ARTICLE

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ADME PROPERTIES PREDICTION OF 5-PHENYL-5,6-DIHYDROTETRAZOLO[1,5-*c*] QUINAZOLINES

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Summary. *Due to the recent predicted affinity of 13 novel 5-phenyl-5,6-dihydrotetrazolo[1,5-c]-quinazolines to the ribosomal 50S protein L2P (2QEX) by molecular docking, their ADME properties were calculated at the site SwissADME to predict their drug-likeness. Hence, substances* ***6****,* ***10****, and* ***12*** *appeared to be the leading compounds among all studied ones and are of definite interest for further in vitro antimicrobial activity investigation.*

Keywords: *ADME properties, 5-phenyl-5,6-dihydrotetrazolo[1,5-c]quinazolines, drug-likeness.*

Introduction. A molecule could be a drug if it can reach its target in the body in sufficient concentration and remains there in a biologically active form long enough for the expected biological events to occur and has low toxicity. The so-called Rule-of-five of Lipinski *et al.* [1] is delineating the relationship between pharmacokinetic and physicochemical parameters. Drug development involves assessment of absorption, distribution, metabolism and excretion (ADME) increasingly earlier in the discovery process, at a stage when considered compounds are numerous, but

access to the physical samples is limited. In this regard, computer models are a real alternative to experimentation. Recently, the affinity to the ribosomal 50S protein L2P (2QEX) of 13 novel 5-phenyl-5,6-dihydrotetrazolo[1,5-*c*]-quinazolines with reference Tedizolid was predicted by molecular docking [2]. So, before testing these substances for antimicrobial activity, it's advised to check their bioavailability and toxicity profile. And the SwissADME Web tool enables the computation of key physicochemical, pharmacokinetic, drug-like and related parameters for one or multiple molecules [3]. This site gives free open-access and fast predictive models showing statistical significance, predictive power, intuitive interpretation, and straightforward translation to molecular design.

Aim: It was decided to investigate and compare ADME properties of Tedizolid and derivatives of 5-phenyl-5,6-dihydrotetrazolo[1,5-*c*]quinazoline (Fig. 1).

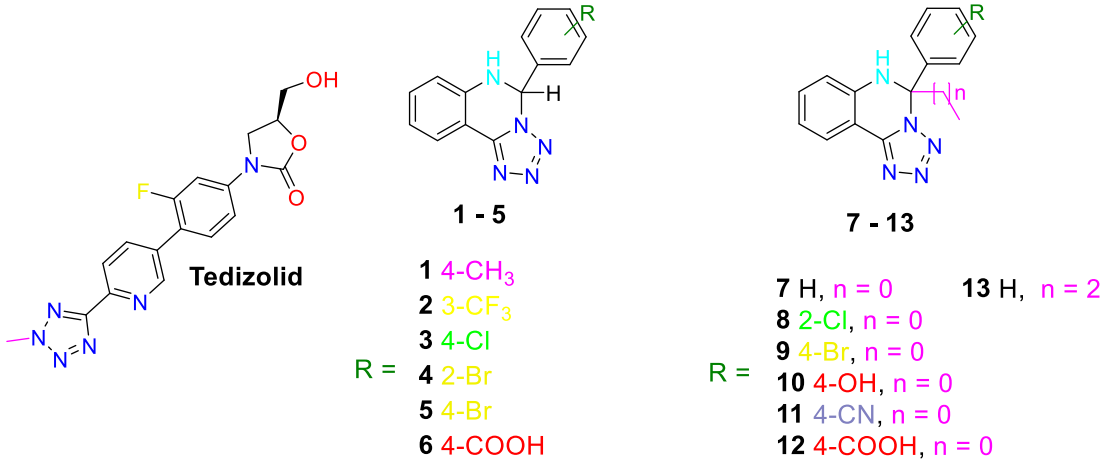

Fig. 1. **Structural formula of Tedizolid as antimicrobial and structural analogue and proposed 5-phenyl-5,6-dihydrotetrazolo[1,5-*c*]quinazolines**

Materials and methods. The ergonomic and user-friendly graphical interface for the cost- and login-free Website SwissADME was used to calculate ADME [3]. All descriptors and molecular parameters (physico-chemical properties, lipophilicity, water solubility, pharmacokinetics, drug-likeness) were computed by the protocols explained by SwissADME paper [4]. Tables were formed based on data obtained from the site.

Results and discussion. As a result, firstly, the following physico-chemical properties were calculated, and substances are placed in Table 1 by decreasing of the sum of all their characteristics.

