CORRELATION STUDIES BETWEEN ADMET PROPERTIES, DRUG-LIKENESS SCORES AND MOLECULAR DESCRIPTORS IN A SERIES OF PROTEIN TYROSINE KINASE INHIBITORS

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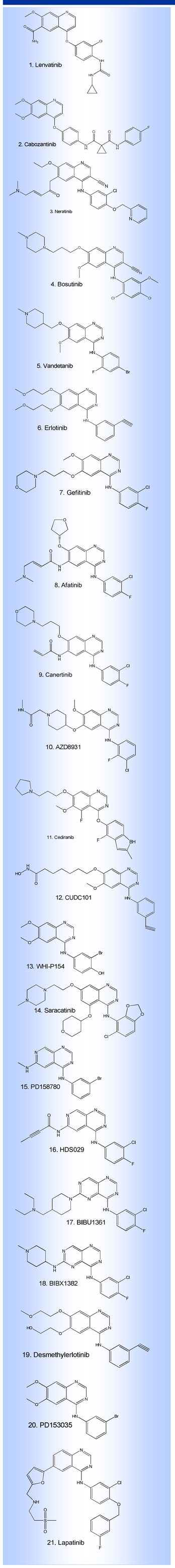

INTRODUCTION AND OBJECTIVES

The design of specific inhibitors of protein tyrosine kinases (PTKI) is important both for fundamental research and for developing therapeutic strategies in treatment of diseases such as cancer. Numerous PTKIs are currently in discovery and preclinical phases. and the number of PTKIs that have been approved for the market. still remains low. The need for early predictions of the possible failure of a drug candidate with the aim of reducing the risk of failure in late stages or after introduction at market is becoming an absolute requirement in drug discovery process from the initial phases of lead candidate development.
In these correlation studies we explored PTKIs molecular descriptors (MDs). drug-likeness (dls) and ADMET parameters that could be relevant for potential target and anti-target profile of investigated PTKIs.

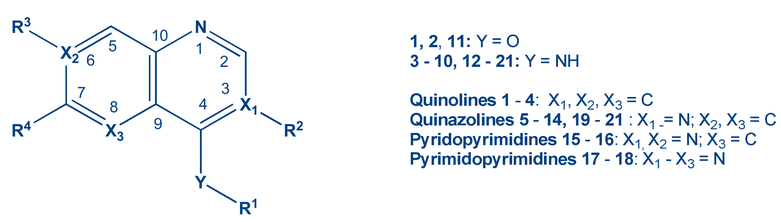

Fig. 1. General structure of PTK inhibitors

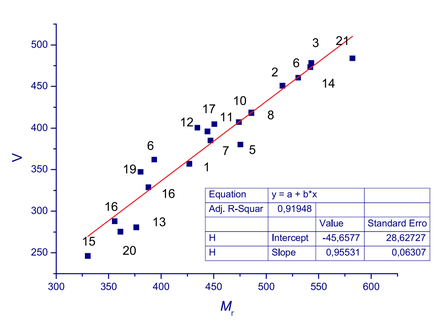

Fig. 3. The relationship between M_r and V

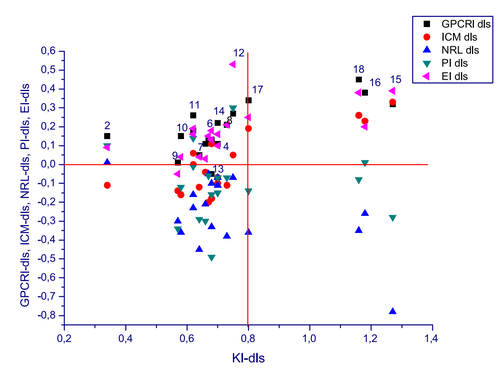

Fig. 2. Relationships between KI-dls and GPCR I-dls. ICM-dls. NRL-dls.PI-dls and EI-dls

