a cGMP-dependent protein kinase and chloride-ion channel, cystic fibrosis transmembrane conductance regulator (CFTR). Finally, activation of CFTR triggers the flux of chloride ions into the intestinal lumen and the accumulation of water and sodium ions, thus causing diarrhea [11,12].

The experimentally defined percentage of the inhibition of accumulation in T84 cells cGMP (owing to presence of *E. coli*) is the measure of the ability of a compound to become the possible addition to therapeutic arsenal against diarrhea [11,12]. Computational studies provide useful way to propose the most promising candidates for further experimental evaluation of their biological activities, including the anti-diarrhea efficiency.

The aims of the present study are: (i) the evaluation of the CORAL software [13] as a tool of the QSAR modeling of the above-mentioned percentage of inhibition; and (ii) the theoretically aided selection of compounds which can be efficiently therapeutic agents for treatment of diarrhea (using of the CORAL models).

2. Method

2.1. Data set

The molecular structures and percentage of inhibition of STa-stimulated cGMP accumulation in T84 cells for 31 compounds are taken from the literature [11,12]. Table 1 contains the list of

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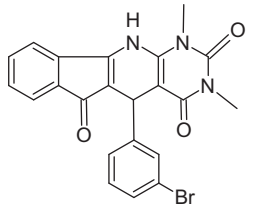
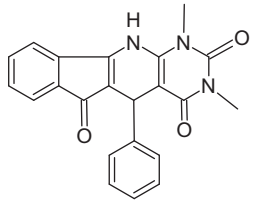
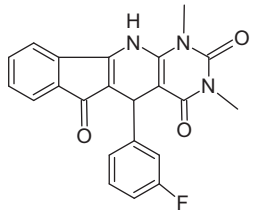
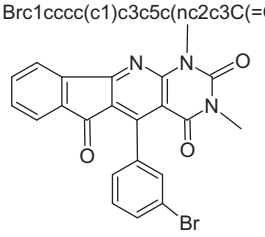
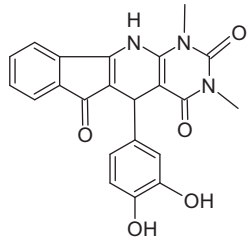
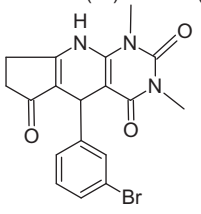
Table 1
Inhibition of STa-stimulated cGMP accumulation in T84 cells.

ID*	SMILES and structure	% Inhibition experimental [11,12]	% Inhibition calculation with Eq. (4)
1	Brc1cccc(c1)C2C5=C(NC3=C2C(=O)c4ccccc34)N(C)C(=O)N(C)C5=O 	86	51.762
2	O=C2C=1C(C4=C(NC=1c3ccccc23)N(C)C(=O)N(C)C4=O)c5ccccc5 	7	−4.210
3	Fc1cccc(c1)C2C5=C(NC3=C2C(=O)c4ccccc34)N(C)C(=O)N(C)C5=O 	63	51.762
4	Brc1cccc(c1)c3c5c(nc2c3C(=O)N(C)C(=O)N2C)c4ccccc4C5=O 	2	23.709
5	Oc1ccc(cc1O)C2C5=C(NC3=C2C(=O)c4ccccc34)N(C)C(=O)N(C)C5=O 	26	43.060
6	Brc1cccc(c1)C3C4=C(NC=2CCC(=O)C=23)N(C)C(=O)N(C)C4=O 	56	63.739

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