Table 1

The calculated physico-chemical properties

#	MW*, g/mol	HA	Csp3	RB	HBA	HBD	Ref.	TPSA, Å²
Tedizolid	370.34	27	0.24	4	8	1	95.18	106.26
12	307.31	23	0.12	2	5	2	85.97	92.93
9	342.19	21	0.13	1	3	1	86.71	55.63
6	293.28	22	0.07	2	5	2	81.28	92.93
4	328.17	20	0.07	1	3	1	82.02	55.63

Continuation of the table 1

#	MW*, g/mol	HA	Csp3	RB	HBA	HBD	Ref.	TPSA, Å²
5	328.17	20	0.07	1	3	1	82.02	55.63
2	317.27	23	0.13	2	6	1	79.32	55.63
13	291.35	22	0.24	3	3	1	88.63	55.63
10	279.30	21	0.13	1	4	2	81.03	75.86
8	297.74	21	0.13	1	3	1	84.02	55.63
11	287.32	22	0.12	1	3	1	86.95	55.63
3	283.72	20	0.07	1	3	1	79.33	55.63
1	263.30	20	0.13	1	3	1	79.29	55.63
7	263.30	20	0.13	1	3	1	79.01	55.63
Number of aromatic heavy atoms is 17 for all.								

MW - molecular weight, HA - number of heavy atoms, Csp3 - Fraction Csp3, RB - number of rotatable bonds, HBA - number of H-bond acceptors, HBD - number of H-bond donors, Ref - molar refractivity, TPSA - topological polar surface area.

According to the ratio of sp3 hybridized carbons saturation should be at least 0.25 [5], only Tedizolid and substance 13 have the highest value: 0.24. Substances 3-6 have the lowest number of 0.07.

For size, the molecular weight (MW, calculated by OpenBabel) should be between 150 and 500 g/mol [6]. For polarity, the TPSA should be between 20 and 130 $Å^2$, considering sulfur and phosphorus as polar atoms [7]. For flexibility, the molecule should not have more than 9 rotatable bonds [6]. For molar refractivity: 40 to 130 [8]. And the characteristics of all test substances are found in the required ranges.

SwissADME gives a Consensus lipophilicity (log $P_{o/w}$) value, which is the arithmetic mean of the five predictive values (XLOGP3, atomistic method including corrective factors and knowledge-based library; WLOGP, atomistic method based on the fragmental system; MLOGP, Moriguchi octanol-water partition coefficient based on structural parameters; and Log P calculated by Silicos IT) [4]. And obtained values were placed in Table 2 according to decreasing of their Consensus score.

Table 2

The calculated lipophilicity

#	iLOGP	XLOGP3	WLOGP	MLOGP	Silicos-IT	Consensus
2	2.42	3.60	3.59	4.21	2.20	3.20
9	2.79	3.59	2.57	4.21	2.34	3.10
13	2.90	3.78	2.59	3.66	2.40	3.06
8	2.46	3.53	2.46	4.09	2.30	2.97
11	2.82	3.15	1.87	3.99	2.36	2.84
4	2.63	3.40	2.18	3.97	1.88	2.81
5	2.53	3.40	2.18	3.97	1.88	2.79
3	2.43	3.34	2.07	3.84	1.84	2.70
1	2.46	3.08	1.72	3.57	1.70	2.51
7	2.46	2.90	1.81	3.57	1.68	2.48

Continuation of the table 2

#	iLOGP	XLOGP3	WLOGP	MLOGP	Silicos-IT	Consensus
10	2.08	2.55	1.51	3.03	1.18	2.07
12	1.99	2.43	1.50	3.22	1.07	2.04
6	1.78	2.24	1.11	2.97	0.60	1.74
Tedizolid	2.46	1.39	1.44	0.93	1.07	1.46

iLOGP relies on Gibbs free energy of solvation calculated by GB/SA in water and *n*-octanol [9, 10] and its optimal range is from −3.93 to 6.46. Considering MLOGP, it should be < 4.15, and XLOGP3 between − 0.7 and + 5.0 [11, 12]. So, only substances 2 and 9 had violations with MLOGP > 4.15, and XLOGP3 > 3.5, while 8 and 13 had violation only of XLOGP3. While 6, 10, and 12 results were closest to Tedizolid data.

Afterwards water solubility (log S) of compounds was also found (Table 3).

