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Search for Structural Requirements of 2–Phenylimidazo[1,2–α] pyridineacetamide Analogs to Improve Affinity and Selectivity towards Central and/or Peripheral Benzodiazepine Receptors

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Abstract

Motivation. Central benzodiazepine receptors (CBRs) and peripheral benzodiazepine receptors (PBRs) are benzodiazepine receptors present in the brain. These receptors play valuable roles in calcium flow, cell proliferation, cellular immunity, cellular respiration, malignancy, muscle relaxation and sedation. 2–Phenylimidazo[1,2–α]pyridineacetamide analogs are potent and selective ligands for CBRs and PBRs. An attempt is made to find out the required structural features responsible for high affinity and selectivity of 2–phenylimidazo[1,2–α]pyridineacetamide analogs towards CBRs or PBRs through computational design.

Method. A QSAR study of 37 analogs of 2–phenylimidazo[1,2–α]pyridineacetamide was performed using topological and quantum chemical descriptors. Correlation and multiple regression analyses were performed to develop QSAR models.

Results. The present study showed that some atoms played important roles in electronic and hydrophobic interactions with central benzodiazepine receptors (CBRs) for improving affinity and selectivity of these compounds. Atomic charges of some atoms, dipole moment, total energy as well as the presence of acetamide group and double substitution on carboxamide nitrogen favor the high affinities and selectivities of PBRs.

Conclusions. The QSAR models developed in this study are used to generate a possible mapping of the pharmacophore. The QSAR equations explain the importance of particular atoms/groups for CBRs or PBRs affinity. The presence of a chlorine atom at 'Y' is favorable to the CBRs affinity whereas the presence of an acetamide group and disubstitution on carboxamide nitrogen favor PBRs affinity.

Keywords. Pyridineacetamides; central benzodiazepine receptor; peripheral benzodiazepine receptor; quantitative structure–activity relationships; QSAR.

Abbreviations and notations

CBR, central benzodiazepine receptor
PBR, peripheral benzodiazepine receptor
QSAR, quantitative structure–activity relationships

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1 INTRODUCTION

In the brain, benzodiazepines [1–2] interact with two types of receptors, i.e. the central benzodiazepine receptors (CBRs) located mainly in the central nervous system [3–5] and the peripheral benzodiazepine receptors (PBRs) found generally in the peripheral tissues and glial cells [6–7]. CBRs are a part of a macromolecular complex that contains GABA regulated chloride ion channels [8]. Benzodiazepines exert muscle relaxant, anxiolytic, sedative, hypnotic and anticonvulsant effects mediated primarily via CBRs [7]. PBRs are distinctly different from CBRs in pharmacological actions, tissue distribution and protein characteristics [9]. PBRs are multimeric complexes composed of a 18–kDa protein which contains isoquinoline and carboxamide binding sites [10–12]. PBRs play important roles in steroidogenesis by regulating the entry of the substrate (cholesterol) in the steroidogenic pathway (rate limiting step). It was found that the binding of ligands to PBR receptors resulted in translocation of cholesterol from the outer to the inner mitrochondrial membranes. Ligands with high affinity to PBRs stimulate the biosynthesis of neurosteroids like pregnenolone in glial cells [12–13]. PBRs also possess valuable roles in calcium flow, cell proliferation, cellular immunity, cellular respiration and malignancy [7,9,12]. Ligands of PBRs have potential for the treatment of neurodegenerative diseases [14].

PBRs differ from CBRs in their drug specificity. The prototype benzodiazepine (BZ) clonazepam binds to CBRs with high affinity. Another benzodiazepine, i.e., BZ Ro5–4864 (4'–chlorodiazepam) [15] as well as the non–BZ ligand PK11195 (an isoquinoline carboxamide derivative) and SSR180575 (a pyridazinoindole derivative) bind to CBRs with negligible affinity. These compounds have high affinity and specificity for PBRs [14–16]. Imidazopyridines bind with high affinity to both CBRs and PBRs [17]. 2–Phenylimidazo[1,2–α]pyridineacetamide derivatives are potent and selective ligands for PBRs. These compounds stimulate steroidogenesis in both the brain and the periphery and also have anticonflict action in rats. Agonists of PBRs may be beneficial for the treatment of stress and anxiety–related diseases [18]. Most of *N*,*N*–dialkyl (2–phenylimidazo[1,2–α]pyridine–3–yl) acetamides proved to possess high affinity and selectivity for CBRs or PBRs [19].

