EVALUATION OF SUBSTITUTED UREAS POTENTIAL TOXICITY BY CORRELATION STUDIES USING TOPOLOGICAL INDICES, MOLECULAR DESCRIPTORS AND ADMET PARAMETERS

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INTRODUCTION

The potential toxicity of several cyclic and acyclic urea derivatives (n = 17) (Fig. 1 and Table 1) were evaluated in correlation studies using molecular descriptors (MD), topological indices (TI) and ADMET toxicological parameters. Urea derivatives were synthesized in our laboratories and tested on cell viability on human acute monocytic leukemia THP-1 and human acute T cell leukemia Jurkat cell lines, as well as on the antibacterial activity against three *E. coli strains*, *i.e.*, a strain susceptible to antibiotics (DH5α(*sup*E44Δ*lac*U169 (Θ80*lac* ZΔM15) *hsd*R17 *rec*A1*end*A1 *gyr*A96 *thi*-1 *rel*A1)), a strain resistant to macrolide antibiotics (DH5Δ/pUC18-*ermC'*) and a strain resistant to aminoglycoside antibiotics (BL21(DE3)/pET25b (+)-*sgm* (*F- ompT hsdSB(rBmB-)gal dcm* (DE3)). [1] In this study, the structural features of urea derivatives and the impact of different substituents on their physico chemical, biological and toxicological properties were analyzed.

MATERIAL AND METHODS

Urea derivatives were obtained in our laboratories in the course of synthetic work with reactive hydroxyureas as potential biological active compounds. Topological indices (TIs) were calculated by the software *DRAGON* 6.0, molecular descriptors (MDs) and ADMET parameters were predicted by MedChem StudioTM and ADMET PredictorTM 6.5 (Simulations Plus, Inc., USA). All analyses were performed using OriginPro 8.0 software (Origin Laboratories, USA).

RESULTS AND DISCUSSION

Out of 16 topological indices (TIs) were used in these studies and the best correlations were obtained with: Wiener number (W), Randić number (CID), Randić connectivity index (χ**1**) and information index (ISIZ) with molecular descriptors (Sv – sum of the van der Waals volume scaled on C, M_r - relative molecular mass and MLog P – lipophilicity) (Fig. 2 – Fig. 7). The following correlations were obtained: W vs Mr (R = 0.9464), ISIZ vs MLog P (R = 0.7926), χ**1** vs MLog P (R = 0.7825), CID vs MLog P (R = 0.7797), Mr vs MLogP (R = 0.8761) and MLog P vs Sv (R = 0.8491). The best linear correlation was obtained between MLogP and TOX hERG scores (R = 0.8945, Fig. 7) and between ISIZ and TOX ATTP (Fig. 8), TOX DM (Fig. 9) and TOX hERG (R = 0.8170, Fig. 7) while correlations of TIs and MDs with metabolic activity on THP 1 or Jurkat cell lines were of less significance (Table 2).

ADMET predicted parameters for these compounds are: ADMET risk between 1.0 - 7.0, CYP risk 0.0 - 2.0 and TOX risk between 1.0 - 5.0.

More than 50 % of metabolic activity of both, THP 1 and Jurkat cell lines, were decreased by compounds with MLogP -1 to -2 (**11**, **13** and **14**) and MLogP 3 to 4.5 (**8** and **10**).

According to ADMET Predictor analysis, investigated compounds are mostly CYP 2E1 and CYP 1A2 substrates and CYP 1A2 inhibitors. The main predicted biotransformation pathways with corresponding CYP enzymes and metabolites are displayed in Scheme 1.

CONCLUSIONS

Topological indices (W, CID, χ1 and ISIZ) were successfully used in correlation studies with molecular descriptors (MDs) and ADMET parameters in a series of substituted urea derivatives. For compounds with the most significant metabolic activity either on THP 1 or Jurkat cell line (*N*-hidroxy- (**13**) and *N*,*N'*-bisbenzyloxy-urea (**8**), *N*-hydroxy- (**11**), *N*,*N'*,*N''*-tribenzyloxy- (**10**) and *N*,*N'*,*N''*-trihydroxy-biuret (**14**) the highest scores for their toxicological parameters were revealed.

The most active compound against *E. coli* strains is *N'*,*N''*,*N'''*–trihydroxy biuret (**14**) which is also among the most active compounds that decrease the metabolic activity of both, THP1 and Jurkat cell lines (**8**, **10**, **11**, **13** and **14**).