Table 3

The calculated water solubility with Silicos-IT log P decreasing

#	ESOL	mg/ml; mol/l	S*	Ali	mg/ml; mol/l	S*	Sili-cos-IT	mg/ml; mol/l	S*
Tedizolid	-3.21	2.26e-01; 6.11e-04	S	-3.23	2.21e-01; 0.000596	S	-4.33	1.71e-02; 4.62e-05	M
6	-3.51	9.08e-02; 3.09e-04	S	-3.83	4.37e-02; 0.000149	S	-4.16	2.04e-02; 6.95e-05	M
10	-3.71	5.43e-02; 1.94e-04	S	-3.79	4.53e-02; 1.62e-05	S	-4.82	4.22e-03; 1.51e-05	M
12	-3.69	6.26e-02; 2.04e-04	S	-4.02	2.91e-02; 9.45e-05	M	-4.76	5.37e-03; 1.75e-05	M
7	-3.86	3.61e-02; 1.37e-04	S	-3.73	4.92e-02; 1.87e-05	S	-5.40	1.05e-03; 3.97e-06	M
1	-3.98	2.78e-02; 1.06e-04	S	-3.92	3.20e-02; 1.21e-05	S	-5.18	1.73e-03; 6.58e-06	M
11	-4.11	2.22e-02; 7.73e-05	M	-3.99	2.95e-02; 1.03e-05	S	-5.48	9.60e-04; 3.34e-06	M
3	-4.27	1.54e-02; 5.42e-05	M	-4.19	1.85e-02; 6.53e-05	M	-5.40	1.12e-03; 3.94e-06	M
4	-4.58	8.64e-03; 2.63e-05	M	-4.25	1.86e-02; 5.65e-05	M	-5.62	7.89e-04; 2.4e-06	M
5	-4.58	8.64e-03; 2.63e-05	M	-4.25	1.86e-02; 5.65e-05	M	-5.62	7.89e-04; 2.4e-06	M
2	-4.49	1.03e-02; 3.24e-05	M	-4.46	1.11e-02; 3.51e-05	M	-5.66	6.96e-04; 2.19e-06	M
8	-4.44	1.07e-02; 3.61e-05	M	-4.38	1.23e-02; 4.14e-05	M	-6.00	2.94e-04; 9.89e-07	P
13	-4.40	1.16e-02; 3.97e-05	M	-4.64	6.64e-03; 2.28e-05	M	-6.20	1.83e-04; 6.3e-07	P
9	-4.76	6.00e-03; 1.75e-05	M	-4.44	1.23e-02; 3.59e-05	M	-6.22	2.08e-04; 6.08e-07	P

S – soluble, M – moderately soluble, P – poorly soluble.

Its known, that a drug, meant for parenteral usage, has to be highly soluble in water to deliver a sufficient quantity of active ingredient in the small volume of the pharmaceutical dosage form. A qualitative estimation of the solubility class is given according to the following ESOL model log S scale (insoluble < − 10 < poorly < − 6 < moderately < − 4 < soluble < − 2 < very < 0 < highly soluble) [13]; and the second one is Ali scale (insoluble < -10 poorly < -6, moderately < -4 soluble < -2 very < 0 < highly) [14]. The third one of Swiss ADME was developed by Silicos-IT (insoluble < -10 poorly < -6, moderately < -4 soluble < -2 very < 0 < highly) [4]. And for optimal solubility, log S (ESOL) should not exceed 6. Thus, the majority of substances are moderately soluble in water according to this model. And Tedizolid, 6, 10, 12, 7, and 1 are soluble, but 8, 13 and 9 are the less soluble ones.

Afterwards, the pharmacokinetic parameters were calculated (Table 4).

Table 4

The calculated pharmacokinetics

#	Log Kp (skin perm.), cm/s	BBB* perm.	P-gp. 1 substr.	CYP1A2* inhibitor	CYP2C9 inhibitor
13	-5.39	+	No	+	+
8	-5.61	+	+	+	No
3	-5.66	+	+	+	No
2	-5.68	+	+	+	No
1	-5.72	+	+	+	No
11	-5.82	+	No	+	+
9	-5.84	+	No	+	No
7	-5.85	+	+	+	No
4	-5.89	+	No	+	No
5	-5.89	+	No	+	No
10	-6.19	No	+	No	No
12	-6.45	No			
6	-6.50				
Tedizolid	-7.57	No	+	+	No

P-gp - P-glycoprotein 1, BBB - blood-brain barrier,
CYP2D6 - all no, CYP3A4 – only Tedizolid yes, CYP2C19 - only Tedizolid no.

The more negative the log *K*p (with *K*p in cm/s), the less skin permeant is the molecule [15]. So, 13 has the highest skin permeation with Log Kp = -5.39 cm/s and 8 with -5.61 cm/s, so they could be used in ointments. But their low molecular weight and high degree of lipid solubility favor crossing BBB as the majority of the presented compounds. And, Tedizolid and substances 6, 10 and 12 appeared to be the least skin permeant with no BBB permeation.