As quantitative structure activity relationship study relates variations in biological activity to change in molecular structures having different properties, an attempt was made to identify the required structural features of 2–phenylimidazo[1,2–α]pyridineacetamides for their affinity and selectivity towards CBRs and/or PBRs at the molecular level [20]. The general structures with arbitrary numbering of thirty–seven compounds belonging to 2–phenylimidazo[1,2–α]pyridineacetamide derivatives are shown in Figure 1a and 1b.

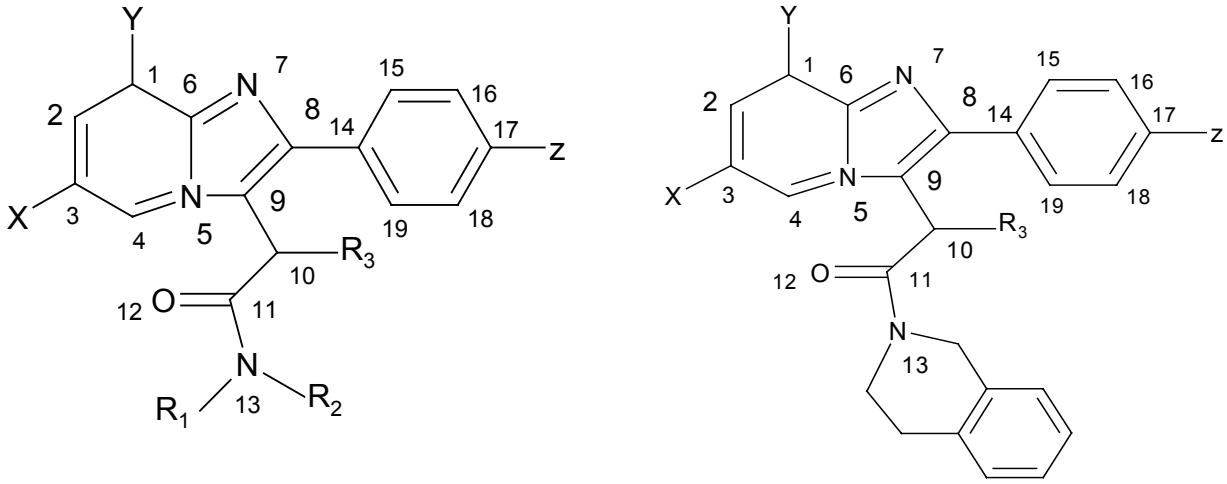

Figure 1. (*a*) General structure of substituted 2–phenylimidazo[1,2–α]pyridineacetamides with arbitrarily numbered common skeletal atoms for compound **1**–**21** and **24**–**37**; (*b*) general structure of substituted 2–phenylimidazo[1,2–α]pyridineacetamides with arbitrarily numbered common skeletal atoms for compounds **22** and **23**.

As a part of our composite program of rational drug design [21–25], quantitative structure activity relationship (QSAR) study was performed. Electrotopological state atom (ETSA) indices, refractotopological state atom (RTSA) indices and semi–empirical quantum chemical descriptors were used as the independent parameters. Binding affinity data for CBRs and PBRs from different tissues were treated as the dependent variables. The objective of the work is to search of structural requirements of these analogs for improving affinity and selectivity towards CBRs and/or PBRs. Binding affinity data for CBRs and PBRs from different tissues were collected from the work of Trapani *et al.* [20]. Improvement of affinity and selectivity of these analogs towards CBRs and/or PBRs through QSAR study are reported here.

2 MATERIALS AND METHODS

Dataset and computational procedures used for the QSAR study are described in this section. Independent parameters like ETSA and RTSA indices as well as quantum chemical descriptors are described briefly in dataset and parameters. The statistical methods and parameters used for the study are mentioned in computational procedures.

