QSAR STUDIES ON ANTIMICROBIAL ACTIVITY OF BENZOXAZINDIONE ANALOGUES

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INTRODUCTION

Recently, different benzoxazindione analogues were investigated for their antiviral, antiallergic and tocolytic oxytocin receptor activities. The benzoxazinone analogue efavirenz, *i.e.* 6-chloro-4-(cycloprophylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one, was approved as antiretroviral drug, a non-nucleoside type of reverse transcriptase inhibitor.

In extension of our previous QSAR studies using topological indices, TIs (W, χ1, J), the QSAR of 1,4-benzoxazin-2,3-dione (**1** - **35**) and 3,1-benzoxazin-2,4-dione (**36** – **62**) analogues (Table 1) were explored using 67 different computed molecular descriptors (MDs) and experimentally obtained parameters (MIC) for antimicrobial activity against 7 microorganisms (Table 2).

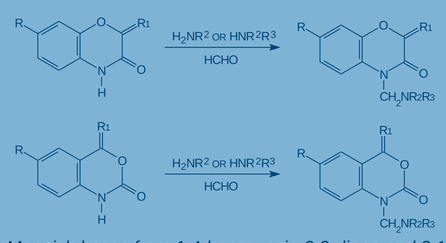


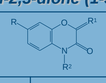
Figure 1. *Synthesis of N-Mannich bases from 1,4-benzoxazin-2,3-dione and 3,1-benzoxazin-2,4-dione*

METHODS

The biological activity were evaluated using G(+) and G(-) test bacteria (Table 2) and *Candida monosa*. In this study additional TIs and other MDs (Table 3) were explored (CID, χ^1, χMOD, VRA1, BID, Sv, Se and ALOGP,...) using multiple linear regression analysis.

Molecular descriptors were calculated with DRAGON® software, and multiple regression analyses using OriginPro 7.5®.

Table 1. ***Chemical structures of 1,4-benzoxazin-2,3-dione (1-35) and 3,1-benzoxazin-2,4-dione (36-62)***



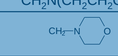
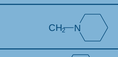
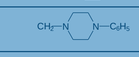
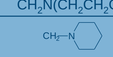
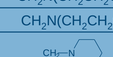
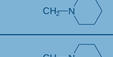
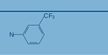
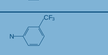
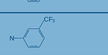
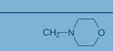
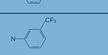
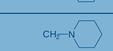
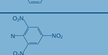
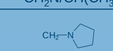
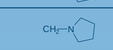
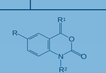
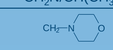
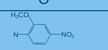
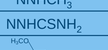
N_0	R	R^1	R^2
1	H	O	$CH_2NHCH_2CH_2OH$
2	H	O	$CH_2N(CH_2CH_2Cl)_2$
3	H	O	
4	H	NO_2	
5	H	O	
6	H	$NNHCH_3$	H
7	H	$NNHCH_3$	$CH_2N(CH_2CH_2OH)_2$
8	H	$NNHCH_3$	
9	H	$NNHCOCH_3$	H
10	H	$NNHCOCH_3$	$CH_2NHCH_2CH_2OH$
11	H	$NNHCOCH_3$	$CH_2N(CH_2CH_2OH)_2$
12	H	$NNHCOCH_3$	$CH_2N(CH_2CH_2Cl)_2$
13	H	$NNHCOCH_3$	
14	H	$NNHCOCH_3$	
15	H		H
16	H		$CH_2N(CH_2CH_2OH)_2$
17	H		
18	H		
19	H		H
20	NO_2	O	H
21	NO_2	O	CH_2NHCH_2COOH
22	NO_2	O	$CH_2NHCH_2COOC_2H_5$
23	NO_2	O	$CH_2NHCH_2CONH_2$
24	NO_2	O	$CH_2NHCH_2CH_2CH_2COOH$
25	NO_2	O	$CH_2NHCH(COOH)CH(CH_3)_2$
26	NO_2	O	$CH_2NHCH(COOH)CH_2CH(CH_3)_2$
27	NO_2	O	$CH_2NHCH(COOH)CH(OH)C_6H_5$
28	NO_2	O	$CH_2NHCH(COOH)CH(OH)C_6H_5$
29	NO_2	$NNHCSNH_2$	H
30	H	$NNHCSNH_2$	$CH_2NHCH(COOH)CH(CH_3)_2$
31	H	$NNHCSNH_2$	$CH_2N/CH(CH_3)_2/_2$
32	NO_2	O	$CH_2N/CH(CH_3)_2/_2$
33	NO_2	O	
34	NO_2	$NNHCSNH_2$	
35	NO_2	$NNHCSNH_2$	$NHCH(CH_3)COOH$
			
