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ORIGINAL RESEARCH

Atomic and molecular parameters-based comparative QSAR study on tetrahydroimidazodiazepinone derivatives

Ahmad Khalid Raza Khan · Sunil Kumar Mishra · Suhail Ahmad Khan · Mohiuddin Ansari

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Abstract The Quantitative Structure Activity Relationship (QSAR) models of 21 tetrahydroimidazodiazepinone (TIBO) derivatives have been made with the help of atomic and molecular properties. The molecular modeling and geometry optimization have been carried out using CAChe software employing semiempirical methods. The values of atomic properties have been calculated by softness calculator, and molecular properties by PM3 method using MOPAC 2002. The study indicates that molecular properties predict the activity of tetrahydroimidazodiazepinone derivatives in a better way as indicated by correlation coefficient values of the QSAR models. In molecular properties, molecular weight in combination with energies of frontier orbitals, electronegativity, and hardness provides better result. The predicted activities as calculated by molecular properties have been found to be very close to the observed activity.

Keywords Tetrahydroimidazodiazepinone · QSAR · Atomic property · Molecular property

Introduction

In our communication, we have made a comparative QSTR study on a series of alcohol derivatives (Singh *et al.*, 2009). In this article, a comparative QSAR study (Singh *et al.*, 2004; Pasha *et al.*, 2005a, b, c) on tetrahydroimidazodiazepinone (TIBO) derivatives is studied. The Quantitative Structure Activity Relationship (QSAR) study is mainly based on two sets of parameters. One is based on the atomic properties (Srivastava *et al.*, 2005; Pasha *et al.*, 2005a, b, c) viz. ionization potential, electron affinity, atomic density, and effective atomic softness, and the other is based on molecular properties (Singh *et al.*, 2003; Pasha *et al.*, 2005a, b, c) viz. heat of formation, molecular weight, total energy, HOMO energy, LUMO energy, absolute hardness, and electronegativity. These two sets of descriptors have been used in deriving regression models. The regression models as obtained by atomic parameters have been compared with those obtained from molecular parameters. The predicted biological activity (PA) as calculated by each set of descriptors has also been compared with observed biological activity (A).

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Theory

The values of atomic and molecular properties have been derived by solving the relevant equations given below:

The softness of an atom in a molecule was described by Singh et al. (Pasha *et al.*, 2006; Singh *et al.*, 1980). The Klopman equation is given by

$$E_n^{\ddagger} = \mathrm{IP}_n - b^2\,(\mathrm{IP}_n - \mathrm{EA}_n) - \left[\chi_s\left(C_s^{\,n}\right)^2 / R_s\right](1 - 1/\epsilon)\left[q_s + 2b^2\,\chi_s\left(C_s^{\,n}\right)^2\right] \quad (1)$$

$$E_m^{\ddagger} = \mathrm{IP}_m - a^2 - (\mathrm{IP}_m - \mathrm{EA}_m) \left[\chi_r\left(C_r^{\,m}\right)^2 / R_r\right](1 - 1/\epsilon)\left[q_r + 2b^2\,\chi_r\left(C_r^{\,m}\right)^2\right] \quad (2)$$

where $E_n^{\ddagger}$ is the softness of Lewis acid, $E_m^{\ddagger}$ is the softness of a Lewis base, ϵ is the dielectric constant of the medium

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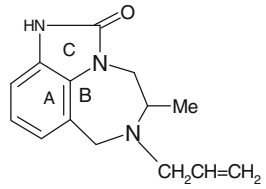
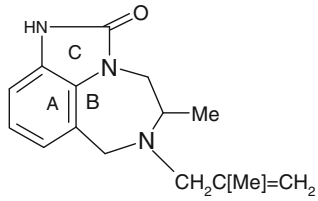
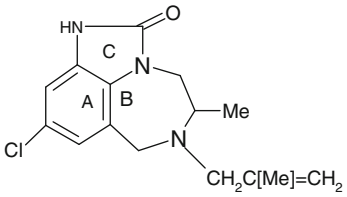
Table 1 TIBO derivatives with their biological activity in terms of EC_{50}