These compounds are hydroxyurea (**8** and **13**) and biuret derivatives (**10**, **11** and **14**). In compounds **8** and **10** hydroxamic acid moiety is masked with benzyl substituent, while in compounds **11**, **13** and **14** this functional group is free. It can be assumed that the benzyloxy group in **8** and **10** is removed in the conditions of biological testing and that the recovered hydroxamic acid moiety is responsible for the activity of these compounds.

The MLogP proved to be valuable molecular descriptor in these correlation studies and it seems that the lipophilicity, in addition to hydroxamic acid moiety, plays an important role in biological activity of investigated compounds.

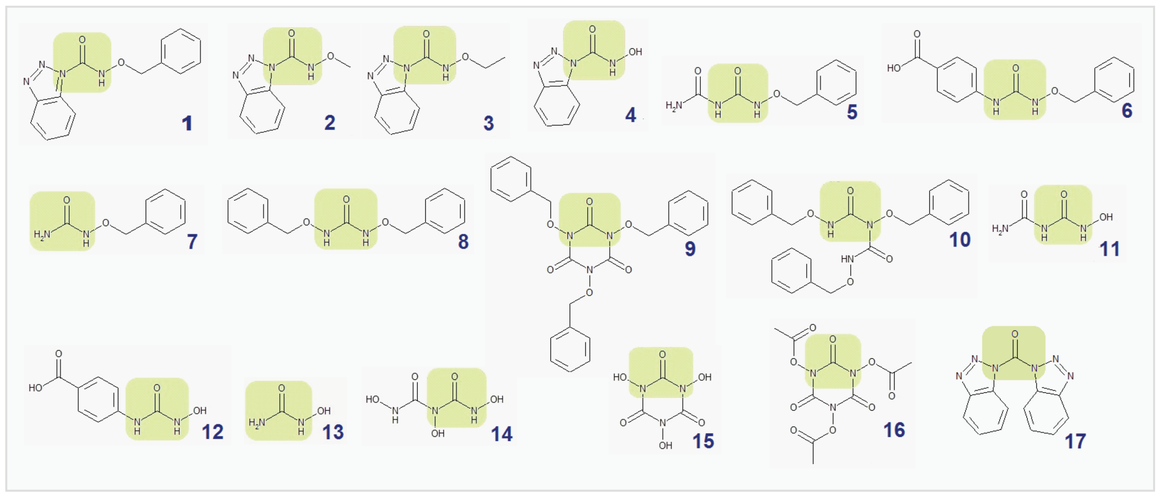


Fig. 1. Chemical structures of investigated compounds **1** - **17**

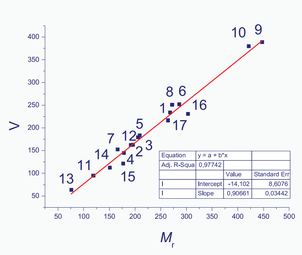


