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Evaluation of the Lipophilicity of New Anticancer 1,2,3-Triazole-Dipyridothiazine Hybrids Using RP TLC and Different Computational Methods

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Abstract: Two new anticancer-active 1,2,3-triazole-dipyridothiazine hybrids were evaluated for their lipophilicity using thin-layer chromatography (TLC) and computational methods. The experimental lipophilicity was evaluated with mobile phases (mixtures of TRIS buffer and acetone), exploiting a linear correlation between the retention parameter (R_M) and the volume of acetone. The relative lipophilicity parameter (R_{M0}) was obtained by extrapolation to 0% acetone concentration. This parameter was intercorrelated with a specific hydrophobic surface area (*b*) revealing two congeneric subgroups: hybrids of 1,2,3-triazole-2,7-diazaphenothiazines and 1,2,3-triazole-3,6-diazaphenothiazines. The parameter R_{M0} was converted into the absolute lipophilicity parameter $\log P_{TLC}$ using a calibration curve prepared on the basis of compounds of known $\log P$ values. Triazole–dipyridothiazine hybrids turned out to be medium lipophilic with $\log P_{TLC}$ values of 1.232–2.979. The chromatographically established parameter $\log P_{TLC}$ was compared to the calculated lipophilic parameter $\log P_{calcd}$ obtained with various algorithms. The lipophilicity was correlated with molecular descriptors and ADME properties. The new triazole–dipyridothiazine hybrids followed Lipinski's rule of five. The lipophilicity of these hybrids was dependent on the substituents attached to the triazole ring and the location of the azine nitrogen atoms.

Keywords: TLC; lipophilicity parameter $\log P_{TLC}$; anticancer 1,2,3-triazole-dipyridothiazine hybrids; structure–activity relationship; correlation analysis; congeneric classes; Lipinski's rule of five

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1. Introduction

Lipophilicity is one of the most crucial physicochemical properties. It plays a fundamental role in determining absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties, and, therefore, in determining the general appropriateness of drug candidates. There is increasing evidence suggesting that controlling molecular properties, such as lipophilicity, in an optimal range, can improve a drug's quality and its therapeutic success [1]. Lipophilicity is an important parameter because it constitutes the single most informative and successful physicochemical property in medicinal chemistry [2–4]. Lipophilicity contributes to the ADMET characteristics of drugs by contributing to their solubility, permeability through membranes, potency, selectivity, and promiscuity, impacting upon their metabolism and pharmacokinetics, and also affecting their pharmacodynamic and toxicological profile [5,6].

Furthermore, the quantitative structure–activity relationship (QSAR) demonstrated that lipophilicity, evaluated with varied experimental methods, correlates well with other molecular properties (for example, polarity and the dissociation constant) and topological indices, and performs

an essential role in predicting a drug's behavior in a biological system (for example, in tissues and biological membranes) [7–11].

Lipophilicity also belongs to one of the five factors determining the bioavailability of a drug in Lipinski's rule of five criteria. According to this rule, an orally active drug should not violate more than one of the following criterion: no more than 5 hydrogen bond donors, no more than 10 hydrogen bond acceptors, no more than 10 rotatable bonds, a molecular mass less than 500 Da, a lipophilicity parameter (log$P$) not greater than 5, and a polar molar surface area less than 140 Å [1,12,13] (Figure 1). Therefore, the lipophilicity property is recognized to be one of the most significant elements in the rationalization of drug design and discovery.
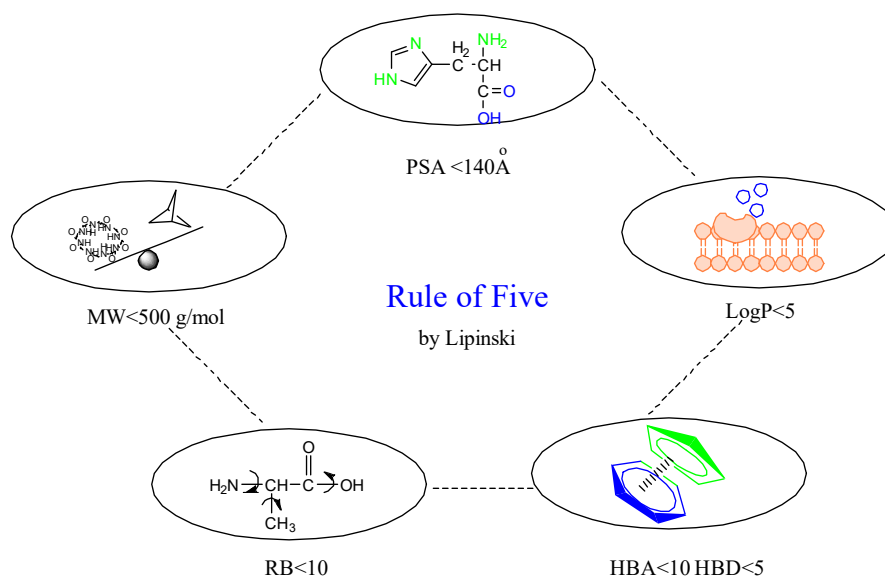