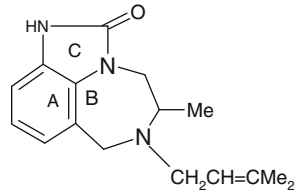
Compound No. 1 EC_{50} = 4.23



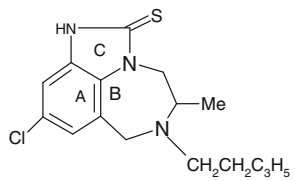
Compound No. 2 EC_{50} = 4.85



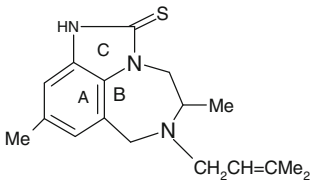
Compound No. 3 EC_{50} = 5.33



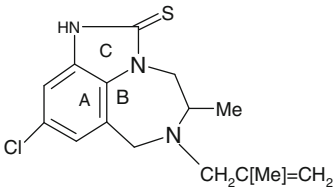
Compound No. 4 EC_{50} = 5.38



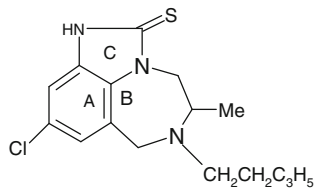
Compound No. 5 EC_{50} = 5.66



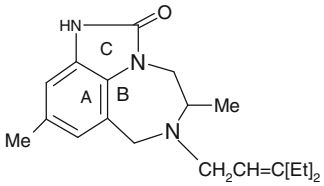
Compound No. 6 EC_{50} = 6.10



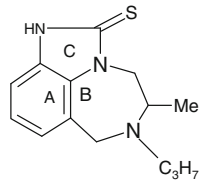
Compound No. 7 EC_{50} = 6.35



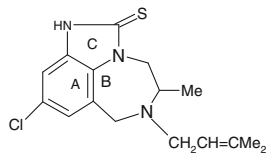
Compound No. 8 EC_{50} = 6.48



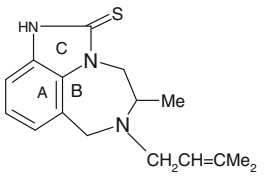
Compound No. 9 EC_{50} = 6.51



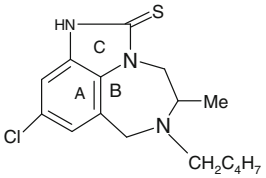
Compound No. 10 EC_{50} = 6.62



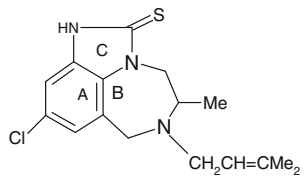
Compound No. 11 EC_{50} = 7.04



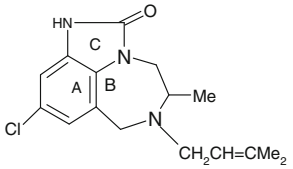
Compound No. 12 EC_{50} = 7.36



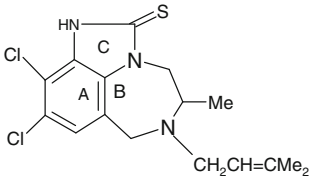
Compound No. 13 EC_{50} = 7.37



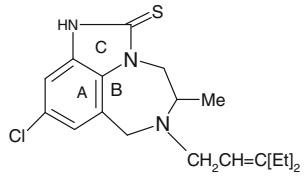
Compound No. 14 EC_{50} = 7.48



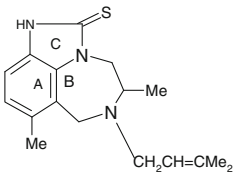
Compound No. 15 EC_{50} = 7.60



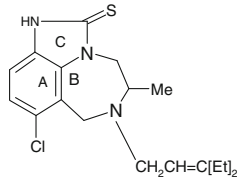
Compound No. 16 EC_{50} = 7.60



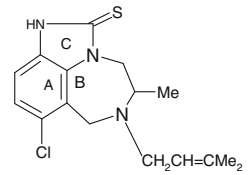
Compound No. 17 EC_{50} = 7.82



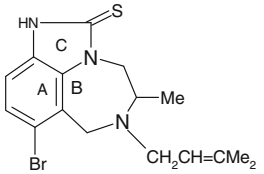
Compound No. 18 EC_{50} = 7.85



Compound No. 19 EC_{50} = 8.29



Compound No. 20 EC_{50} = 8.34



Compound No. 21 EC_{50} = 8.52

in which the reaction is carried out. R, q are the Radius and charge of atom s and r, C is the electron density, χ is $q - (q-1)\sqrt{k}$ and $k = 0.75$, and a, b are the variation parameters defined as $a^2 + b^2 = 1$.

The method for the calculation of ionization potential of an atom in a molecule (IP) has been described by Dewar and Morita (Dewar and Morita, 1999; Cocchi *et al.*, 1992; Hanai *et al.*, 1994; Kourounakis and Bodor, 1995) by the following equation.

$$\mathrm{IP} = a + bq + cq^2 \tag{3}$$

where q is the charge of an atom in a molecule and C is the electron density of an atom in a molecule.

The method for calculation of the electron affinity (Tuppurainen, 1994) of an atom in a molecule (EA) has been described by us earlier as given in Eq. 4

$$\mathrm{EA} = -(\mathrm{eHOMO} + \mathrm{eLUMO}) - (\mathrm{IP}) \tag{4}$$

where HOMO and LUMO are the highest occupied and lowest unoccupied molecular orbitals, respectively.