Fig. 2

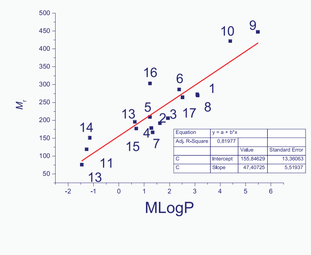


Fig. 3

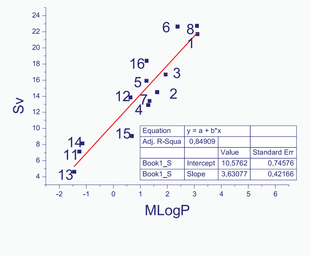


Fig. 4

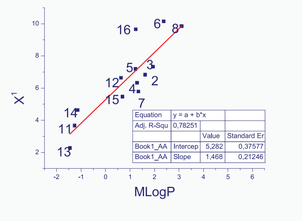


Fig. 5

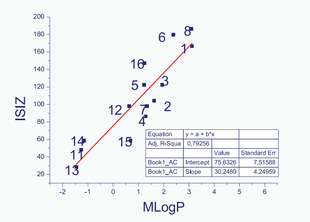


Fig. 6

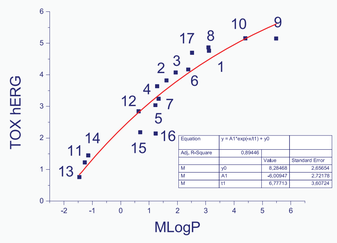


Fig. 7

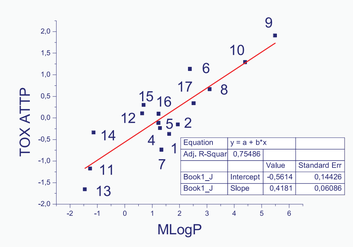


Fig. 8

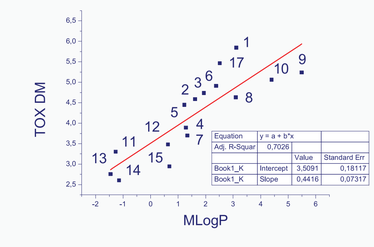
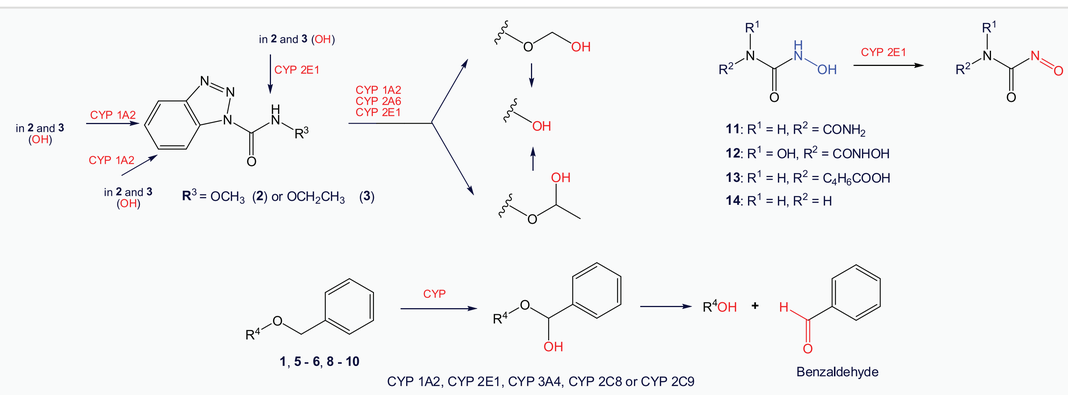


Fig. 9

Table 2

Descriptor	R	
	Metabolic activity on	
	JURKAT cell line	THP-1 cell line
CID	0,783	0,690
χ1	0,780	0,679
XMOD	0,717	0,668
VRA1	0,791	0,691
BID	0,741	0,687
Sv	0,860	0,600
Se	0,836	0,629



Scheme 1. Predicted biotransformation pathways of synthesized compounds

Table 1. Computed molecular descriptors (MD and topological indices (TI), evaluated biological activities and predicted ADMET parameters for compounds 1 - 17