36	H	O	$CH_2N/CH(CH_3)_2/_2$
37	H	O	
38	H	O	$CH_2N(CH_2CH_2OH)_2$
39	H	N-OH	$CH_2N(CH_2CH_2Cl)_2$
40	H	$NNHCSNH_2$	
41	H	O	$CH_2NHCH_2CH_2OH$
42	H	O	$CH_2N(CH_2CH_2OH)_2$
43	H	O	
44	H	O	
45	H	O	
46	H	O	$CH_2N/CH(CH_3)_2/_2$
47	H	O	$CH_2N(CH_2CH_2Cl)_2$
48	H	O	
49	H	O	CH_2NHCH_2COOH
50	H	O	$CH_2NHCH(CH_3)COOH$
51	H	O	$CH_2NHCH_2COOC_2H_5$
52	H	O	$CH_2NHCH_2CH_2CH_2COOH$
53	H	O	$CH_2NHCH(COOH)CH_2CH_2SCH_3$
54	H	O	$CH_2NHCH(COOH)CH_2CONH_2$
55	H	O	$CH_2NHCH(COOH)CH_2COOH$
56	H		$CH_2NHCH(CH_3)COOH$
57	H	O	H
58	H	O	$CH_2NH(CH_2)_3COOH$
59	H	$NNHCH_3$	H
60	H	$NNHCSNH_2$	H
61	H		H
62	NO_2	O	H

Table 2. ***Minimal inhibitory concentration (MIC) against various bacteria and fungi of investigated compounds***

Compd.	MIC x 10^{-3} mol dm^{-3}						
	SARCINA LUTEA ATCC 9341	*STAPHILOCOCCUS AUREUS* ATCC 56511	*BACILLUS SUBTILIS* ATCC 8236	*KLEBSIELLA PNEUMONIAE* ATCC 10031	*ESCHERICHIA COLI* ATCC 99-1	*ESCHERICHIA COLI* ATCC 0536	*CANDIDA MONOSA*
21	-	3,38	3,38	3,38	1,62		3,38
22	-	3,09	3,09	3,09	1,55		3,09
23	4,8	3,39	3,39	3,39	1,7		3,39
24	-	3,09	3,09	3,09	1,55		1,55
25	-	2,96	2,96	2,96	1,48		2,96
26	-	2,85	2,85	2,85	1,43		2,85
27	-	2,49	2,49	2,49	+		1,25
28	-	2,49	2,49	2,49	1,25		2,49
30	-	2,44	2,44	2,44	1,22		1,22
32	-	3,11	3,11	3,11	2,12		2,12
33	-	3,43	3,43	3,43	1,58		3,43
44	3,28	3,28	-	1,64	-		1,64
49		3,99	-	3,99	-	3,99	
50	3,78	3,78	-	3,78	-	3,78	
51	3,59	3,59	-	3,59	-	3,59	
53	3,08	3,08	-	3,08	-	3,08	
56	1,21	1,21	-	0,6	-	1,21	0,3
60	4,23	4,23	-	2,12	-	4,23	2,12
61	1,6	1,6	-	0,79	-	1,59	0,79
62	2,4	4,8	-	2,4	-	2,4	1,2