The method for calculation of the electron density of an atom in a molecule (ρ) has been described by us earlier as given in Eq. 5 (Parr and Yang, 1994)

$$E(\rho) = F(\rho) + \mathrm{d}r\,\rho(r)\,v(r) \tag{5}$$

where $F(\rho) = T(\rho) + V_{ee}(\rho)$, $T(\rho)$ is the electronic kinetic energy functional, $V_{ee}(\rho)$ is the electron–electron interaction energy functional, and $v(r)$ is the external potential.

In QSAR of a chemical system, a more useful quantity is heat of formation (Bodor *et al.*, 1989) of the compound from its elements in their standard state. This is obtained when the energy required for ionizing the valence electrons of atoms involved. The heat of formation is defined as:

$$\Delta H_f^{\circ} = E_{\mathrm{elect}} + E_{\mathrm{nuc}} - E_{\mathrm{isol}} + E_{\mathrm{atom}} \tag{6}$$

where E_{elect} is the electronic energy, E_{nuc} is the nuclear–nuclear repulsion energy, E_{isol} is the energy required to strip all the valence electrons of all the atoms in the system, and E_{atom} is the total heat of atomization of all the atoms in the system.

Total energy (Pauling, 1960; Mulliken, 1934 Parr and Young, 1995) of a molecular system is sum of the total electronic energy, E_{ee} and the energy of internuclear repulsion, E_{nr}. The total electronic energy of the system is given by

$$\mathrm{TE} = E_{ee} + E_{nr} \tag{7}$$

$$E_{ee} = {}^1\!/_2\,P(H + F) \tag{8}$$

where P is the density matrix, H is the one-electron matrix, and F is the Fock matrix.

According to Koopman's theorem, electronegativity and absolute hardness are defined as

$$\chi = -{}^1\!/_2\,(\varepsilon\mathrm{LUMO} + \varepsilon\mathrm{HOMO}) \tag{9}$$

$$\eta = {}^1\!/_2\,(\varepsilon\mathrm{LUMO} - \varepsilon\mathrm{HOMO}) \tag{10}$$

where εLUMO and εHOMO are the frontier orbital energies.(highest occupied molecular orbital energy and lowest unoccupied molecular orbital energy).

Materials and methods

Twenty-one Tetrahydroimidazodiazepinone derivatives that have been taken from literature (Khan *et al.*, 2010), used as study materials and are listed in Table 1 along with their observed biological activity in terms of EC_{50} (the concentration of compound leading to 50% effect and expressed in mol/l or mol/g). The logarithms of the inverse of EC_{50} have been used as biological end point (log1/C) in the QSAR study. Softness calculator that has been developed by us, by solving Klopman equations given in theory, has calculated the atomic parameters of all the compounds for various sites. While the molecular parameters have been calculated using PM3 method by solving the equations give in the theory. For QSAR prediction, the molecular modeling and geometry optimization of all the derivatives have been carried out with CAChe Pro software.

Results and discussion

Tetrahydroimidazodiazepinone derivatives are included in Table 1, along with their observed biological activities in terms of EC_{50} values, as reported by Pauwels et al. The skeleton structure (Fig. 1) of TIBO is based on following parent skeleton, which have 10 sites.

The atomic properties of all the compounds at the various sites are presented in Table 2. The most reactive site as a base will be that site which will have the highest value of $E_m^{\ddagger}$. Similarly, the most reactive site as an acid will be that site which will have the highest value of $E_n^{\ddagger}$. So the highest value of $E_n^{\ddagger}$ and $E_m^{\ddagger}$ of each derivatives has also been tabulated in Tables 3 and 4, respectively. The values of molecular properties of all the derivatives are presented in

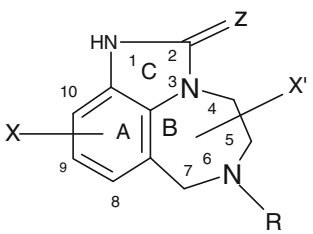


Fig. 1 Parent skeleton of TIBO

Table 2 The values of atomic descriptor of TIBO derivatives at various reactive sites