2.1 Dataset and Parameters

The binding affinity data of 2–phenylimidazo[1,2–α]pyridineacetamides for CBR and PBR have been used for the present study. The pIC_{50} values were collected from the published work of Trapani *et al.* [20]. The general structures of 2–phenylimidazo[1,2–α]pyridineacetamides are shown in Figures 1a and 1b. The activity data is listed in Table 1. The affinities of each compound towards CBRs and PBRs were determined by Trapani *et al*. [20] using *in vitro* and *in vivo* studies by measuring their ability to displace [^{3}H]flunitrazepam and [^{3}H]PK 11195 from binding to membrane

preparations from cerebral cortex and ovary.

Table 1. Binding affinities data of 2–phenylimidazo[1,2–α]pyridineacetamide derivatives for central and peripheral benzodiazepine receptors from different tissues.

Cpd[a]	X	Y	Z	R_1	R_2	R_3	pC_1[b]	pC_2[b]	pC_3[b]
1	H	H	Cl	n–C_4H_9	n–C_4H_9	H	7.040	8.230	7.980
2	H	Cl	Cl	n–C_4H_9	n–C_4H_9	H	5.000	8.104	7.646
3	Cl	Cl	Cl	n–C_4H_9	n–C_4H_9	H	5.000	8.284	7.731
4	Cl	Cl	Cl	n–C_6H_{13}	n–C_6H_{13}	H	5.000	6.424	5.584
5	Cl	H	Cl	n–C_4H_9	n–C_4H_9	H	7.051	8.485	8.172
6	Cl	H	Cl	n–C_6H_{13}	n–C_6H_{13}	H	5.481	8.292	7.312
7	Cl	Cl	H	n–C_4H_9	C_6H_5	H	5.000	7.939	8.337
8	Cl	Cl	Cl	n–C_4H_9	C_6H_5	H	5.000	7.876	8.319
9	Cl	H	Cl	n–C_4H_9	C_6H_5	H	6.133	8.824	7.936
10	Cl	Cl	H	n–C_4H_9	$CH_2C_6H_5$	H	5.000	7.616	7.047
11	Cl	Cl	Cl	*tert*–C_4H_9	$CH_2C_6H_5$	H	5.000	5.464	4.740
12	Cl	Cl	Cl	n–C_3H_7	4–NO_2–$CH_2C_6H_5$	H	5.000	7.566	7.157
13	Cl	Cl	Cl	C_6H_5	H	H	5.000	7.701	7.599
14	Cl	Cl	Cl	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	H	5.000	8.092	8.252
15	Cl	Cl	Cl	– $(CH_2)_4$–		H	5.000	6.668	6.074
16	Cl	Cl	H	– $(CH_2)_4$–		H	5.000	5.907	5.029
17	Cl	Cl	H	– $(CH_2)_5$–		H	5.000	6.804	5.837
18	Cl	Cl	Cl	– $(CH_2)_5$–		H	5.000	8.301	7.036
19	Cl	H	Cl	– $CH_2CH(COOC_2H_5)(CH_2)_3$–		H	6.725	7.454	6.520
20	Cl	Cl	Cl	– $CH_2CH(COOC_2H_5)(CH_2)_3$–		H	5.000	6.845	5.597
21	Cl	Cl	Cl	– $(CH_2)_2N(CH_2C_6H_5)(CH_2)_2$–		H	5.000	4.682	3.139
22	Cl	Cl	H			H	5.000	7.412	6.636
23	Cl	Cl	Cl			H	5.000	8.313	7.449
24	Cl	Cl	H	2–pyridylethyl	CH_3	H	5.000	5.663	5.296
25	Cl	Cl	Cl	2–pyridylethyl	CH_3	H	5.000	6.046	5.294
26	Cl	Cl	H	4–pyridyl	H	H	5.000	5.677	5.387
27	Cl	Cl	Cl	n–C_4H_9	H	H	5.000	6.409	6.538
28	Cl	Cl	Cl	C_6H_{11}	H	H	5.000	6.640	5.977
29	Cl	Cl	H	C_6H_{11}	H	H	5.000	5.878	5.884
30	Cl	Cl	Cl	$CH_2C_6H_5$	H	H	5.000	6.772	ND[c]
31	Cl	Cl	Cl	n–C_3H_7	n–C_3H_7	CH_3	5.000	5.920	5.572
32	Cl	Cl	Cl	C_6H_{11}	CH_3	CH_3	5.000	5.288	5.513
33	Cl	Cl	Cl	$CH_2C_6H_5$	CH_3	CH_3	5.000	5.005	4.937
34	Cl	Cl	Cl	n–C_4H_9	CH_3	H	5.000	9.347	8.481
35	Cl	Cl	H	n–C_4H_9	CH_3	H	5.000	8.456	8.638
36	Cl	Cl	Cl	C_6H_5	CH_3	H	5.000	9.481	8.770
37	Cl	Cl	Cl	$CH_2C_6H_5$	CH_3	H	5.000	8.623	ND[c]