Table 3. ***Computed molecular descriptors***

Compd.	Sv	Se	Mv	ZM1v	W	J	CID	BID	χ^1	XMOD	MLOGP	ALOGP	ALOGP2
1	18,02	29,93	0,62	268	512	1,965	34,241	17,337	8,236	53,134	0,736	-0,05	0,003
2	22,11	35,02	65	279,21	789	2,035	40,092	20,297	9,9668	68,909	2,581	2,354	5,539
3	20,62	33,81	0,62	314	670	1,672	39,129	19,326	9,254	59,645	0,897	0,713	0,508
4	21,71	35,37	0,62	282	670	1,672	39,129	19,326	9,254	58,645	1,933	1,942	3,773
5	28,3	44,36	0,64	364	1576	1,316	51,92	25,238	12,22	77,018	2,408	2,655	7,047
6	16,4	26,49	0,63	240	344	2,026	30,225	15,394	7,236	46,492	1,623	0,744	0,554
7	24,8	42,79	0,59	334	1028	2,075	44,132	22,275	10,706	69,253	0,857	-0,214	0,046
8	27,78	41,13	0,6	288	890	1,685	43,169	51,299	10,292	65,354	2,229	1,783	3,177
9	17,91	28,82	0,64	292	514	1,946	34,065	17,333	8,092	52,055	1,466	0,334	0,111
10	22,61	38,02	0,61	344	946	1,978	42,121	21,275	10,13	65,405	0,917	-0,62	0,385
11	26,32	45,11	0,6	386	1334	2,065	47,973	24,252	11,562	74,816	0,698	-0,624	0,389
12	26,7	43,11	0,64	337,21	1334	2,065	47,973	24,252	11,562	81,18	2,678	1,783	3,18
13	24,7	40,57	0,62	366	1031	1,668	44,895	22,283	10,648	67,916	1,793	0,916	0,839
14	26,29	43,46	0,61	340	1174	1,66	47,011	23,27	11,148	70,916	2,043	1,372	1,883
15	22,93	35,7	0,67	454	1196	1,603	46,61	23,261	10,859	69,829	3,871	3,684	13,569
16	31,34	51,99	0,63	548	2473	1,684	60,52	30,213	14,329	92,59	2,869	2,726	7,43
17	31,23	48,78	0,64	534	2240	1,42	59,557	29,224	13,915	89,961	3,236	3,492	12,196
18	31,32	50,3	0,64	502	2240	1,42	59,557	29,224	13,915	89,961	4,225	4,722	22,295
19	24,53	38,36	0,66	432	1345	1,617	48,715	24,253	11,507	74,482	2,539	2,619	6,861
20	14,74	23,61	0,67	388	412	2,037	31,904	16,372	7,503	49,509	1,342	0,799	0,638
21	19,36	32,25	0,65	438	944	1,979	41,79	21,275	9,897	65,443	0,855	0,053	0,003
22	22,55	38,01	0,63	454	1268	1,913	45,781	23,243	10,935	72,002	1,407	0,653	0,426
23	19,84	33,02	0,64	422	944	1,979	4,79	21,275	9,897	65,154	0,449	-0,549	0,301
24	20,96	35,13	0,64	442	1112	1,922	43,791	22,255	10,397	68,443	1,136	0,088	0,008
25	24,15	40,9	0,62	454	1341	2,038	47,463	24,248	11,218	73,325	1,671	1,274	1,622
26	25,75	43,78	0,61	458	1526	2,016	49,468	25,236	11,701	76,224	1,927	1,662	2,764
27	27,06	43,34	0,66	436	2000	1,695	56,262	28,229	13,236	85,904	2,137	1,276	1,627
28	27,06	43,34	0,6	536	2000	1,695	56,262	28,229	13,236	85,904	2,137	1,276	1,627
29	19,3	30,66	0,67	368,445	813	1,986	39,78	20,29	9,397	64,379	1,294	0,917	0,842
30	28,81	47,95	0,62	484,445	2042	2,116	55,345	28,222	13,112	88,194	1,625	1,393	1,939