Compd. no.	Site	Atom	IP	EA	ρ	$E_n^{\ddagger}$	$E_m^{\ddagger}$
1	1	N	18.52295	−9.88017	1.49523	12.43046	11.31648
	2	O	21.19465	−12.5519	1.91724	15.27072	−4.91829
	3	N	17.81905	−9.17627	1.50619	12.07770	9.56649
	6	N	18.78054	−10.1378	1.54170	12.68469	9.12744
2	1	N	18.99339	−10.4769	1.45221	12.55264	15.14833
	2	O	21.54129	−13.0248	1.91804	15.42599	−5.26359
	3	N	18.18565	−9.66917	1.47156	12.16249	11.93646
	6	N	18.44873	−9.93225	1.57160	12.55380	7.11931
3	1	N	18.57437	−9.37824	1.48180	12.56484	12.77617
	2	O	21.01054	−11.8144	1.91708	15.31104	−4.32223
	3	N	17.60974	−8.41361	1.52229	12.14243	9.01248
	6	N	18.43346	−9.23733	1.56188	12.68917	8.18826
	9	Cl	12.98474	−3.78861	1.98162	10.73951	−0.75205
4	1	N	18.45474	−9.85756	1.49753	12.38787	11.01345
	2	O	21.32174	−12.7246	1.91754	15.32786	−5.04345
	3	N	18.19864	−9.60146	1.47456	12.19648	11.86300
	6	N	18.49947	−9.90229	1.56894	12.59411	7.37078
5	1	N	18.12255	−9.21221	1.45593	12.19209	13.11558
	2	S	13.40617	−4.49583	1.91061	10.64279	−0.18487
	3	N	17.06460	−8.15426	1.47564	11.66642	10.13336
	6	N	18.39242	−9.48208	1.57231	12.62380	7.39327
	9	Cl	13.04581	−4.14770	1.98208	10.71125	−0.92913
6	1	N	18.16672	−9.38398	1.45505	12.18198	13.14606
	2	S	13.38567	−4.60293	1.91020	10.59855	−0.24676
	3	N	18.49332	−9.71058	1.56260	12.62006	7.83707
	6	N	17.15027	−8.36753	1.48398	11.69971	9.77012
7	1	N	18.16644	−9.04828	1.45659	12.26908	13.37116
	2	S	13.13525	−4.01709	1.90965	10.54663	1.56999
	3	N	16.99161	−7.87345	1.50646	11.75047	8.85713
	6	N	18.44548	−9.32732	1.55612	12.66080	8.40559
	9	Cl	13.03259	−3.91443	1.98207	10.74880	−0.81497
8	1	N	18.15564	−9.05595	1.45548	12.25622	13.39772
	2	S	13.20912	−4.10943	1.91008	10.58296	−1.88768
	3	N	17.16231	−8.06262	1.48261	11.78231	10.11946
	6	N	18.61142	−9.51173	1.55515	12.74309	8.64245
	9	Cl	13.03626	−3.93657	1.98210	10.74637	−0.82579
9	1	N	18.70179	−10.4318	1.48340	12.40549	12.02284
	2	O	21.37184	−13.1019	1.91731	15.27142	−5.35722
	3	N	17.82525	−9.55527	1.50794	11.99206	9.15484
	6	N	18.41013	−10.1402	1.56710	12.45910	7.05827
10	1	N	18.15842	−9.38380	1.45510	12.17560	13.11665
	2	S	13.41821	−4.64359	1.91032	10.61433	−0.26184
	3	N	17.17026	−8.39564	1.48218	11.70434	9.87497
	6	N	18.57660	−9.80198	1.55788	12.65031	8.15551
11	1	N	18.16180	−9.07060	1.45524	12.25687	13.41833
	2	S	13.21262	−4.12142	1.91009	10.58275	−2.46622
	3	N	17.16441	−8.07321	1.48070	11.77696	10.20358
	6	N	18.52363	−9.43242	1.55930	12.70530	8.30974
	9	Cl	13.03778	−3.94658	1.98210	10.74511	−0.83061

