COMPUTATIONAL DRUG DESIGN ON ORAL ANTIINFLAMMATORY DRUGS

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ABSTRACT:

In the present work in computational drug design(modelling), constitutive structure activity relationships they perform on some oral anti-inflammatory compounds using statistical work. Using only distance based topological molecular descriptors, we have achieved 99% of correlation; the best molecular descriptor is log Rb, which is highest correlated with W(winer index), Branching(B), connecting (X), Sz(Szeged index). Multi regression analysis has been used as the data processing step for the selection of independent variables.

Tri parametric model is the most appropriate model for designing (modelling) of anti-inflammatory activity log Kinm . Thus shape, size, extent of branching is responsible for computational drug designing (modelling) anti-inflammatory activity log Kinm.

KEYWORDS: QSAR, Molecular descriptors, Anti-inflammatory drug, log Kinm.

INTRODUCTION:

In this study in table 1we discuss the computational drug of a series of good oral anti-inflammatory compounds in chronic pain models. The structure of these compounds is found as below:

significant correlations (Table -5) are presented in Table -4 . The results are discussed below.

RESULTS AND DISCUSSION:

A perusal of Table -2 shows that W, B, χ, J, Sz and log RB goes on increasing with increase in size, shape and extent of branching present in the compound used. However, the corresponding change in Id is not that significant. This shows that the activity (log Kinm) does not depend on the information content of the compound used, meaning thereby better models will be obtained with the same combinations of the distance-based computational Indices used. However, the data presented in Table -3 show that some of the computational indices used have the capability to model log Kinm. Further, the ability of the computational indices: Id, W, B, %, and log RB to model logKinm is identical.

The failure of mono-parametric correlation of the activity with topological indices made us attempt for multi-parametric correlations. We have obtained several such correlations as presented in Table -4 .

A perusal of Table -4 shows that all the six mono-parametric regressions are statistically insignificant. The six biparametric regressions give statistically poor results. Therefore, no bi-parametric models are possible for modelling log

Kinm.

1.Consequently, above we have carried out tri-parametric regressions. Here also we obtained six tri-parametric regressions (Table -4). Out of these six tri-parametric regressions, the regression containing: (i) Id, W, IP3 and (ii) log RB, IP1, IP, gave statistically better models. The model based on the combination of Id, W and IP3 is found as under log Kinm-0.3695 +0.0947 (±0.0685) Id +1.3338 x 10 (± 1.1251x 10) W - 0.3695 (±0.4829) IP3 (table-1).

This model suffers from the defect that in this model the coefficient of IP3 is smaller than its standard deviation. Such models are not statistically allowed. Furthermore, this model has a lower value of R than the other tri-parametric model discussed below. This is another support to detect/neglect the above model expressed by equation (table-1). Another tri-parametric model consisting of log RB, IP, and IP, is found as under: log Kim = -0.2855 +3.6905 x 10 (±0.4 .5581x 10) log RB -1.1771(±0.4212) IP_1 +1.8176 (±0.4223) IP, V-3-2

We have also attempted higher parametric regressions However, none of them resulted in better models. This shows that the tri-parametric model expressed by eq. table-2 is the most appropriate model for modelling tog Kinm.

Conclusion: This model is the best model as it contains log RB as one of the correlating parameters which means

that once again the shape, size, extent of branching is responsible for modelling anti-inflammatory activity, here expressed by log Ki.

Table -1

Structural details, oral anti-inflammatory activity (log Kinm) and molecular indicator parameters for effect of ring substitution on vitro and in vivo activity of a series of phenyl ureas (Chronic pain models)

Compd. No.	R	Human NK1receptor binding Kinm Mean ± SEM (n≥ 3) log Knm	IP1	IP2	IP3
1.	Ph	-0.0555	0	0	0
2.	3-Pyridyl	0.8261	0	0	0
3.	Ph-2No2	-0.7959	1	0	0
4.	Ph-4No2	0	0	0	0
5.	Ph-2CN	0.0414	0	0	0
6.	Ph-3CN	0.6232	0	0	0
7.	Ph-4CN	0.0414	0	0	0
8.	Ph-2F	0.5441	0	0	0
9.	Ph-3F	0.1549	0	0	0
10.	Ph-4F	0.3424	0	0	0