31	28,46	47,19	0,61	314,445	1292	2,128	47,628	24,259	11,307	74,397	2,435	2,597	6,742
32	25,32	43,1	0,6	388	1138	2,131	45,462	23,271	10,718	69,254	2,668	2,372	5,627
33	21,53	35,36	0,63	382	893	1,684	42,729	21,299	10,059	65,371	1,756	1,381	1,906
34	26,09	42,41	0,64	412,445	1463	1,702	50,611	25,256	11,952	80,24	1,685	1,499	2,248
35	25,51	42,19	0,64	474,445	1680	2,079	51,496	26,234	12,201	82,73	1,105	0,549	0,302
36	27,1	45,91	0,59	300	956	2,207	43,287	22,294	10,015	63,091	3,48	3,402	11,57
37	20,62	33,81	0,62	314	674	1,663	39,127	19,324	9,254	59,645	1,303	1,227	1,505
38	21,73	37,03	0,6	328	794	2,024	40,09	20,295	9,668	62,545	0,936	0,46	0,212
39	23,1	37,12	0,64	293,21	908	2,048	42,121	21,285	10,206	72,824	3,027	2,954	8,728
40	25,18	40,87	0,63	344,445	1194	1,638	47,016	23,266	11,148	74,515	1,195	1,345	1,81
41	19,44	32,8	0,63	390	813	2,002	39,954	20,292	9,541	62,86	1,262	0,358	0,128
42	23,15	39,9	0,61	432	1180	2,062	45,805	23,262	10,973	72,271	1,084	0,345	0,126
43	21,53	35,36	0,63	382	893	1,686	42,727	21,299	10,059	65,371	2,162	1,894	3,588
44	23,13	38,24	0,63	386	1028	1,669	44,843	22,283	10,559	68,371	2,425	2,35	5,525
45	22,04	36,69	0,63	418	1028	1,669	44,843	22,283	10,559	69,371	1,423	1,121	1,257
46	28,52	48,78	0,59	404	1394	2,215	49,002	25,26	11,319	72,817	3,566	3,296	10,863
47	23,53	37,89	0,65	383,21	1180	2,062	45,805	23,262	10,973	78,635	3,074	2,762	7,627
48	29,72	47,23	0,65	468	2177	1,322	57,634	28,215	13,525	86,744	2,933	3,063	9,38
49	17,94	29,37	0,64	334	613	1,931	36,073	18,312	8,592	55,717	1,113	0,673	0,452
50	19,54	32,26	0,63	340	702	1,964	37,898	19,301	9,003	58,135	1,394	1,05	1,103
51	21,13	35,14	0,62	350	866	1,845	40,064	20,269	9,63	62,276	1,666	1,272	1,619
52	21,13	35,14	0,62	342	894	1,788	40,075	2,26	9,592	61,717	1,666	1,029	1,058
53	23,82	39,1	0,63	348,455	1087	1,934	43,92	22,256	10,541	73,398	1,929	1,377	1,897
54	23,46	39,56	0,63	508	1530	2,011	49,466	25,235	11,701	77,09	0,699	-0,302	0,091
55	22,98	38,79	0,64	524	1530	2,011	49,466	25,235	11,701	77,379	1,105	0,3	0,09
56	30,74	49,88	0,64	538	2556	1,638	60,439	30,207	14,312	92,833	2,607	2,765	7,646
57	11,72	17,85	0,69	224	179	2,015	24,352	12,491	5,771	37,005	1,384	1,212	1,469
58	17,94	29,37	0,64	334	613	1,931	36,073	18,312	8,592	55,671	1,519	0,702	0,493
59	14,8	23,61	0,64	230	286	1,991	28,394	14,414	6,809	43,713	1,726	1,052	1,107
60	16,28	24,91	0,68	254,44	436	1,92	32,235	16,349	7,665	51,874	1,277	1,331	1,771
61	22,93	35,48	0,67	422	1188	1,623	46,888	23,264	11,08	71,703	2,696	2,927	8,568
62	13,14	20,72	0,69	328	348	1,996	30,065	15,388	7,075	46,73	1,431	1,106	1,224