Table 2 continued

Compd. no.	Site	Atom	IP	EA	ρ	$E_n^{\ddagger}$	$E_m^{\ddagger}$
12	1	N	18.14773	−9.44417	1.45443	12.15062	13.06627
	2	S	13.51424	−4.81068	1.91056	10.64871	−0.33213
	3	N	17.16225	−8.45869	1.47625	11.66878	10.07771
	6	N	18.54956	−9.84600	1.55507	12.61050	8.19378
13	1	N	18.15436	−9.03303	1.45586	12.26177	13.39205
	2	S	13.19858	−4.07725	1.91006	10.58267	−3.75667
	3	N	17.16246	−8.04113	1.48300	11.78869	10.12012
	6	N	18.61042	−9.48909	1.55470	12.74677	8.68429
	9	Cl	13.03529	−3.91389	1.98210	10.75119	−0.81447
14	1	N	18.16357	−9.07281	1.45511	12.25743	13.42998
	2	S	13.21352	−4.12276	1.91010	10.58315	−2.52535
	3	N	17.16290	−8.07214	1.48092	11.77654	10.19075
	6	N	18.50668	−9.41592	1.56056	12.69879	8.23933
	9	Cl	13.03778	−3.94702	1.98210	10.74499	−0.83084
15	1	N	18.53976	−9.45690	1.47879	12.51094	13.42998
	2	O	21.21047	−12.12770	1.91751	15.39036	−2.52535
	3	N	18.08111	−8.99830	1.48298	12.27403	10.19075
	6	N	18.41974	−9.90370	1.57369	12.68544	8.23933
	9	Cl	12.98651	−3.90370	1.98163	10.71222	−0.83084
16	1	N	18.06384	−8.61078	1.45564	12.29559	13.51744
	2	S	12.93454	−3.48148	1.90935	10.52194	0.25628
	3	N	17.03203	−7.57897	1.50089	11.84281	9.42247
	6	N	18.37074	−8.91768	1.56371	12.72447	8.26762
	9	Cl	12.83423	−3.38117	1.98201	10.72018	−0.58173
	10	Cl	12.75531	−3.30225	1.98159	10.67384	−0.55384
17	1	N	18.16158	−9.07362	1.45525	12.25597	13.41416
	2	S	13.21581	−4.12785	1.91009	10.58364	−2.73354
	3	N	17.15986	−8.07190	1.48152	11.77556	10.15609
	6	N	18.53230	−9.44434	1.55955	12.70921	8.31616
	9	Cl	13.03760	−3.94964	1.98210	10.74419	−0.83220
18	1	N	18.15209	−9.40046	1.45514	12.16654	13.07816
	2	S	13.36359	−4.61196	1.91000	10.57830	−0.25593
	3	N	17.04291	−8.29128	1.50039	11.67215	8.87309
	6	N	18.37463	−9.623	1.56510	12.55495	7.55893
19	1	N	18.15275	−9.01565	1.45583	12.26479	13.40533
	2	S	13.17268	−4.03558	1.90987	10.57212	1.39270
	3	N	17.04982	−7.91272	1.49796	11.76652	9.30833
	6	N	18.39462	−9.25752	1.56172	12.65303	8.09595
	9	Cl	13.03253	−3.89543	1.98210	10.75362	−0.80557
20	1	N	18.15925	−9.01197	1.45587	12.27091	13.42725
	2	S	13.13927	−3.99200	1.90971	10.55625	3.01793
	3	N	17.02327	−7.87600	1.50149	11.76304	9.13078
	6	N	18.36810	−9.22083	1.56283	12.64423	8.02299
	9	Cl	13.03400	−3.88673	1.98210	10.75698	−0.80091
21	1	N	18.16920	−8.96248	1.45589	12.29116	13.50541
	2	S	13.12643	−3.91971	1.90977	10.56445	0.06601
	3	N	17.03586	−7.82914	1.49850	11.77765	9.32473
	6	N	18.35451	−9.14779	1.56243	12.65068	8.08113
	9	Br	18.65450	−7.86130	1.96674	9.413960	9.16464

Table 3 The highest acidic atomic softness values ($E_n^{\ddagger}$) of the TIBO derivatives

Compd. no.	Site	Atom	IP	EA	ρ	$E_n^{\ddagger}$	EC_{50}
1	2	O	21.19465	−12.5519	1.91724	15.27072	4.23
2	2	O	21.54129	−13.0248	1.91804	15.42599	4.85
3	2	O	21.01054	−11.8144	1.91708	15.31104	5.33
4	2	O	21.32174	−12.7246	1.91754	15.32786	5.38
5	6	N	18.39242	−9.48208	1.57231	12.62380	5.66
6	3	N	18.49332	−9.71058	1.56260	12.62006	6.10
7	6	N	18.44548	−9.32732	1.55612	12.66080	6.35
8	6	N	18.61142	−9.51173	1.55515	12.74309	6.48
9	2	O	21.37184	−13.1019	1.91731	15.27142	6.51
10	6	N	18.57660	−9.80198	1.55788	12.65031	6.62
11	6	N	18.52363	−9.43242	1.55930	12.70530	7.04
12	6	N	18.54956	−9.84600	1.55507	12.61050	7.36
13	6	N	18.61042	−9.48909	1.55470	12.74677	7.37
14	6	N	18.50668	−9.41592	1.56056	12.69879	7.48
15	6	N	18.41974	−9.9037	1.57369	12.68544	7.60
16	6	N	18.37074	−8.91768	1.56371	12.72447	7.60
17	6	N	18.53230	−9.44434	1.55955	12.70921	7.82
18	6	N	18.37463	−9.62300	1.56510	12.55495	7.85
19	6	N	18.39462	−9.25752	1.56172	12.65303	8.29
20	6	N	18.36810	−9.22083	1.56283	12.64423	8.34
21	6	N	18.35451	−9.14779	1.56243	12.65068	8.52

Table 4 The highest basic atomic softness values ($E_m^{\ddagger}$) of the TIBO derivatives