[a] Cpd indicates compound numbers; [b] pC_1, pC_2 and pC_3 are the negative logarithms of IC_{50} values in molar unit of binding affinities of 2–phenylimidazo[1,2–α]pyridineacetamides derivatives for central and peripheral benzodiazepine receptors to membrane preparations from the cerebral cortex and ovary; [c] ND indicates not determined.

ETSA index is a non–empirical index encoding the value of electronegativity distributed over an atom according to its bonding degree of non–hydrogen atoms, the inductive influence of other atoms in the chemical graph and its topological state. It is calculated as a sum of the intrinsic state value and perturbation effect of the surrounding atoms [26–28]. This index is a powerful atom level descriptor of structural attributes and information content that may be correlated well with the biological activity.

RTSA index has a direct structural interpretation since it expresses the atomic contribution of an

important physicochemical property (molar refractivity) related to dispersive forces in biologically active sites and also contains topological information about the chemical structure of atomic environment. R–state indices are important for modeling the dispersive/van der Waals interactions with the receptors [29–30]. ETSA and RTSA indices were calculated using the computer program 'Mouse' developed in our laboratory [31].

Quantum chemical descriptors like atomic charges (qC_n), highest occupied molecular orbital energy (E_{HOMO}), lowest unoccupied molecular orbital energy (E_{LUMO}), dipole moment (μ), total energy (E_T), heat of formation (ΔH_f), binding energy (E_b), electronic energy (E_{el}), nuclear energy (E_n), molecular surface area (A), volume (Vol), partition coefficient (log P), molar refractivity (MR), molecular polarizability (α) were calculated using Hyperchem Release 7.0 Pro Package [32] running on a Pentium IV 2.40 GHz computer with 512 MB RAM. The Molecular Mechanics (MM+) force field was applied for the preliminary structure optimization and study of the conformational behavior of each compound. These energy minimized structures were used as the starting structures for geometrical optimization by a semi–empirical method, Austin Model 1 (AM1), using Polok Ribiere (conjugate gradient) algorithm with RMS gradient of 0.01 kcal/ Å mol. The AM1 method produces reliable total energies as a function of atomic positions and is able to probe the energy surface to find the minimum energy configurations [33].

Atomic charges have been used as static chemical reactivity indices and are also used for description of the weak intermolecular interactions as well as the molecular polarity of molecules. The total dipole moment reflects only the global polarity of a molecule. Dipole moment indicates the strength and orientational behavior of a molecule in an electrostatic field. The total energy has been used as a measure of non–specific interactions between a solute and the stationary phase in gas–chromatography [34]. Besides these, indicator parameters were also used in order to find out the role of a specific substituent at a specific position towards the biological activity.

2.2 Computational Procedures

QSAR models can be developed using different techniques like multiple linear regression (MLR), factor analysis with multiple linear regression (FA–MLR), principle component regression analysis (PCRA), discriminant analysis (DA), partial least square (PLS), neural networks etc [35–39]. In the present study, MLR analysis was performed to develop QSAR models. Different combinations of descriptors were subjected to multiple regression analysis [40] employing a computer program 'Multi Regress', developed in our laboratory [41]. In developing QSAR equations, predictor variables with higher p–values and higher intercorrelation coefficient (>0.5) were removed to get the best QSAR model. Descriptors used to build the QSAR models are summarized in Table 2.