The permeability glycoprotein 1 (multidrug resistance protein 1 (MDR1) or ATP-binding cassette sub-family B member 1 (ABCB1), cluster of differentiation 243 (CD243)) is an important protein of the cell membrane that pumps many foreign substances out of cells, for instance from the gastrointestinal wall to the lumen or from the brain [16], and protects the central nervous system (CNS) from xenobiotics [17]. And only half of the substances with Tedizolid are substrates of P-gp. 1 (Table 4).

Although there are different routes of drug administration, oral dosing is highly preferred for the patient's comfort and compliance [18]. And substances 10, 6, 12 are the closest to Tetrazolid by pharmacokinetic properties of passive gastrointestinal absorption. While only 10 is substrate for P-gp. 1. Other substances are predicted to have brain access, which is still can be good in case of treatment of the brain infections.

Besides, it's known that a key player in drug elimination through metabolic biotransformation are five major isoforms of cytochrome P450 (CYP) (CYP1A2, CYP2C19, CYP2C9, etc.) [19], to which about 50 to 90% of therapeutic molecules are substrates of. Thus, all investigated substances are inhibitors of CYP2C19, except Tedizolid; all no - for CYP2D6; only Tedizolid for CYP3A4 (Table 4). Substances 6, 10 and 12 are inhibitors of only one cytochrome CYP2C19. For the reference Tedizolid only two cytochromes are also calculated: CYP1A2 and CYP3A4.

The next presented data (Table 5) is drug likeness according to the filters originated from analyses by major pharmaceutical companies aiming to improve the quality of their proprietary chemical collections:

- ✓ Lipinski (Pfizer): MW ≤ 500; LogP ≤ 5; HBA ≤ 10; HBD ≤ 5 [1];
- ✓ Ghose (Amgen): 160 ≤ MW ≤ 480; -0.4 ≤ WLOGP ≤ 5.6; − 0.4 ≤ MR ≤ 130; 20 ≤ atoms ≤ 70 [20];
- ✓ Veber (GSK): Rotatable bonds ≤1 0; TPSA ≤ 140 [21];
- ✓ Egan (Pharmacia): WLOGP ≤ 5.88; TPSA ≤ 131.6 [22];
- ✓ Muegge (Bayer): 200 ≤ MW ≤ 600; −2 ≤ XLOGP ≤ 5; TPSA ≤ 150; rings ≤ 7; carbon atoms > 4; heteroatoms > 1; rotatable bonds ≤ 15; HBA≤10; HBD≤5 [23].

Table 5

Drug likeness

<table>
<tr><th>#</th><th>Lipinski; violation</th><th>Bioavailability Score</th><th>#</th><th>Lipinski; violation</th><th>Bioavailability Score</th></tr>
<tr><td>6</td><td rowspan="7">Yes; 0</td><td rowspan="2">0.56</td><td>8</td><td rowspan="5">Yes; 0</td><td rowspan="7">0.55</td></tr>
<tr><td>12</td><td>10</td></tr>
<tr><td>1</td><td rowspan="5">0.55</td><td>11</td></tr>
<tr><td>3</td><td>13</td></tr>
<tr><td>4</td><td>Ted.</td></tr>
<tr><td>5</td><td>2</td><td rowspan="2">Yes, 1: MLOGP>4.15</td></tr>
<tr><td>7</td><td>9</td></tr>
<tr><td colspan="6">Ghose, Veber, Egan, Muegge for all - Yes</td></tr>
</table>

In the result only substances 2 and 9 had violations of the Lipinski rule of lipophilicity: MLOGP > 4.15 (4.21). All other substances comply with all the mentioned authors rules.

Moreover, the Abbot Bioavailability Score seeks to predict the probability of a compound to have at least 10% oral bioavailability in rat or measurable Caco-2 permeability [24]. And, obtained results of 0.55-0.56 are considered as sufficiently absorbable *via* oral route, with substance 6 and 12 having the best values among all.

And SwissADME Bioavailability Radar displays for a rapid appraisal of drug-likeness (Fig. 3). Six physicochemical properties are taken into account: lipophilicity,

size, polarity, solubility, flexibility, and saturation [5, 25]. It is depicted as a pink area in which the radar plot of the molecule has to fall entirely to be considered drug-like with: lipophilicity: XLOGP3 between −0.7 and+5.0, size: molecular weight between 150 and 500 g/mol, polarity: TPSA between 20 and 130Å^2, solubility: log S not higher than 6, saturation: fraction of carbons in the sp3 hybridization not less than 0.25, and flexibility: no more than 9 rotatable bonds. And it's interesting, that only Tedizolid's and substance's 13 graphs were entirely in the pink area (Fig. 3).