11.	Ph-2CF3	1.2601	0	1	0
12.	Ph-2CO2H	2.2355	0	0	1
13.	Ph-2CO2NH2	0.0969	0	0	0
14.	Ph-3CO2NH2	0.699	0	0	0
15.	Ph-2CO2NHCH3	0.5798	0	0	0
16.	Ph-2CO2N(CH3)2	0.7853	0	0	0
17.	Ph-3CH2OCH3	0	0	0	0
18.	Ph-3CH2OH	0.2304	0	0	0
19.	Ph-2OH	0.415	0	0	0
20.	Ph-2NHCOCH3	0.9823	0	0	0

where IP1 = 1when Ph-2NO2 present in R otherwise 0. IP2 = 1when Ph-2CF3 present in R otherwise 0. IP3 = 1when Ph-2CO2H present in R otherwise 0. Table -2

Topological indices for effect of ring substitution on in vitro and in vivo oral anti-inflammatory activity of series of phenyl ureas (Chronic pain models)

Compd. No.	Id	W	B	X	J	Sz	log RB
1	-3.6882	6199	20.3294	20.3294	1.1144	8259	1534 .0300
2	-3.6882	6330	19.7908	19.7908	1.6233	7091	1504 .6830
3	-3.7489	7460	21.6508	21.6508	1.1245	9793	1806.3460
4	-3.7489	7568	21.6339	21.6339	1.1100	1009	1817.1500
5	-3.7489	7460	21.6508	21.6508	1.1245	9793	1806.3460
6	-3.7311	9361	22.6880	22.6880	1.6291	10320	2104 .7850
7	-3.7311	7096	21.2613	21.2613	1.1110	9410	1720.3990
8	-3.7071	7168	21.2613	21.2613	1.1016	9554	1726.9550
9	-3.7071	6590	20.7401	20.7401	1.1197	8741	1620.4380
10	-3.7071	6626	20.7233	20.7233	1.1143	8831	1624 .3410
11	-3.7071	6662	20.7233	20.7233	1.1092	8885	1627.2920
12	-3.7361	7898	21.9514	21.9514	1.1296	10433	1900.3400
13	-37.728	7941	22.1888	22.1888	1.1244	10476	1905.8050
14	-3.8114	8997	23.0446	23.0446	1.1206	11656	2116.9040
15	-3.8114	9213	23.0779	23.0779	1.0962	11932	2136.4740
16	-3.8114	8997	23.0446	23.0446	1.1206	11507	2116.9040
17	-3.8114	8997	23.0446	23.0446	1.1206	11507	2116.9040
18	-3.7542	7502	21.7781	21.7781	1.1192	9835	1811.4060

19	-3.7542	7502	21.7781	21.7781	1.1920	9835	1811.4060
20	-3.7311	7024	21.2781	2,12,781	1.1211	9266	1713.0450
21	-3.7897	8424	22.5615	22.5615	1.1263	11021	2005.9580

Table -3

Correlation matrix for the correlation of structural parameters (Id, W, B, X, J, Sz, log RB, IP1, IP2, IP3) and oral anti-inflammatory activity (log Kine) for effect of ring substitution on in vitro,in vivo anti-inflammatory activity of series of phenyl ureas (Chronic pain models)

	log Kinm	Id	W	B	X	J	Sz	Log RB	IP1	IP2	IP3
log Kinm	1.0000										
Id	0.14197	1.0000									
W	0.17323	-0.32795	1.0000								
B	0.17749	-0.48221	0.96976	1.0000							
X	0.17749	-0.48221	0.96976	1.00000	1.0000						
J	0.00756	0.68170	0.06256	-0.15766	-0.15766	1.0000					
Sz	0.19214	-0.55234	0.91976	0.97899	0.97899	-0.32719	1.0000				
Log RB	0.18427	-0.39312	0.99317	0.99026	0.99026	-0.43410	0.95610	1.0000			
IP1	-0.44794	-0.04959	-0.04800	-0.01751	-0.01751	-0.06690	-0.02253	-0.03214	1.0000		
IP2	0.30818	-0.04787	0.05337	0.05456	0.05456	-0.05915	0.09856	0.07446	-0.0500	1.0000	
IP3	0.66690	-0.05297	0.06333	0.11147	0.11147	-0.06693	0.10670	0.08066	-0.0500	-0.0500	1.0000

where IP1 = 1when Ph-2NO2 present in R otherwise 0.

IP2 = 1when Ph-2CF3 present in R otherwise 0.

IP3 = 1when Ph-2CO2H present in R otherwise 0.