Figure 1. The visual interpretation of Lipinski's rule of five criteria.

Dipyridothiazines (modified phenothiazines where the central thiazine ring is fused with two pyridine rings instead of two benzene rings) have turned out to be attractive scaffolds for new drug candidates, possessing anticancer activity and an improved safety profile. Structurally, dipyridothiazines differ in the tricyclic ring system (the pyridine nitrogen atoms in positions 1,6, 1,8, 1,9, 2,7, and 3,6) and the substituents at the central nitrogen atom (alkyl, dialkylaminoalkyl, cycloalkylaminoalkynyl, amidoalkyl, sulfonamidoalkyl, aryl, heteroaryl, and "half-mustard" groups). Some dipyridothiazines exhibited not only very promising anticancer activity, but also anti-inflammatory, antioxidant, and immunosuppressant activities, with a low toxicity [14–23]. Our previous research showed the relationship between biological properties and the lipophilicity of modified azaphenothiazines [24–27].

Recently, we synthesized a new group of 1,2,3-triazole-dipyridothiazine hybrids, which are derivatives of 2,7- and 3,6-diazaphenothiazines, possessing in vitro anticancer activity against cancer cell lines (breast cancer MDA-MB231, colorectal carcinoma Caco-2, glioblastoma SNB-19, and lung cancer A549) [28].

The main goal of this work was the evaluation of the lipophilicity of two new series of 1,2,3-triazole-2,7-diazaphenothiazine (**1–5**) and 1,2,3-triazole-3,6-diazaphenothiazine (**6–10**) hybrids, performed experimentally by reversed-phase thin-layer chromatography (RP TLC), and theoretically using computer programs. Furthermore, it was interesting to find correlations between experimental and theoretically predicted lipophilicity, and relationships between experimental lipophilicity and physicochemical and ADME properties. This study was performed with the hope of providing a deeper insight into the compounds' properties and their biological activities. The structures of the investigated

1,2,3-triazole-2,7-diazaphenothiazine (**1–5**) and 1,2,3-triazole-3,6-diazaphenothiazine (**6–10**) hybrids are presented in Figure 2.
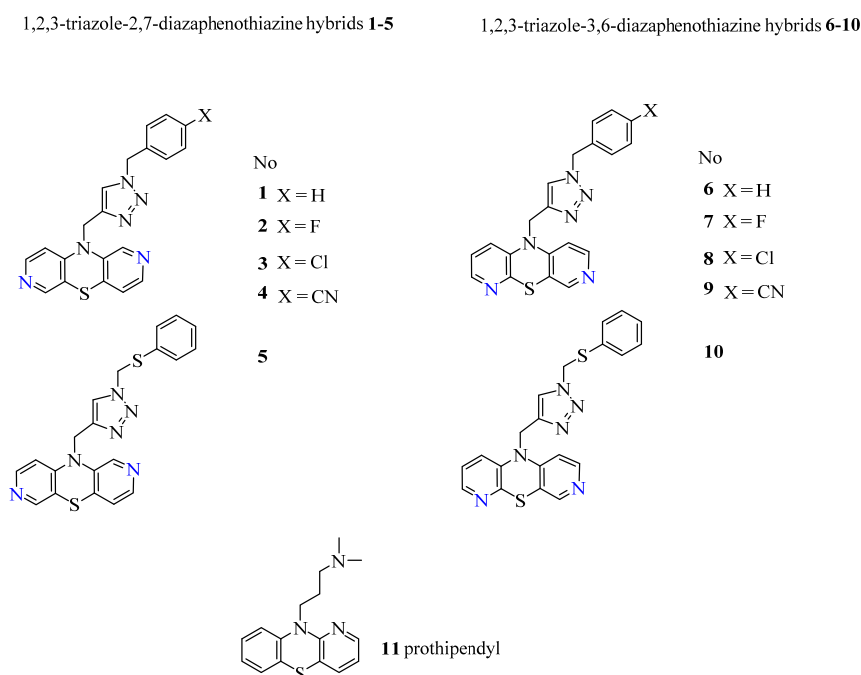