Table 2. Values of properties of substituted 2–phenylimidazo[1,2–α]pyridineacetamides and indicator parameters

Cpd	S_1[a]	S_6[a]	R_1[b]	R_{17}[b]	I_1[c]	I_2[c]	qC_1[d]	qC_6[d]	qC_{16}[d]	qC_{19}[d]	μ[e]	E_T[f]
1	1.971	0.852	5.172	2.219	1.000	1.000	–0.090	–0.000	–0.123	–0.088	6.232	–0.107
2	0.566	0.663	2.462	2.207	1.000	1.000	–0.038	–0.004	–0.131	–0.089	6.422	–0.115
3	0.450	0.586	2.433	2.198	1.000	1.000	–0.030	–0.006	–0.130	–0.088	5.837	–0.124
4	0.457	0.595	2.408	2.179	1.000	1.000	–0.022	–0.005	–0.131	–0.088	6.470	–0.138
5	1.876	0.775	5.200	2.209	1.000	1.000	–0.089	–0.004	–0.130	–0.090	4.964	–0.115
6	1.892	0.783	5.198	2.190	1.000	1.000	–0.081	–0.002	–0.131	–0.089	5.778	–0.130
7	0.454	0.591	2.456	4.687	1.000	1.000	–0.032	–0.006	–0.137	–0.094	5.138	–0.120
8	0.429	0.560	2.444	2.205	1.000	1.000	–0.032	–0.005	–0.132	–0.087	4.734	–0.128
9	1.863	0.748	5.232	2.217	1.000	1.000	–0.081	–0.002	–0.123	–0.086	4.991	–0.120
10	0.460	0.599	2.447	4.684	1.000	1.000	–0.022	–0.002	–0.122	–0.087	5.128	–0.132
11	0.425	0.556	2.430	2.196	1.000	1.000	–0.034	–0.004	–0.133	–0.094	6.447	–0.132
12	0.378	0.502	2.463	2.220	1.000	1.000	–0.030	–0.004	–0.132	–0.088	7.669	–0.147
13	0.415	0.541	2.486	2.235	0.000	1.000	–0.030	–0.003	–0.127	–0.084	0.626	–0.114
14	0.413	0.540	2.444	2.206	1.000	1.000	–0.032	–0.005	–0.132	–0.087	5.146	–0.115
15	0.452	0.589	2.489	2.238	1.000	1.000	–0.034	–0.005	–0.129	–0.118	4.683	–0.109
16	0.477	0.620	2.501	4.683	1.000	1.000	–0.034	–0.006	–0.135	–0.125	5.230	–0.100
17	0.479	0.622	2.490	4.681	1.000	1.000	–0.032	–0.008	–0.135	–0.121	2.813	–0.104
18	0.454	0.591	2.478	2.230	1.000	1.000	–0.032	–0.007	–0.129	–0.114	2.176	–0.112
19	1.827	0.709	5.282	2.258	1.000	1.000	–0.091	–0.004	–0.129	–0.115	1.585	–0.129
20	0.396	0.521	2.503	2.247	1.000	1.000	–0.032	–0.006	–0.129	–0.114	1.056	–0.137
21	0.441	0.576	2.461	2.216	1.000	1.000	–0.032	–0.007	–0.129	–0.114	1.567	–0.136
22	0.464	0.604	2.484	4.698	1.000	1.000	–0.031	–0.006	–0.136	–0.121	2.586	–0.116
23	0.439	0.573	2.473	2.225	1.000	1.000	–0.032	–0.005	–0.131	–0.115	2.243	–0.124
24	0.449	0.586	2.475	4.687	1.000	1.000	–0.032	–0.009	–0.135	–0.122	2.919	–0.118
25	0.424	0.555	2.463	2.219	1.000	1.000	–0.032	–0.008	–0.129	–0.115	1.647	–0.126
26	0.432	0.562	2.508	4.696	0.000	1.000	–0.029	–0.003	–0.131	–0.125	2.574	–0.107
27	0.436	0.568	2.474	2.227	0.000	1.000	–0.031	–0.005	–0.127	–0.116	1.499	–0.109
28	0.447	0.581	2.471	2.224	0.000	1.000	–0.030	–0.005	–0.127	–0.116	1.652	–0.116
29	0.472	0.612	2.482	4.678	0.000	1.000	–0.023	–0.006	–0.132	–0.091	2.752	–0.108
30	0.421	0.549	2.477	2.228	0.000	1.000	–0.030	–0.005	–0.127	–0.086	1.775	–0.118
31	0.443	0.578	2.428	2.196	1.000	0.000	–0.033	–0.008	–0.131	–0.088	5.296	–0.120
32	0.449	0.585	2.437	2.202	1.000	0.000	–0.020	–0.019	–0.122	–0.088	4.661	–0.123
33	0.423	0.553	2.443	2.206	1.000	0.000	–0.020	–0.018	–0.124	–0.084	4.583	–0.125
34	0.441	0.575	2.461	2.218	1.000	1.000	–0.023	–0.005	–0.123	–0.086	4.746	–0.113
35	0.466	0.606	2.472	4.667	1.000	1.000	–0.023	–0.007	–0.129	–0.093	3.367	–0.105
36	0.42	0.548	2.472	2.225	1.000	1.000	–0.023	–0.005	–0.124	–0.084	4.804	–0.118
37	0.426	0.556	2.463	2.219	1.000	1.000	–0.023	–0.005	–0.125	–0.081	4.734	–0.121