Compd. no.	Site	Atom	IP	EA	ρ	$E_m^{\ddagger}$	EC_{50}
1	1	N	18.52295	−9.88017	1.49523	11.31648	4.23
2	1	N	18.99339	−10.47690	1.45221	15.14833	4.85
3	1	N	18.57437	−9.37824	1.48180	12.77617	5.33
4	3	N	18.19864	−9.60146	1.47456	11.86300	5.38
5	1	N	18.12255	−9.21221	1.45593	13.11558	5.66
6	1	N	18.16672	−9.38398	1.45505	13.14606	6.10
7	1	N	18.16644	−9.04828	1.45659	13.37116	6.35
8	1	N	18.15564	−9.05595	1.45548	13.39772	6.48
9	1	N	18.70179	−10.43180	1.48340	12.02284	6.51
10	1	N	18.15842	−9.38380	1.45510	13.11665	6.62
11	1	N	18.16180	−9.07060	1.45524	13.41833	7.04
12	1	N	18.14773	−9.44417	1.45443	13.06627	7.36
13	1	N	18.15436	−9.03303	1.45586	13.39205	7.37
14	1	N	18.16357	−9.07281	1.45511	13.42998	7.48
15	1	N	18.53976	−9.45695	1.47879	12.77834	7.60
16	1	N	18.06384	−8.61078	1.45564	13.51744	7.60
17	1	N	18.16158	−9.07362	1.45525	13.41416	7.82
18	1	N	18.15209	−9.40046	1.45514	13.07816	7.85
19	1	N	18.15275	−9.01565	1.45583	13.40533	8.29
20	1	N	18.15925	−9.01197	1.45587	13.42725	8.34
21	1	N	18.16920	−8.96248	1.45589	13.50541	8.52

Table 5. Although a number of atomic and molecular properties are known, in the present study, only five atomic and seven molecular properties, which provide better results, have been used. For QSAR modeling, we have performed the Multi Linear Regression analysis using all the atomic parameters in one group, and all the molecular parameters in the another group. Various QSAR models for each set of compounds using descriptors in different combinations have been developed but only six top models of each set were reported. The predicted activities as obtained from these QSAR models are presented in Tables 6 (atomic parameters) and 7 (molecular parameters). For simplicity each set has been discussed separately as below.

First set

The main factors, which influence the reactivity of any compound, are ionization potential, electron affinity, charge, and radius of atom. An intrinsic quantity called softness defines these factors at the site of the reactive atom in a molecule. Correlation with this dominating factor, softness parameter, with action mechanism of various therapeutic agents and the pharmacoactivity, would be very valuable in search of a new advance drug before its synthesis, since receptors are proteins having large number of amino acids. For QSAR study, regression analyses with the help of atomic property parameters have been made using different combinations of descriptors. Top six models are selected for QSAR study. Model no. 6 has been recognized as the best model. The regression equations of these models are presented below and predicted activities are placed in Table 6.

$$^{A}PA_1 = -0.72217 * EA + 20.6222$$

$$rCV^2 = 0.471605$$

$$r^2 = 0.550394$$

$$^{A}PA_2 = 0.622391 * r + 13.1637$$

$$rCV^2 = 0.436419$$

$$r^2 = 0.541951$$

$$^{A}PA_3 = -5.66615 * E_n^{\ddagger} + 16.1266$$

$$rCV^2 = 0.438105$$

$$r^2 = 0.536431$$

$$^{A}PA_4 = -0.761303 * IP + 16.924$$

$$rCV^2 = 0.453909$$

$$r^2 = 0.538702$$

$$^{A}PA_5 = -1.08323 * EA + 2.88788 * E_n^{\ddagger} + 22.7793$$

Table 5 The values of molecular property descriptors of TIBO derivatives

Compd. no.	ΔH_f°	MW	TE	εHOMO	εLUMO	η	χ	EC_{50}
1	5.340	243.308	−128.64	−8.825	−0.097	4.364	−4.461	4.23
2	−4.047	257.335	−135.82	−8.847	−0.148	4.350	−4.498	4.85
3	−14.032	271.361	−143.00	−8.838	−0.136	4.351	−4.487	5.33
4	−6.369	291.780	−147.60	−9.031	−0.400	4.316	−4.715	5.38
5	−53.302	329.484	−173.44	−8.725	−0.049	4.338	−4.387	5.66
6	−19.905	305.807	−154.77	−8.962	−0.386	4.288	−4.674	6.10
7	52.181	287.422	−140.20	−8.329	−0.848	3.741	−4.588	6.35
8	47.634	301.449	−147.34	−8.371	−0.894	3.739	−4.632	6.48
9	38.511	275.411	−134.81	−8.380	−0.899	3.741	−4.640	6.51
10	43.333	335.894	−159.11	−8.444	−1.044	3.700	−4.744	6.62
11	46.936	335.894	−159.08	−8.456	−1.050	3.703	−4.753	7.04
12	43.719	335.894	−159.11	−8.444	−1.044	3.700	−4.744	7.36
13	51.991	335.894	−159.06	−8.462	−1.058	3.702	−4.760	7.37
14	35.352	363.948	−173.42	−8.449	−1.048	3.701	−4.749	7.48
15	25.489	323.883	−153.74	−8.404	−1.024	3.690	−4.714	7.60
16	53.621	321.867	−151.91	−8.308	−0.904	3.702	−4.606	7.60
17	41.740	356.312	−163.73	−8.510	−1.188	3.661	−4.849	7.82
18	46.957	321.867	−151.96	−8.446	−1.044	3.701	−4.745	7.85
19	38.729	349.921	−166.27	−8.448	−1.048	3.700	−4.748	8.29
20	61.508	366.318	−150.08	−8.496	−1.076	3.710	−4.786	8.34
21	44.510	301.449	−147.37	−8.318	−0.855	3.732	−4.587	8.52