Figure 2. Structure of 1,2,3-triazole-dipyridothiazine hybrids (**1–10**) and prothipendyl (**11**).

2. Materials and Methods

2.1. Materials

1,2,3-Triazole-dipyridothiazine hybrids (**1–10**) were synthesized as described recently [28]. Prothipendyl (**11**) (AWD Pharma, Dresden, Germany) was used (as a free base, 10-dimethylaminopropyl-1-azaphenothiazine) as the reference phenothiazine [24].

2.2. Chromatographic Procedure

TLC was carried out on 10 cm × 10 cm RP 18F$_{254S}$ plates precoated with silica gel (Merck, Warsaw, Poland) by the ascending technique at room temperature. The mobile phase was a mixture of acetone (POCh, Gliwice, Poland) and aqueous TRIS buffer (Fluka, Loughborough, England, pH 7.4, ionic strength 0.2 M) to satisfy physiological conditions with a concentration of acetone of 40–70% (*v/v*) in 5% increments. The investigated compounds (**1–10**), the reference compound (**11**), and the standards (I–V) of known lipophilicity (acetanilide, acetophenone, 4-bromoacetophenone, benzophenone, and anthracene [29,30]) were dissolved in ethanol (POCh, Gliwice, Poland, 2.0 mg/mL) and 2 μL of these solutions were spotted on the plates. The chromatograms were observed under UV light at μ = 254 nm. At least three experiments were carried out for each solution, and R_F values were averaged.

2.3. Computational Programs

Eleven computational programs were employed to calculate the parameter logP_{calcd} using the internet databases VCCLAB [31] and SwissADME [32]. Molecular descriptors (topological polar surface area, molar mass, and refractivity) were calculated using CS Chem 3D Ultra 7.0 [33]. PreAdmet was used for the prediction of biological activities, such as human intestinal absorption (HIA), plasma protein binding (PB), blood–brain barrier (BBB) penetration, cell permeability MDCK, skin permeability (SP), and Caco-2 penetration [34].

3. Results

The lipophilicity of the tested 1,2,3-triazole-dipyridothiazine hybrids (**1–10**) was first evaluated using eleven of the most popular computer programs that are available on the online platforms VCCLAB and SwissADME [31,32]. The computational programs use diverse theoretical approaches, such as atomic, atomic–fragmental, fragmental, topological (relying on a linear relationship with molecular descriptors), hybrid (relying on fragments and topological descriptors), and neural networks (Alogps, AC_Logp, ALOGP, MLOGP, XLOGP2, XLOGP3, ILopP, XlogP, WlogP, MlogP, and SILICOS-IT). These programs are based on advanced mathematical models that are the basis of computational chemistry [31a,b; 32a,b]. The obtained $\log P_{calcd}$ values for hybrids **1–10** were totally distinct, depending on the engaged program ($\log P_{calcd}$ = 1.26–4.88, Table 1).

Table 1. The calculated $\log P_{calcd}$ values for 1,2,3-triazole-dipyridothiazine hybrids (**1–10**) using the internet databases: VCCLAB [31] and SwissADME [32].