[a] S_1 and S_6 are the ETSA indices of atom numbers 1 and 6 respectively; [b] R_1 and R_{17} are the RTSA indices of atom numbers 1 and 17 respectively; [c] I_1 and I_2 are the indicator parameters indicating the presence of the double substitution on carboxamide nitrogen and an acetamide group respectively; [d] qC_1 , qC_6, qC_{16} , and qC_{19} are the atomic charges of the atom numbers 1, 6, 16 and 19 respectively; [e] μ is dipole moment in Debye unit; [f] E_T is the total energy (kcal/mol) scaled by 1×10^{-6}.

The statistical quality of regression equations were justified by parameters like correlation coefficient (*R*), percentage of explained variance (*%EV*), adjusted R^2 (R^2_A), variance ratio (*F*), probability factor related to *F*–ratio (*p*) and standard error of estimate (*SEE*). The predictive powers of equations were validated with the leave–one–out (LOO) cross validation method. The predicted residual sum of square (*PRESS*), total sum of squares (*SSY*), cross–validated R^2 (R^2_{cv}), standard deviation error of prediction (*PSE*) and Standard error of *PRESS* (S_{PRESS}) were considered for the validation of QSAR models.

3 RESULTS AND DISCUSSION

The binding affinities of 2–phenylimidazo[1,2–α]pyridineacetamide derivatives for CBRs and PBRs from different tissues (expressed in terms of pIC_{50}) are presented in Table 1. For the calculation of E–state indices, R–state–indices and semi–empirical quantum–chemical descriptors, the general structures with arbitrary numbering are used and shown in Figure 1a and 1b. The descriptors used in developing models along with the indicator parameters are summarized in Table 2. Correlation analysis of various parameters was performed to develop QSAR equations. The intercorrelated parameters were discarded depending on their individual correlation with the binding affinity data for CBRs and PBRs from different tissues. All possible combinations of parameters were considered. The resultant parameters were subjected to regression analysis.

3.1 QSAR Models for the CBR Affinity

The best univariate equation for binding affinities of 2–phenylimidazo[1,2–α]pyridineacetamides (pC_1) for central benzodiazepine receptors was obtained by taking the ETSA index of atom number 1 (S_1) as an independent parameter and shown in Eq. (1).