Table 6 Predicted activities ($^{A}PA_1$ to $^{A}PA_6$) of TIBO derivatives as calculated by $^{A}RE_1$–$^{A}RE_6$ equations

Compd. no.	EC_{50}	$^{A}PA_1$	$^{A}PA_2$	$^{A}PA_3$	$^{A}PA_4$	$^{A}PA_5$	$^{A}PA_6$
1	4.23	6.138	5.936	5.188	5.946	5.364	5.250
2	4.85	4.880	4.994	7.263	7.749	5.728	5.841
3	5.33	6.000	6.729	5.836	6.633	5.657	5.821
4	5.38	7.005	6.376	6.185	6.203	6.574	6.392
5	5.66	7.208	6.991	7.084	6.793	7.258	7.206
6	6.10	7.090	6.719	7.126	6.807	7.201	7.101
7	6.35	7.091	7.249	7.052	6.913	7.156	7.211
8	6.48	7.120	7.237	7.105	6.926	7.209	7.254
9	6.51	5.659	5.065	5.759	6.279	5.371	5.111
10	6.62	7.112	6.720	7.124	6.793	7.215	7.109
11	7.04	7.103	7.214	7.117	6.935	7.204	7.247
12	7.36	7.141	6.624	7.156	6.770	7.254	7.114
13	7.37	7.123	7.274	7.087	6.923	7.200	7.254
14	7.48	7.099	7.211	7.123	6.941	7.205	7.248
15	7.60	6.093	6.604	5.981	6.634	5.810	5.915
16	7.60	7.365	7.940	7.098	6.982	7.377	7.560
17	7.82	7.104	7.209	7.116	6.933	7.204	7.245
18	7.85	7.129	6.693	7.122	6.775	7.226	7.108
19	8.29	7.127	7.301	7.088	6.929	7.204	7.265
20	8.34	7.110	7.307	7.086	6.939	7.191	7.258
21	8.52	7.083	7.385	7.085	6.976	7.172	7.269

$$rCV^2 = 0.460739$$

$$r^2 = 0.552164$$

$$^{A}PA_6 = -1.47044 * EA + 0.800114 * IP + 24.304$$

$$rCV^2 = 0.470689$$

$$r^2 = 0.554518$$

A reference to Table 8 indicates that QSAR models of TIBO derivatives as developed by $^{A}PA_6$ are better than those obtained by $^{A}PA_1$ to $^{A}PA_5$.

Second set

To obtain a significant correlation, appropriate parameters should be employed, whether they are theoretical, empirical, or derived from readily available experimental characteristics of the structures. Many parameters reflect simple molecular properties, and thus, can provide insight into the physicochemical nature of the activity/property under consideration. Thus, quantum chemical calculations are an attractive source of new molecular properties. These can express all the electronic and geometrical properties of the molecules and their interactions with another. For QSAR study, regression analysis performed with the help of molecular properties. Heat of formation, molecular weight,

Table 7 Predicted activities ($^{M}PA_1$ to $^{M}PA_6$) of TIBO derivatives as calculated by $^{M}RE_1$–$^{M}RE_6$ equations