No	Alogps	AC_Logp	ALOGP	MLOGP	XLOGP2	XLOGP3	ILogP	XLogP	WlogP	MlogP	SILICOS-IT
1	3.36	2.73	3.89	1.61	2.98	2.83	2.71	2.16	2.26	1.91	2.19
2	3.72	3.34	4.55	2.10	3.61	3.46	3.02	2.79	2.91	2.40	2.82
3	3.31	2.79	4.10	1.99	2.94	4.12	2.78	2.26	2.81	2.29	2.60
4	3.04	2.54	3.77	1.27	2.71	2.55	2.52	1.88	2.13	1.26	2.21
5	3.50	4.88	4.48	1.88	3.41	3.48	2.57	2.81	2.81	2.18	2.28
6	2.98	2.64	3.35	1.61	2.90	2.50	2.47	2.50	3.39	2.37	2.64
7	2.91	2.70	3.56	1.99	3.06	2.60	2.97	2.60	3.95	2.75	3.04
8	2.62	1.63	2.86	2.58	3.63	4.65	3.22	3.13	4.04	2.87	3.27
9	2.90	2.45	3.23	1.27	2.62	2.22	2.40	2.22	3.26	1.73	2.65
10	3.32	4.79	3.94	1.88	3.32	3.14	3.04	2.94	3.88	2.64	2.72

The experimental RP TLC method provided the retention parameter R_M (calculated from the R_F values) using the following equation:

$$R_M = \log(1/R_F - 1).$$

The R_M values decreased linearly, with an increasing concentration of acetone in the mobile phase (r = 0.9744–0.9950). These values extrapolated to 0% acetone gave the relative lipophilicity parameter (R_{M0}) values, which characterize the partitioning between the non-polar stationary and polar mobile phases, using the equation:

$$R_M = R_{M0} + bC,$$

where C is the concentration of acetone. The R_{M0} values are found within the range of 1.150–2.823 (Table 2).

Table 2. The R_{M0}, b (slope), and r values of the equation $R_M = R_{M0} + bC$ for compounds **1–10**.

No	$-b$	R_{M0}	r
1	0.0227	1.229	0.9897
2	0.0198	1.150	0.9788
3	0.0215	1.155	0.9950
4	0.0253	1.274	0.9869
5	0.0426	2.407	0.9831
6	0.0416	2.217	0.9744
7	0.0341	1.867	0.9859
8	0.0492	2.823	0.9853
9	0.0261	1.332	0.9899
10	0.0417	2.388	0.9781

The linear relationship between the relative lipophilicity parameter (R_{M0}) and the slope (b), representing a specific hydrophobic surface area (R_{M0} = Bb + a), enabled us to find congeneric compound subclasses in the set of investigated compounds [35]. In addition, 1,2,3-Triazole-dipyridothiazine

hybrids (**1–10**) belong to two groups of isomeric dipyridothiazines, with the structure of 2,7- and 3,6-diazaphenothiazines. They do not differ significantly in molecular descriptors, but differ in ADME activities (Tables 3 and 4). The range of molar mass (372–406) and molar refractivity (108–116) could indicate the substituent diversity in the tested compounds. All tested derivatives meet the requirements of Lipinski's rule of five.

Table 3. The molecular descriptors and parameters of Lipinski's rule for 1,2,3-triazole-dipyridothiazine hybrids (**1–10**) and prothipendyl (**11**) [32,33].

No	Molecular Mass (M)	H-bond Acceptors	H-bond Donors	Rotatable Bonds	TPSA	Mol Refractivity (MR)
1	372	4	0	4	85.03	108
2	390	4	0	4	85.03	109
3	406	4	0	4	85.03	113
4	397	5	0	4	108.8	114
5	404	4	0	5	110.3	116
6	372	4	0	4	85.03	108
7	390	4	0	4	85.03	109
8	406	4	0	4	85.03	113
9	397	5	0	4	108.8	114
10	404	4	0	5	110.3	116
11	286	2	0	4	44.6	86

Table 4. The predicted ADME activities for 1,2,3-triazole-dipyridothiazine hybrids (**1–10**) and prothipendyl (**11**) [34].