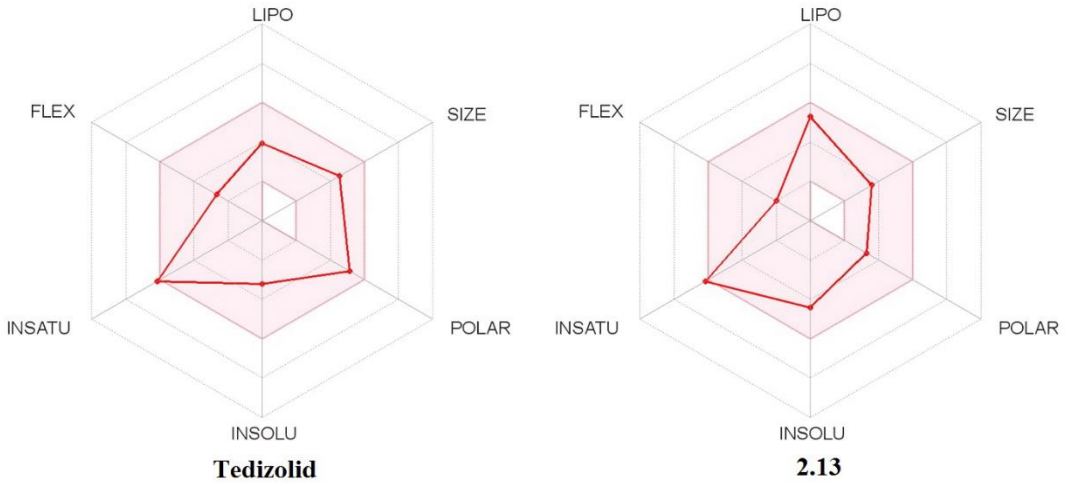

Fig. 3. SwissADME Bioavailability Radar:
lipophilicity, size, polarity, solubility, flexibility and saturation

Considering Medical Chemistry parameters calculations (Table 6), according to the SwissADME Synthetic Accessibility Score (SA), that is based primarily on the assumption that the frequency of molecular fragments in 'really' obtainable molecules correlates with the ease of synthesis: 1 (very easy) to 10 (very difficult) (Table 6).

So, Tedizolid has the most difficult SA among all compounds, still of the moderate level (3.55). All proposed compounds were practically of the same level of SA (3.15-3.38).

Searching for PAINS (pan assay interference compounds, a.k.a. frequent hitters or promiscuous compounds), that are molecules containing substructures showing potent response in assays irrespective of the protein target, there were no alerts for all studied compounds [26]. When analyzing the structural Brenk Alert, consisting of a list of 105 fragments [27] to be putatively toxic, chemically reactive, metabolically unstable, or to bear properties responsible for poor pharmacokinetics, there was only one triple bond detected in the cyano group of substance 11 (Table 6).

Table 6

Medicinal chemistry data

#	Synthetic accessibility	Brenk, alert	Lead likeness; violation
3	3.15	0	Yes; 0
5	3.16		
6	3.19		
7	3.20		

Continuation of the table 6

#	Synthetic accessibility	Brenk, alert	Lead likeness; violation
10	3.20		
4	3.22		
1	3.24		
12	3.25		
11	3.36	1: triple bond	
9	3.23	0	No; 1: XLOGP3>3.5
8	3.25		
2	3.31		
13	3.38		
Tedizolid	3.55		No; 1: MW>350
PAINS, alert for all – 0.			

Considering lead-likeness, only **2**, **9**, **13**, and **8** had violations of lipophilicity XLOGP3 > 3.5 (3.60, 3.59, 3.78, and 3.53 respectively). Moreover, Tedizolid could be excluded from potential studies, too, if to consider its MW > 350. But it still was found to be a potent antimicrobial agent.

Conclusions. Hence, summing up all above-mentioned data, substances **2**, **3**, **8**, **9**, **11**, and **13** had violations of some kind. And 4-(5-methyl-5,6-dihydrotetrazolo[1,5-*c*]-quinazolin-5-yl)phenol (**10**) was the most promising molecule for synthesis and drug purposeful search, along with 4-(5,6-dihydrotetrazolo[1,5-*c*]quinazolin-5-yl)-benzoic acid (**6**) and its 5-methyl analogue **12**, although the two latter permeate the BBB. Therefore, the *in vitro* antimicrobial activity is planned to do as the promising next study stage.

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