Table 4. ***Computed molecular descriptors' legend***

Descriptor	Descriptor name	Descriptor type
W	Wiener W index	topological descriptor
Sv	sum of atomic van der Waals volumes	constitutional descriptor (scaled on Carbon atom)
Se	sum of atomic Sanderson electronegativities	constitutional descriptor (scaled on Carbon atom)
Mv	mean atomic van der Waals volume	constitutional descriptor (scaled on Carbon atom)
ZM1v	first Zagreb index by valence vertex degrees	topological descriptor
CID	Randic ID number	walk and path counts
χ1	connectivity index chi-1 (Randic connectivity index)	connectivity index
XMOD	modified Randic connectivity index	connectivity index
VRA1	Randic-type eigenvector-based index from adjacency matrix	eigenvalue-based index
J	Balaban distance connectivity index	topological descriptor
BID	Balaban ID number	walk and path counts
MLOGP	Moriguchi octanol-water partition coeff (logP)	molecular property
ALOGP	Ghose-Crippen octanol-water partition coeff. (logP)	molecular property
ALOGP2	Squared Ghose-Crippen octanol-water partition coeff. (logP^2)	molecular property

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68th International Congress of FIP, August 29 - September 4, 2008, Basel, Switzerland

RESULTS

2D and 3D Correlations with biological activities against *Staphylococcus aureus*, ATCC 56511

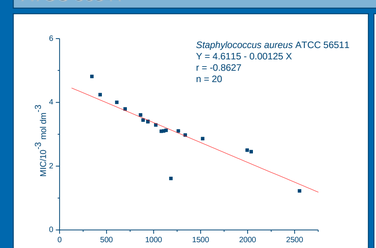

Figure 2. 2D Correlation of Wiener W index and MIC (10^{-3} mol dm^{-3}) against *Staphylococcus aureus* ATCC 56511

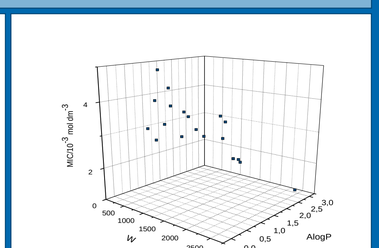

Figure 3. 3D Correlation of Wiener W index, lipophylicity (AlogP) and MIC (10^{-3} mol dm^{-3}) against *Staphylococcus aureus* ATCC 56511

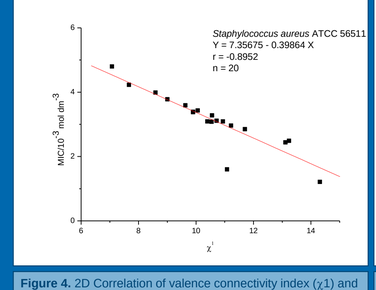

Figure 4. 2D Correlation of valence connectivity index (χ1) and MIC (10^{-3} mol dm^{-3}) against *Staphylococcus aureus*, ATCC 56511

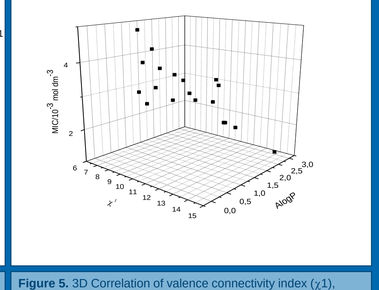

Figure 5. 3D Correlation of valence connectivity index (χ1), AlogP and MIC (10^{-3} mol dm^{-3}) against *Staphylococcus aureus*, ATCC 56511

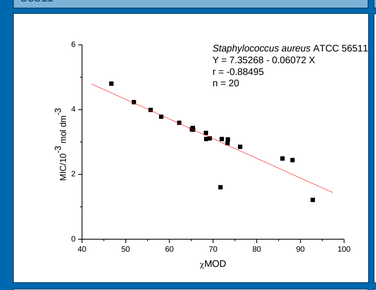

Figure 6. 2D Correlation of modified Randic connectivity index (χMOD) and MIC (10^{-3} mol dm^{-3}) against *Staphylococcus aureus*, ATCC 56511

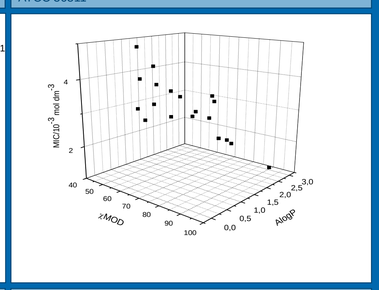

Figure 7. 3D Correlation of modified Randic connectivity index (χMOD), lipophylicity (AlogP) and MIC (10^{-3} mol dm^{-3}) against *Staphylococcus aureus*, ATCC 56511

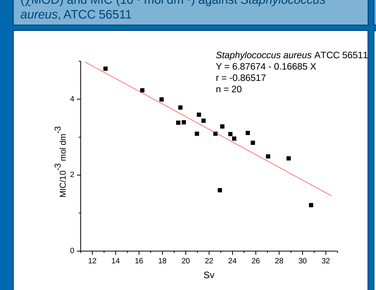

Figure 8. 2D Correlation of sum of atomic van der Waals volumes (Sv) and MIC (10^{-3} mol dm^{-3}) against *Staphylococcus aureus* ATCC 56511