No	BBB	Caco2	HIA	MDCK	PPB	SP
1	0.547	24.769	98.110	94.808	88.062	−3.742
2	0.283	26.146	98.558	3.203	73.476	−4.184
3	0.982	50.735	97.663	34.206	89.739	−3.795
4	0.196	22.382	99.752	30.308	87.208	−3.682
5	0.273	25.465	99.026	4.763	94.100	−3.491
6	0.836	27.476	98.110	74.714	91.502	−3.508
7	1.061	29.803	98.099	12.723	91.532	−3.881
8	1.439	51.402	97.663	33.067	93.582	−3.634
9	0.224	23.546	99.752	25.266	89.391	−3.517
10	0.406	27.037	99.026	4.277	98.907	−3.320
11	3.103	22.684	97.476	18.983	75.453	−3.100

The drugs selected to assess the intestinal absorption of drug candidates needed to use in vitro methods. Among them, the Caco-2 cell [36,37] and the MDCK cell models [38] are approved as reliable models in predicting oral drug absorption. The in silico HIA (human intestinal absorption) model and the skin permeability (SP) model are able to predict and identify drug candidates for oral and transdermal deliveries. Blood–brain barrier (BBB) penetration can provide information on a therapeutic drug in the central nervous system (CNS) and the plasma protein binding (PPB) model on its disposition and efficacy [34,36–38]. The compounds possess high indexes of HIA and PPB, although the indexes of BBB and MDCK (of selected compounds) are low in comparison with prothipendyl. Skin permeability (SP) and penetration of Caco-2 are comparable with the reference compound prothipendyl. The R_{M0} values were correlated with molecular descriptors and ADME activities (Table 5).

Table 5. The correlation of the R_{M0} values with the molecular descriptors and predicted ADME activities for compounds **1–10**.

No	Molecular Descriptor or ADME Activities	Equation	r
1–5	M	$R_{M0} = 69.511M^2 - 240.09M + 579.21$	0.4987
6–10		$R_{M0} = 30.107M^2 - 118.14M + 501.3$	0.6546
1–5	TPSA	$R_{M0} = 17.351TPSA + 69.8$	0.6989
6–10		$R_{M0} = -9.699TPSA + 115.45$	0.4051
1–5	MR	$R_{M0} = 4.235MR + 105.89$	0.6761
6–10		$R_{M0} = 6.099M^2 - 24.708M + 135.43$	0.5020
1–10	BBB	$BBB = 8.8792R_{M0}{}^3 - 22.208R_{M0}{}^2 + 16.225R_{M0} - 0.9889$	0.8769
1–10	Caco-2	$Caco\text{-}2 = 0.002R_{M0}{}^3 - 0.2097R_{M0}{}^2 + 6.9362R_{M0} - 71.729$	0.6545
1–10	HIA	$HIA = -1.1492R_{M0}{}^3 + 340.02R_{M0}{}^2 - 335.35R_{M0} + 0.01$	0.5377
1–10	MDCK	$MDCK = 0.0005R_{M0}{}^3 + 0.0018R_{M0}{}^2 - 0.0583R_{M0} + 2.1802$	0.4144
1–10	PPB	$PPB = -0.0012R_{M0}{}^3 + 0.3263R_{M0}{}^2 - 28.461R_{M0} + 820.96$	0.9145
1–10	SP	$SP = -1.5107R_{M0}{}^3 - 15.909R_{M0}{}^2 - 53.876R_{M0} - 56.38$	0.5870

In order to transform the relative lipophilicity (R_{M0}) values of hybrids **1–10** into the $\log P_{TLC}$ values, the calibration curve was formed under the same chromatographic conditions using a set of standards (I–V), and by having the known literature values of $\log P_{lit.}$ within the range of 1.21–4.45 (Table 6).

Table 6. The R_{M0}, $\log P_{lit.}$, b (slope), and r values of the equation $R_M = R_{M0} + bC$ for standards I–V.

No	$-b$	R_{M0}	r	$\log P_{TLC}$
I	0.018	1.001	0.9979	1.21 (29)
II	0.019	1.501	0.9974	1.58 (29)
III	0.033	2.231	0.9960	2.43 (30)
IV	0.034	2.886	0.9944	3.18 (29)
V	0.044	3.488	0.9964	4.45 (29)

The $\log P_{TLC}$ values for all 10 hybrids are presented in Table 7.

Table 7. The $\log P_{TLC}$ values of investigated compounds **1–10**.