Compd. no	EC_{50}	$^{M}PA_1$	$^{M}PA_2$	$^{M}PA_3$	$^{M}PA_4$	$^{M}PA_5$	$^{M}PA_6$
1	4.230	4.722	4.645	4.645	4.645	4.645	4.645
2	4.850	4.944	4.866	4.866	4.866	4.866	4.866
3	5.330	5.067	5.062	5.062	5.062	5.062	5.062
4	5.380	5.772	5.357	5.357	5.357	5.357	5.357
5	5.660	5.530	5.943	5.943	5.943	5.943	5.943
6	6.100	5.877	5.639	5.639	5.639	5.639	5.639
7	6.350	6.658	6.817	6.817	6.817	6.817	6.817
8	6.480	6.894	7.002	7.002	7.002	7.002	7.002
9	6.510	6.515	6.631	6.631	6.631	6.631	6.631
10	6.620	7.559	7.543	7.543	7.543	7.543	7.543
11	7.040	7.585	7.532	7.532	7.532	7.532	7.532
12	7.360	7.561	7.543	7.543	7.543	7.543	7.543
13	7.370	7.620	7.532	7.532	7.532	7.532	7.532
14	7.480	7.902	7.932	7.932	7.932	7.932	7.932
15	7.600	7.288	7.411	7.411	7.411	7.411	7.411
16	7.600	7.207	7.390	7.390	7.390	7.390	7.390
17	7.820	8.042	7.892	7.892	7.892	7.892	7.892
18	7.850	7.389	7.344	7.344	7.344	7.344	7.344
19	8.290	7.730	7.737	7.737	7.737	7.737	7.737
20	8.340	8.095	7.927	7.927	7.927	7.927	7.927
21	8.520	6.821	7.036	7.036	7.036	7.036	7.036

total energy, highest occupied molecular orbital energy, lowest unoccupied molecular orbital energy, absolute hardness, and electronegativity have been made separately using different combinations of these parameters. Top six models are selected for QSAR study. The regression equation of these models is presented below and predicted activities are placed in Table 7.

$$^{M}PA_1 = -0.000820201\,\Delta H_f^{\circ} + 0.0132027\ MW - 2.59807\,\eta + 12.7634$$

$$rCV^2 = 0.600598$$

$$r^2 = 0.812228$$

Table 8 Top six models of TIBO derivatives with atomic property descriptors

S. no.	RE	rCV^2	r^2	Variable used	Variable count
1	$^{A}RE_1$	0.471605	0.550394	EA	1
2	$^{A}RE_2$	0.436419	0.541951	ρ	1
3	$^{A}RE_3$	0.438105	0.536431	$E_n^{\ddagger}$	1
4	$^{A}RE_4$	0.453909	0.538702	IP	1
5	$^{A}RE_5$	0.460739	0.554518	EA, $E_n^{\ddagger}$	2
6	$^{A}RE_6$	0.470689	0.554518	EA, IP	2

Table 9 Top six models of TIBO derivatives with molecular property descriptors

S. no.	RE	rCV^2	r^2	Variable used	Variable count
1	$^{M}RE_1$	0.600598	0.812228	ΔH_f°, MW, η	3
2	$^{M}RE_2$	0.623394	0.812674	MW, εHOMO, η	3
3	$^{M}RE_3$	0.623394	0.812674	MW, εHOMO, χ	3
4	$^{M}RE_4$	0.623394	0.812674	MW, εLUMO,η	3
5	$^{M}RE_5$	0.623394	0.812674	MW, εLUMO, χ	3
6	$^{M}RE_6$	0.623394	0.812674	MW, η, χ	3

$$^{M}PA_2 = 0.0139659\ MW + 0.353192\,\varepsilon HOMO - 2.21305\,\eta + 14.0227$$

$$rCV^2 = 0.623394$$

$$r^2 = 0.812674$$

$$^{M}PA_3 = 0.0139659\ MW + 2.56624\,\varepsilon HOMO - 2.21305\,\chi + 14.0227$$

$$rCV^2 = 0.623394$$

$$r^2 = 0.812674$$

$$^{M}PA_4 = 0.0139659\ MW + 0.353192\,\varepsilon LUMO - 2.91943\,\eta + 14.0227$$

$$rCV^2 = 0.623394$$

$$r^2 = 0.812674$$

$$^{M}PA_5 = 0.0139659\ MW - 2.56624\,\varepsilon LUMO + 2.91943\,\chi + 14.0227$$

$$rCV^2 = 0.623394$$

$$r^2 = 0.812674$$

$$^{M}PA_6 = 0.0139659\ MW - 2.56624\,\eta + 0.353192\,\chi + 14.0227$$

$$rCV^2 = 0.623394$$

$$r^2 = 0.812674$$

Table 9 indicates that QSAR models ($^{M}PA_2$ to $^{M}PA_6$) of TIBO derivatives as developed by molecular properties, all have same predictive power, except model no-1.

Conclusion

1. The QSAR model developed by molecular properties for all the sets of TIBO derivatives provide higher values of cross validation and correlation coefficient as compared with the value derived by atomic properties are presented in Tables 8 and 9.

2. In molecular properties, molecular weight in combination with energies of frontier orbitals, electronegativity, and hardness provides better result.
3. The predicted activities as calculated by molecular properties are close to the observed activities. Thus, they show good results with the observed activity.
4. The molecular properties thus, can better predict the activity of any new TIBO derivatives before their synthesis.

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