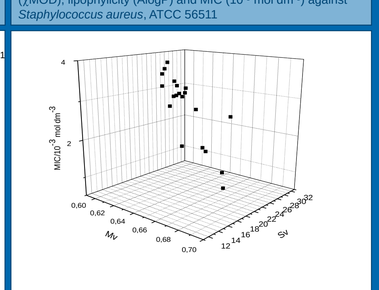

Figure 9. 3D Correlation of sum of atomic van der Waals volumes (Sv), mean atomic van der Waals volume (Mv) and MIC (10^{-3} mol dm^{-3}) against *Staphylococcus aureus*, ATCC 56511

2D and 3D Correlations with biological activities against *Klebsiella pneumoniae*, ATCC 10031

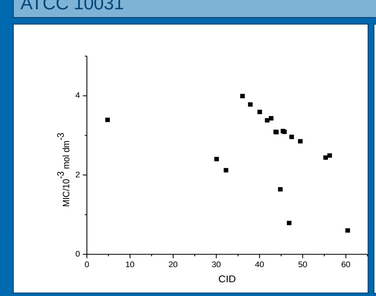

Figure 10. 2D Correlation of Randic ID number (CID) and MIC (10^{-3} mol dm^{-3}) against *Klebsiella pneumoniae* ATCC 10031

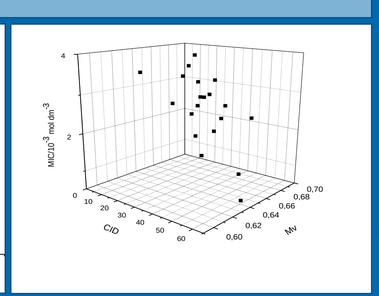

Figure 11. 3D Correlation of Randic ID number (CID), mean atomic van der Waals volume (Mv) and MIC (10^{-3} mol dm^{-3}) against *Klebsiella pneumoniae* ATCC 10031

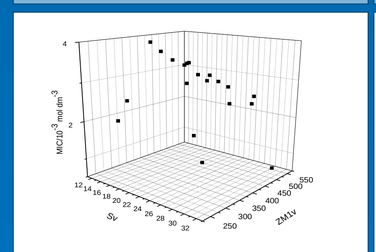

Figure 12. 3D Correlation of sum of atomic van der Waals volumes (Sv), first Zagreb index by valence vertex degrees (ZM1V) and MIC (10^{-3} mol dm^{-3}) against *Klebsiella pneumoniae*, ATCC 10031

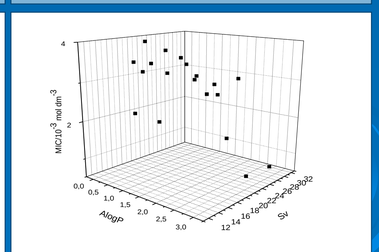

Figure 13. 3D Correlation of sum of atomic van der Waals volumes (Sv), AlogP and MIC (10^{-3} mol dm^{-3}) against *Klebsiella pneumoniae* ATCC 10031

CONCLUSIONS

- Previous 2D QSAR results have shown significant correlation between antimicrobial activity (MIC) and topological indices (TIs)
- Present 2D results are in good agreement with previously obtained.
- 3D QSAR correlations indicate the preference of biological activity prediction on the basis of more than one MD and their influence on particular system, as it is combination of constitutional (Sv, Se,...), topological (W, ZMV1,…), and molecular properties (AlogP, MLogP,...) descriptors.
- 3D correlations allow better spatial dispersion and thus provide an optimal selection of MDs in QSAR study.
- Good correlations in this QSAR study were observed using constitutional (Sv, Mv), topological (W), connectivity (χ1, χMOD), and lipophylicity (AlogP) descriptors with antimicrobial activity (MIC) against *Staphylococcus aureus* ATCC5611
- Suggested method can be useful in prediction of physico-chemical properties and/or biological activity parameters in searching for new lead compound among investigated compounds.

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