					Compound					
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
$\log P_{TLC}$	1.408	1.330	1.335	1.452	2.569	2.382	2.037	2.979	1.509	2.551

4. Discussion

This report deals with the lipophilicity evaluation of new anticancer-active 1,2,3-triazole-dipyridothiazine hybrids (**1–10**). Both series of dipyridothiazines (2,7- and 3,6-diazaphenothiazines) contain in their structure a ring of 1,2,3-triazole, with various benzyl substituents and a phenylthiomethyl substituent (Figure 2). These compounds possess promising anticancer activities in vitro against cancer cell lines (glioblastoma SNB-19, colorectal carcinoma Caco-2, lung cancer A549, and breast cancer MDA-MB231) and low cytotoxicity towards normal human fibroblasts (NHDF). The results of some additional experiments, such as analysis of the gene expression (*H3*, *TP53*, *CDKN1A*, *BCL-2*, and *BAX*), indicated the induction of mitochondrial apoptosis in cancer cell lines. The most active triazole–dipyridothiazine hybrids were found to be compound **1** against cancer lines Caco-2, A549, and MB231, **5** against A549 and MB231, and **7** against Caco-2 and A549, with IC_{50} values less than 1 μM [28].

The used computer software provided different $\log P_{calcd}$ values depending on the compound's structure (the ring system and substituents) and the engaged program. The most lipophilic compound was derivative **5** ($\log P_{calcd}$ = 4.88), but slightly less lipophilic was isomeric compound **10** ($\log P_{calcd}$ = 4.79), both with the phenylthiomethyl group attached to the triazole ring. The least lipophilic

compound was hybrid **4** (logP_{calcd} = 1.26), whereas its isomer **9** was more lipophilic (logP_{calcd} = 1.73). The graphical visualization of the calculated log$P$ values are presented in Figures 3 and 4. For each compound, large differences were observed, reaching close to 3 units. This makes it impossible to select the adequate values to describe the lipophilic property of new 1,2,3-triazole-dipyridothiazine hybrids.
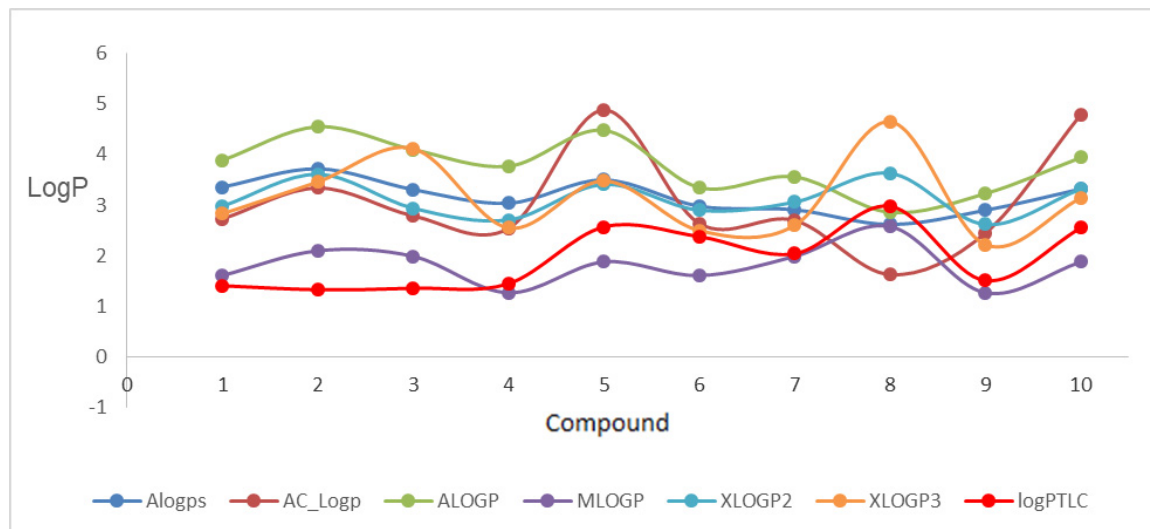