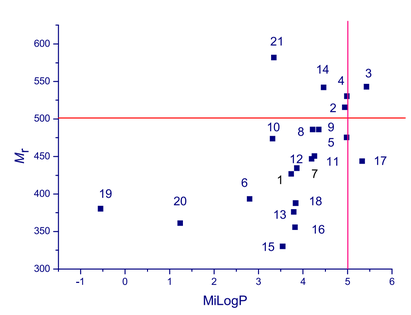

Fig. 4. The relationship between MiLogP and M_r of investigated PTKIs

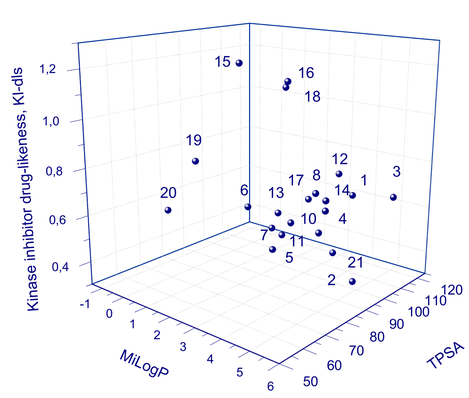

Fig. 5. Relationships between MiLogP. TPSA and KI-dls of investigated PTKIs

Table 1. Computed parameters of investigated PTKIs **1 – 21**

No.	'nib' molecule	miLogP	TPSA	N_a	M_r	N_{ON}	N_{OHNH}	$N_{odst.}$	V	GPCR I-dls	ICM-dls	KI-dls	NRL-dls	PI-dls	EI-dls	*ADMET Risk*	*CYP Risk*	*TOX MUT Risk*	*TOX hERG*
1	Lenvatinib (E7080)	3.735	115.579	30.0	426.86	8	4	0	357.004	0.18	0.00	0.62	-0.23	0.14	0.16	2	1	3	5.476
2	Cabozantinib	4.936	98.790	38.0	515.541	8	2	1	450.893	0.15	-0.11	0.34	0.01	0.10	0.09	6	1	1	5.521
3	Neratinib	5.426	112.407	39.0	543.027	9	2	2	478.18	0.13	-0.20	0.67	-0.05	-0.06	0.15	4	0	3	5.926
4	Bosutinib	4.984	82.889	36.0	530.456	8	1	1	460.597	0.11	-0.07	0.70	-0.07	-0.15	0.10	9	1	4	6.729
5	Vandetanib	4.979	59.517	30.0	475.362	6	1	0	380.22	0.05	-0.12	0.64	-0.45	-0.29	0.04	5	1	4	6.348
6	Erlotinib	2.795	74.747	29.0	393.443	7	1	0	362.06	0.13	0.11	0.68	-0.10	-0.16	0.18	2	1	3	5.502
7	Gefitinib	4.192	68.751	31.0	446.91	7	1	0	385.07	0.11	-0.04	0.66	-0.21	-0.30	0.03	3	0	3	6.398
8	Afatinib	4.215	88.615	34.0	485.947	8	2	0	417.872	0.21	-0.11	0.73	-0.38	-0.07	0.21	5	0	2.5	6.136
9	Canertinib	4.353	88.615	34.0	485.947	8	2	0	418.642	0.01	-0.14	0.57	-0.30	-0.34	-0.05	5	0	3	5.722
10	AZD8931	3.316	88.615	33.0	473.936	8	2	0	407.257	0.15	-0.16	0.58	-0.36	-0.12	0.04	2	0	3	5.746
11	Cediranib	4.253	72.515	33.0	450.514	7	1	0	404.671	0.26	0.06	0.62	-0.16	-0.01	0.19	8	2	3	6.192
12	CUDC101	3.860	105.605	32.0	434.496	8	3	0	400.537	0.27	0.05	0.75	-0.07	0.30	0.53	1	1	3	5.740
13	WHI-P154	3.793	76.507	23.0	376.210	6	2	0	280.528	-0.05	-0.18	0.68	-0.33	-0.49	0.13	2	0	3.5	5.242
14	Saracatinib	4.462	90.457	38.0	542.036	10	1	1	473.244	0.22	-0.10	0.70	-0.11	-0.07	0.16	5	1	4	6.468
15	PD158780	3.542	62.73	20.0	330.189	5	2	0	246.226	0.32	0.33	1.27	-0.78	-0.28	0.39	3	0	4	5.555
16	HDS029	3.82	79.801	25.0	355.76	6	2	0	287.935	0.38	0.23	1.18	-0.26	0.01	0.20	3	1	2	5.144*
17	BIBU1361	5.33	70.071	31.0	443.958	7	1	1	395.976	0.34	0.19	0.80	-0.36	-0.14	0.25	6	2	4	6.769
18	BIBX1382	3.834	78.860	27.0	387.850	7	2	0	328.628	0.45	0.26	1.16	-0.35	-0.08	0.38	5	1	3	6.129
19	Desmethyl-erlotinib	-0.552	86.986	28.0	380.424	7	3	0	347.382	0.17	0.13	0.75	-0.03	-0.12	0.25	1	0	3	5.376*
20	PD153035	1.236	57.524	22.0	361.219	5	2	0	275.361	-0.09	-0.11	0.68	-0.56	-0.54	0.06	3	1	4	5.501
21	Lapatinib	3.343	110.932	40.0	582.077	8	3	1	483.949	-0.04	-0.52	0.36	-0.35	-0.21	-0.08	9	1	1	6.206