Table -4

Regression parameters and quality of correlation for the correlation of log Kinm with the molecular descriptor used in multi- parametric correlations

S.No.	Parameters	AI i=1, 2, 3..	Standard error	Constant B	Se	R^2A	R2	R	F-ratio	Q=R/Se	Prob.
	Id	A_1= .0545	0.0871	0.6072	0.6327		0.0202	0.1420	0.391	0.2244	0.5393
	W	$A_1 = 1.0902\times10^{-4}$	1.4219×10^{-4}	-0.4137	0.6296		0.0300	0.1732	0.588	0.2751	0.4527
	B	A_1= 0.1157	0.1472	-2.0914	0.6291		0.0315	0.1775	0.618	0.2822	0.4415
	J	A_1= 0.0308	0.9340	0.3861	0.6392		0.0001	0.0076	1.0862×10-3	0.0120	0.9741
	Sz	$A_1 = 9.8858\times10^{-4}$	1.1584×10^{-4}	-0.5578	0.6273		0.0369	0.1921	0.728	0.3062	0.4040
	log RB	$A_1 = 9.8858\times10^{-4}$	6.9535×10-4	-0.6205	0.6283		0.0340	0.1843	0.668	0.2933	0.4239
	ID IP3	A1 =0.0682 A2 = 1.9309	0.0655 0.4 877	0.5619	0.4753	0.4181	0.4763	0.6901	8.185	1.4519	2.964x 10-4
	W IP3	A_1=8.2770× 10-5	1.0902×10	-0.3021	0.4 817	0.4022	0.4620	0.6797	7.728	1.4110	$3.777\times10_4$ -
1.		A2= 1.8803	0.4946								
2.	B IP3	A_1 = 0.0681 A2= 1.8708	0.1141 0.4997	-1.1461	0.4 846	0.3950	0.4555	0.6749	7530	13927	4 .205×10-4
3.	J IP3	A = 0.2135 A:= 1.9141	0.7149 0.5013	0.0814	0.4 882	0.3861	0.4475	0.6689	7.289	13701	4 .498×10-4
4.	Sz IP3	A1= 6.2965 × 10-5	8.9662×10- 5	-0.2909	0.4 828	0.3995	0.4596	0.6779	7.653	1.4041	3.933 × 10-3
5.	log RB IP3	A1 = 4 .0502 × 10-4 A2 = 1.8738	5.3493 × 10-4 0.4953	-0.4102	0.4 818	0.4021	0.4619	0.6796	7.725	1.4105	3.783 × 10-3

6.	ID W IP3	A1= 0.0947 A2=1.3338×10- 4 A3=0.3695	0.0685 1.1251× 10-4 0.4 829	-0.3695	0.4700	0.4309	0.5163	0.7185	6.04 8	1.5287	5.386 × 10-3
7.	W B IP3	A1 = 3.3301 × 10-4 A2 = -	4 .6255× 10-4 0.4 812	3.6023	0.4912	0.3784	0.4716	0.6868	5.058	1.3982	0.0110
		0.2682 A3 = 1.9393	0.5154								
8.	B J IP3	A1 = 0.075 A2=0.2841 A3=1.8808	0.1182 0.7355 0.5126	- 1.6291	0.4965	0.3650	0.4603	0.6784	4 .832	1.3664	0.0130
9.	J Sz IP3	A1 = 0.417 A2=8.003× 10-5 A3 = 1.8762	0.7619 9.6626 × 10-5 0.5078	-0.9480	0.4925	0.3752	0.4689	0.684 8	5.003	1.3905	0.0115
10.	Sz Log RB IP3	A1 = 2.0932 × 10-5 A2= 5.2467×10^{-4} A3= 1.8773	3.1396 × 10 -4 0.0019 0.5122	- 0.4224	0.4957	0.3671	0.4620	0,6797	4 .867	1.3712	0.0127
11.	log RB IP1 IP3	A1 =3.6905× 10-4 A2= - 1.1771 A3= 1.8176	4 .5581× 10- 4 0.4212 0.4223	- 0.2855	0.4103	0.5662	0.6313	0.7945	9.702	1.9364	5.826 × 10 -4
12.	W B J IP3	A1 =9.0717 A2= -0.8724 A3= - 1.0023 A4=2.0223	0.0011 1.1435 1.7134 0.5444	13.4930	0.5010	0.3534	0.34827	03.6948	3.732	1.3868	00249

13.	J Sz log RB IP3	A1 =4 .0091 A2= 0.0017 A3=- 0.0090 A4=1.7772	3.3194 0.0014 0.0081 0.5122	-4 .3447	0.4 891	0.38 37	0.507 0	0.7120	4 .113	1.4557	0.0176
14.	B J SZ IP3	A1 =- 1.7630 A2= 2.4278 A3=0.0015 A4=1.9767	1.0010 1.3491 8.2461^4 0.4 825	20.6881	0.4646	0.44 39	0.555 2	0.7451	4 .992	1.6037	8.344× 10-5
15.	Sz log RB IP1 IP3	A1 =3.04 83× 10-4 A2= 3.5162×10^{-4}	2.6806× 10-4 0.0016 0.4344	-0.2837	0.4230	0.53 91	0.631 3	0.7945	6.849	1.8783	2.066× 10-5
		A3=- 1.1772 A4=1.8171	0.4376								
16.	log RB IP1 IP2 IP3	A1 =2.9393× 10-4 A2= - 1.1318 A3=0.8965 A4=1.8703	4 .0418× 10-4 0.3728 0.3738 0.3740	- 0.1950	0.3628	0.66 10	0.728 8	0.8537	10.749	2.3531	1.999× 10-5