Figure 3. Graphical visualization of calculated log$P$ values (using VCCLAB models) of the tested compounds with a comparison to logP_{TLC}.
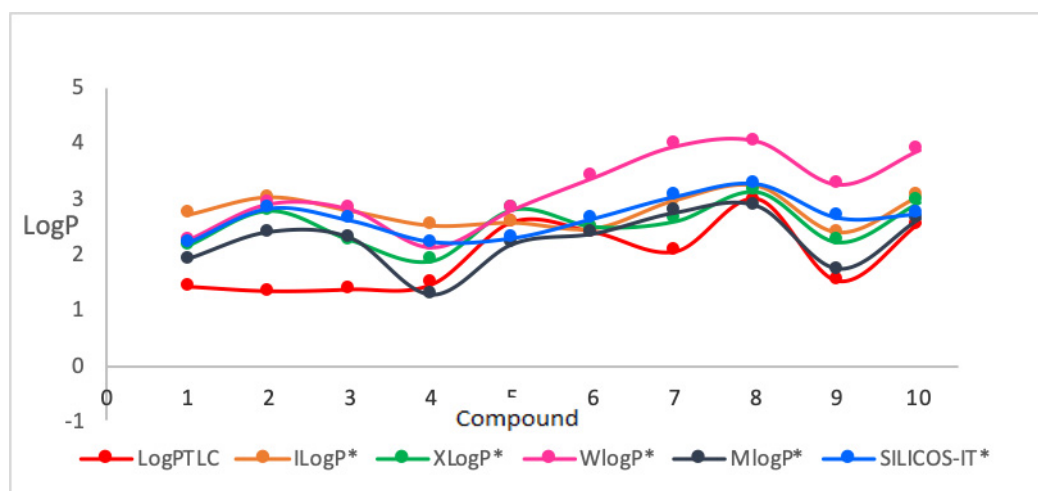
Figure 4. Graphical visualization of the calculated log$P$ values (using SwissADME models) of the tested compounds with a comparison to logP_{TLC}.

The most relative lipophilicity R_{M0} value was shown for the compound **8** (with the *p*-chlorobenzyl substituent in the 1,2,3-triazole ring in 3,6-diazaphenothiazine). In contrast, the 2,7-diazaphenothiazine isomer **4** was among the least lipophilic. The least lipophilic character was exhibited by hybrid **2** (with the *p*-fluorobenzyl substituent) in the series of 2,7-diazaphenothiazines and hybrid **9** (with the *p*-cyanobenzyl substituent) in the series of 3,6-diazaphenothiazines.

The intercorrelation between the relative lipophilicity parameter (R_{M0}) and the specific hydrophobic surface area (*b*) for all compounds (**1–10**) is given by the equation:

$$R_{M0} = -58.95b - 0.1293 \ (r = 0.9915).$$

This relationship indicated the existence of the anticipated congeneric subgroups:

- the 2,7-diazaphenothiazine derivatives **1–5** $R_{M0} = -57.811b - 0.0821$ ($r = 0.9936$)
- the 3,6-diazaphenothiazine derivatives **6–10** $R_{M0} = -63.632b - 0.327$ ($r = 0.9949$)

and was dependent on the places of the azine nitrogen atoms in the diazaphenothiazine structures (positions 2,7 and 3,6).

The values of R_{M0} for diazaphenothiazines (**1–10**) were correlated with molecular descriptors such as molar mass (M), topological polar molar surface area (TPSA), and molar refractivity (MR), giving moderate values of the correlation, which could be a consequence of the non-planar spatial arrangements of the dipyridothiazine ring system, placement of the azine nitrogen atoms, and complex substituents.

Next, the R_{M0} values were correlated with predicted ADME properties, such as blood–brain barrier (BBB) permeability, Caco-2 and MDCK cell base permeability, human intestinal absorption (HIA), plasma protein binding (PPB), and skin permeability (SP). The best correlations were found for the plasma protein binding (PPB) ($r = 0.9145$) and the blood–brain barrier (BBB) penetration ($r = 0.8769$). The correlations of the R_{M0} values with the other ADME parameters were moderate ($r = 0.4144$–0.6545). This fact suggests that the lipophilic property is one of the elements affecting biological activities and behavior during transport through biological tissues.