METHODS

Molecular descriptors (MD) and drug-likeness (DL) parameters of a series of PTKIs (n = 21) were calculated using Molinspiration property engine v2011.04 and Molinspiration bioactivity score v2011.06.
The ADMET properties were computed by MedChem StudioTM and ADMET PredictorTM 6.0 (Simulations Plus. Inc.. USA). All analyses were performed using OriginPro 8.0 software (Origin Laboratories. USA).

RESULTS AND CONCLUSIONS

Protein tyrosine kinase inhibitors (PTKIs) with basic bicyclic ring systems. *i.e.*. quinoline. quinazoline. pyrido- and pyrimido-pyrimidine derivatives (Fig. 1) were used in this study. The highest scores of kinase inhibitor likeness (KI-dls) were computed for pyrimido[5.4-d]pyrimidin-4-amine and pyrido[3.4-d]pyrimidin-4.6-diamine derivatives (**15 - 18**) (Table 1). MiLogP between 3.545 and 3.834 was computed for these molecules with exception for **17** while TPSA was between 62.730 and 79.801. Study results revealed that molecules with computed high KI-dls (0.80-1.27) also have. to a certain degree. a drug-likeness with GPCR ligand (0.21-0.45). ion channel modulator (ICM-dls) (0.22-0.33) and enzyme inhibitor (EI-dls) (0.21-0.36) (Fig. 2. Table 1).
The KI-dls with lower values (0.36 – 0.74) were computed for quinazoline derivatives (Log P 3.5 – 4.5. TPSA < 60. *M*r < 400) (Table 1).
Significant relationships (r = 0.88691- 0.98726) were obtained between MDs (M_r. V. TPSA) (Fig. 3).
Molecules **2** – **4**. **14** and **21**. as well as **3** and **17** were found as unacceptable according to Lipinski's rule 5 due to *M*r > 500. and MiLogP > 5. respectively.
ADMET properties of PTKIs were analyzed by ADMET Predictor TM 6.0 and these molecules were revealed as CYP 2D6 and CYP 3A4 substrates. with CYP Risk 0 - 2. CYP Code D6. and ADMET Risk 1 - 9. TOX MUT Risk 1 - 4. while all investigated PTKIs were revealed as molecule with high values of TOX hERG Risk (5.114 – 6.789).
The results of this study showed that the most promising PTKI is molecule **16** with high score of KI-dls (1.18). and the lowest predicted values for ADMET Risk (3). CYP Risk (1) and TOX MUT Risk (2).

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