No.	MLogP	TPSA	N_a	M_r	n_{ON}	n_{OHNH}	V	Effect on metabolic activity of THP1 cell lines, %	Effect on metabolic activity of Jurkat cell lines, %	S-absn Risk	ADMET Risk	CyP Risk	Tox MUT Risk	TOX Risk	TOX FHM	TOX ATTP	TOX DM	TOX BCF	TOX hERG	TOX Rat	TOX BRM Rat	TOX BRM Mause	Sv	Mv	Se	Me	W	CID	Wap	BID	χ1	χMOD	ISIZ	GGI 1	JGI1	VRA1	VRA2
1	3.118	69.05	20	268.276	6	1	233.671	-15.75±6.88	-18.89±8.34	0	2	0	5	2	0.114	-1.073	5.842	6.582	4.756	936.869	2.061	246.122	21.69	0.66	33.54	1.02	761	39.183	5842	20.256	9.843	62.537	166.465	2.5	0.11	21.442	1.072
2	1.623	69.05	14	192.178	6	1	162.022	-35.00±8.11	3.89±5.89	0	2	0	5	2	0.906	-0.371	4.586	3.150	3.823	416.908	4.653	202.491	14.49	0.63	23.77	1.03	297	28.301	1553	14.401	6.826	44.638	104.042	2	0.133	14.433	1.032
3	1.940	69.05	15	206.205	6	1	178.823	-38.56±4.11	-4.55±1.78	0	4	0	5	4	0.493	-0.151	4.736	3.327	4.072	450.287	3.798	235.722	16.69	0.62	26.65	1.03	375	30.302	1842	15.361	7.326	47.431	122.21	2	0.125	15.443	1.03
4	1.289	80.044	13	178.151	6	2	144.493	54.55±5.71	24.37±1.67	0	3	0	5.5	3	0.666	-0.239	3.890	1.917	3.637	706.527	7.720	239.085	12.9	0.64	20.89	1.04	233	26.3	1298	13.445	6.326	41.242	86.439	2	0.143	13.444	1.034
5	1.230	93.453	15	209.205	6	4	183.09	-4.61±4.38	-5.62±8.87	1	3	1	4	1	212.069	-0.117	4.447	0.749	3.036	1619.147	4.046	453.428	15.91	0.61	26.82	1.03	450	29.364	902	15.272	7.182	46.395	122.211	3	0.200	14.497	0.966
6	2.381	87.658	21	286.287	6	3	252.028	-12.81±4.99	-66.18±4.87	1	3	1	2	0	9.675	1.135	4.909	1.746	4.165	1954.319	41.243	784.108	22.62	0.65	35.81	1.02	1164	42.123	3685	21.212	10.148	64.482	179.525	4	0.182	21.47	1.022
7	1.340	64.355	12	166.18	4	3	152.505	-3.16±8.44	-8.85±8.09	0	1	0	3	1	111.048	-0.738	3.695	1.318	3.241	1562.180	7.852	232.619	13.4	0.61	22.39	1.02	233	23.54	522	12.341	5.788	37.046	98.108	2	0.167	11.507	0.959
8	3.101	59.593	20	272. 304	5	2	250.813	-81.87±7.78	-96.95±14.55	0	3	1	3	2	0.231	0.665	4.629	4.818	4.869	1553.129	2.278	193.475	22.71	0.63	36.37	1.01	1065	40.408	3089	20.208	9.843	62.546	186.117	2.5	0.119	20.478	1.024
9	5.490	93.717	33	447.447	9	0	388.681	1.44±10.89	-0.81±4.21	2	7	2	3	2	0.004	1.909	5.240	212.560	5.147	3677.957	12.325	111.778	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
10	4.398	89.136	31	421.453	8	2	379.776	-98.29±2.34	-90.45±4.21	2	7	2	4	3	0.021	1.290	5.058	6.885	5.156	1577.239	1.766	106.769	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
11	-1.261	104.447	8	119.08	6	5	94.713	-86.63±8.31	-73.93±10.09	2	4	0	5	2	852.505	-1.174	3.302	0.714	1.222	1994.088	20.463	495.455	7.11	0.55	14.17	1.09	71	14.497	71	8.479	3.664	25.1	48.106	2.5	0.357	6.547	0.818
12	0.636	98.652	14	196.162	6	4	162.851	-22.80±9.31	-41.60±4.45	1	4	0	3	3	336.720	0.104	3.482	1.102	2.842	3858.747	132.230	662.003	13.83	0.63	23.16	1.05	383	27.247	768	14.327	6.63	43.186	98.108	3.5	0.25	13.474	0.962
13	-1.453	75.349	5	76.055	4	4	63.327	-94.16±12.12	-99.03±9.89	1	4	0	4	3	488.482	-1.657	2.756	9.939	0.762	1825.077	51.679	332.364	4.61	0.51	9.74	1.08	18	8.697	18	5.75	2.27	15.751	28.529	1.5	0.375	3.609	0.722
14	-1.144	122.118	10	151.078	8	5	112.244	-80.42±10.76	-92.88±4.23	2	4	0	5	2	65.638	-0.336	2.603	0.894	1.449	5494.034	122.992	577.367	8.14	0.54	16.83	1.12	125	18.311	125	10.437	4.629	32.66	58.603	2.5	0.278	8.511	0.851
15	0.689	126.699	12	177.072	9	3	121.149	-1.31±6.65	-54.01±10.11	0	3	0	5	3	3.000	0.300	2.945	1.720	2.18	2066.471	453.117	1146.117	9.05	0.6	17.27	1.15	174	22.897	486	12.49	5.464	38.115	58.603	3	0.25	11.445	0.954
16	1.236	144.93	21	303.183	12	0	230.683	18.81±6.78	-7.42±9.56	1	4	0	4	3	0.005	0.097	6.302	7.685	2.137	3838.058	327.770	960.161	18.38	0.61	32.9	1.1	870	40.479	2097	21.29	9.646	65.4	147.207	6	0.286	20.424	0.973
17	2.518	78.507	20	264.248	7	0	216.528	-	-	0	7	2	5	5	0.029	0.339	5.464	8.189	4.70	695.795	3.704	10.585	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Reference

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