Comparison of the ADME properties of the tested derivatives (**1–10**) with the reference compound prothipendyl (**11**) (neuroleptic phenothiazine with the pyridobenzothiazine structure) provided valuable information. The tested compounds had substantially lower BBB penetration parameters, which may indicate that they were not be active in the central nervous system. All hybrids showed similar cell permeability (Caco-2) to prothipendyl (with the exception of compounds **3** and **8**), but lower values of skin permeability (SP). The derivatives showed a slightly higher HIA compared with prothipendyl. In contrast, the parameters of PPB and MDCK were very diverse, depending largely on the type of substituent in the 1,2,3-triazole system and the type of dipyridothiazine.

The experimental R_{M0} values, showing relative lipophilic properties, of compounds **1–10** were transformed into absolute lipophilic properties as $\log P_{TLC}$ values. For this purpose, the calibration equation was prepared with the same chromatographic procedure using standards I–V (Table 6) of known $\log P_{lit.}$ values:

$$\log P_{TLC} = 0.9862 R_{M0} + 0.1957 \qquad (r = 0.9949, s = 0.2246, F = 359.97, p = 0.0002).$$

The $\log P_{TLC}$ values for all 10 hybrids were within the range of 1.232–2.979 (Table 7). The most lipophililic compound was hybrid **8** ($\log P_{TLC} = 2.979$), but the least lipophilic character was found for hybrid **9** ($\log P_{TLC} = 1.509$) in the series of 3,6-diazaphenothiazines. In the series of isomeric 2,7-diazaphenothiazines, the most lipophilic nature was showed by hybrid 5 ($\log P_{TLC} = 2.569$), but the least lipophilic compound was hybrid **2** ($\log P_{TLC} = 1.330$). The experimental $\log P_{TLC}$ values were lower than the calculated $\log P_{calcd}$ values. In some cases, the differences between the $\log P_{TLC}$ and $\log P_{calcd}$ values reached over 2 units. Figures 3 and 4 show a visual comparison of the $\log P_{TLC}$ and $\log P_{calcd}$ values.

The investigated 1,2,3-triazole-dipyridothiazine hybrids (**1–10**) turned out to be medium lipophilic. An effort to correlate the lipophilicity of these compounds with their anticancer activity (represented by the IC_{50} values) failed. In the most active compound (**1**) (against three cancer cell lines), there was found the same lipophilicity as compounds **2–4**, which were 5–100 times less active.

The lipophilicity of the new 1,2,3-triazole-dipyridothiazine hybrids (**1–10**) was compared to the lipophilicity of the reference neuroleptic phenothiazine (11) of the pyridobenzothiazine structure. Prothipendyl (**11**) ($\log P_{TLC} = 2.1767$ (24)) turned out to be significantly more lipophilic than the 1,2,3-triazole-dipyridothiazine hybrids (**1–4**) and **9**, but hybrids **5,6,8,** and **10** possessed higher lipophilicity.

Analyzing the five factors determining the bioavailability of the drugs in Lipinski's rule of five (hydrogen bond donors and acceptors, rotatable bonds, molecular mass, lipophilicity, and polar molar

surface area), it can be stated that the tested hybrids (**1–10**) meet the rule of five and may become anticancer drug candidates in the future.

5. Conclusions

In summary, the lipophilicity of 10 new anticancer 1,2,3-triazole-dipyridothiazine hybrids was evaluated theoretically and experimentally using 11 computing programs and reversed-phase thin-layer chromatography. The experimental RP TLC method found these compounds to be medium lipophilic. None of the computing programs provided $\log P_{calcd}$ values that were all similar to the $\log P_{TLC}$ values, which can be ascribed to their specific non-planar dipyridothiazine ring system and complex substituents with the triazole and benzene rings. These triazole–dipyridothiazine hybrids followed Lipinski's rule. The lipophilicity of these hybrids was dependent on the substituents attached to the triazole ring and the location of the pyridine nitrogen atoms.

Finally, to search for relationships between physicochemical and pharmacological properties of the tested hybrids, preliminary QSAR examinations were undertaken. Some correlations between molecular descriptors (M, TPSA, and MR) and ADME activities (BBB, Caco-2, HIA, MDCK, PPB, and SP) and lipophilicity were noted. Further in vitro, in vivo, and in silico investigations are necessary to evaluate the potential pharmacological use of the new 1,2,3-triazole-dipyridothiazine hybrids in anticancer therapy.

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