Table -5

Statistically most significant models for effect on ring substitution on in vitro and in vivo antiinflammatory activity of series of phenyl urea (Chronic pain models)

1. log Kinm = 0.0682 (± 0.0655) Id + 1,9309 (± 0.4877) IP3 +0.5619

2. log Kinm = 8.2770 $\times 10^{-5}$ (± 1.0902$\times 10^{-4}$) W+1.8803 (± 0.4946) IP3 -0.3021

3. log Kinm = 0.0947 (± 0.0685) Id + 1.3338$\times 10^{-4}$ (±1.1251-10^{-4}) W -0.3695 (±0.4829) IP3 -0.3695

4 . log Kinm = 3.6905$\times 10^{-4}$ (±4 .5581$\times 10^{-4}$) log RB –1.1771(±0.4212) IP1 + 1.8176 (±0.4223) IP3 -0.2855

5. log Kinm = 4 .0091(±3.3194) J+0.0017 (0.0014) Sz -0.0090 (±0.0081) log RB + 1.7772 (±: 0.5122) IP3 -4 .3447

6. log Kinm = -1.7630 (± 1.0010) B + 2.4278 (± 1.3491) J+0,0015 (±8.2461$\times 10^{-4}$) Sz + 1.9767 (±: 0.4825) IP3 +20.6881

7. log Kinm 3.0483$\times 10^{-6}$ (± 2.6806x10^{-4}) Sz + 3.5162$\times 10^{-4}$ (± 0.0016) log RB –1.1772 (± 0.4344) IP1 +1.8171(± 0.4376) IP3 - 0.2837

8. log Kinm = 2.9393x10^{-4} (4 .0418x10^{-4} log RB - 1.1318 (± 0,3728) IP1 + 0.8965 (± 0.3738) IP2 + 1.8703 (± 0.3740) IP3 - 0.1950

Table -6

Observed and Estimated log Kinm (using eqns. 4 , 7 and 8, Table -5)

Compd No.	Observed log Kinm	Estimated log Kinm using					
		Model (Eq. 4)		Model (Eq. 7)		Model (Eq. 8)	
		Est	Res.	Est	Res.	Est	Res.
1.	-0.056	0.281	-0.3362	0.281	-0.3364	0.256	-0.3114
2.	0.826	0.270	0.5563	0.267	0.5591	0.247	0.5788
3.	-0.796	-0.796	-2.0000 x10 -13	-0.796	-2.0000 ×10 -13	0.796	-3.0000 x10 -13
4.	0.362	0.385	-0.0234	0.386	-0.0241	0.339	0.0226
5.	0.000	0.381	-0.3812	0.381	-0.3813	0.336	-0.3359
6.	0.041	0.491	-0.4499	0.488	-0.4465	0.424	-0.3823

7.	0.623	0.349	0.2738	0.350	-0.2733	0.311	0.3125
8.	0.041	0.352	-0.3105	0.353	-0.3113	0.313	-0.2712
9.	0.544	0.313	0.2316	0.313	0.2314	0.281	0.2628
10.	-0.155	0.314	-0.4689	0.314	-0.4693	0.282	-0.4373
11.	0.342	0.315	0.0271	0.316	0.0266	0.283	0.0590
12.	1.260	0.416	0.8443	0.416	0.8438	1.260	1.0000×10 -13
13.	2.236	0.236	0.0000	2.236	0.0000	2.236	0.0000
14.	-0.097	0.496	-0.5927	0.496	-0.5931	0.427	-0.5241
15.	0.699	0.503	0.1960	0.504	0.1951	0.433	0.2660
16.	0.580	0.496	0.0840	0.496	0.0841	0.427	0.1526
17.	0.785	0.496	0.2895	0.496	0.2896	0.427	0.3581
18.	0.000	0,383	-0.3830	0.383	-0.3832	0.337	-0.3374
19.	0.230	0.383	-0.1526	0.383	-0.1528	0.337	-0.1070
20.	0.415	0.347	0.0683	0.347	0.0681	0.309	0.1065
21.	0.982	0.455	0.5275	0.455	0.5271	0.395	0.5877