$$pC_1 = 4.544\ (\pm 0.061) + 1.029\ (\pm 0.075)\ S_1$$
$$n = 37 \quad R = 0.917 \quad \%EV = 84.14 \quad R_A^2 = 0.837 \quad F_{(1,35)} = 185.72 \quad p<0.0001 \quad SEE = 0.227 \qquad (1)$$
$$PRESS = 1.802 \quad SSY = 11.367 \quad R^2_{cv} = 0.841 \quad S_{PRESS} = 0.227 \quad PSE = 0.221$$

where n is the number of compounds, and R, $\%EV$, $R^2_{A,}$ F, p, SEE, SSY, $PRESS$, $R^2_{cv,}$ S_{PRESS}, PSE are the correlation coefficient, percentage of explained variance, adjusted R^2, variance ratio, probability factor related to F–ratio, standard error of estimate, total sum of squares, predicted residual sum of squares, cross–validated R^2, standard error of $PRESS$ and standard deviation error of prediction respectively. Eq. (1) explains up to 84.14% of variances in the activity data and suggests the importance of atom number 1 in the binding affinity. The equation suggests that the higher value of S_1 corresponds to the greater affinity and selectivity of compounds towards CBRs as evident by the positive regression coefficient in the equation. Stepwise deletion of outliers **6** and **9** yielded Eq. (2).

$$pC_1 = 4.409\ (\pm 0.015) + 1.333\ (\pm 0.022)\ S_1$$
$$n = 35 \quad \mathbf{DC} = \mathbf{6}, \mathbf{9} \quad R = 0.996 \quad \%EV = 99.14 \quad R_A^2 = 0.991 \quad F_{(1,33)} = 3784.7 \quad p<0.0001 \qquad (2)$$
$$SEE = 0.052 \quad PRESS = 0.090 \quad SSY = 10.377 \quad R^2_{cv} = 0.991 \quad S_{PRESS} = 0.052 \quad PSE = 0.051$$

where DC refers to the deleted compounds behaves as outliers. These outliers are two distinct compounds (compounds **6** and **9)** with larger residual where the chlorine atom in position 1 of 2–phenylimidazo[1,2–α]pyridineacetamides is absent which may act indirectly or through a different mechanism of action. Eq. (2) explains 99.14% of variances in the activity data. Eq. (2) has a significant statistical predictivity as shown by its R^2_{cv} value >0.7.

Similarly another model was obtained using R_1 (RTSA index of atom 1) as independent

parameter and shown in Eq. (3).

$$pC_1 = 3.671(\pm0.119) + 0.539\ (\pm0.040)\ R_1$$
$$n = 37 \quad R = 0.916 \quad \%EV = 83.90 \quad R_A^2 = 0.834 \quad F_{(1,35)} = 182.33 \quad p<0.0001 \quad SEE = 0.229 \quad (3)$$
$$PRESS = 1.831 \quad SSY = 11.367 \quad R^2_{cv} = 0.839 \quad S_{PRESS} = 0.229 \quad PSE = 0.222$$

Eq. (3) explains up to 83.90% of variances in the affinity data. The positive coefficient of R_1 in the above model suggests that the higher values of the index are advantageous to the activity. The equation reveals that atom number 1 is important in relation to the dispersive/van der Waals interactions with central benzodiazepine receptors. Stepwise deletion of compounds **6** and **9** yielded Eq. (4).

$$pC_1 = 3.269\ (\pm0.035) + 0.702\ (\pm0.013)\ R_1$$
$$n = 35 \quad \mathbf{DC = 6, 9} \quad R = 0.995 \quad \%EV = 98.95 \quad R_A^2 = 0.989 \quad F_{(1,33)} = 3113.4 \quad p<0.0001 \quad (4)$$
$$SEE = 0.057 \quad PRESS = 0.109 \quad SSY = 10.377 \quad R^2_{cv} = 0.989 \quad S_{PRESS} = 0.057 \quad PSE = 0.056$$

Eq. (4) explains up to 98.95% of variances in the affinity data. It is also revealed that substitution with chlorine atom at C (1) position of 2–phenylimidazo[1,2–α]pyridineacetamide moiety may be a key factor for improving affinity and selectivity towards CBRs binding sites. The combination of S_6 (ETSA index of atom number 6) and R_{17} (RTSA index of atom number 17) yielded another model, Eq. (5).

$$pC_1 = 1.778\ (\pm0.418) + 6.128\ (\pm0.649)\ S_6 - 0.097\ (\pm0.046)\ R_{17}$$
$$n = 37 \quad R = 0.858 \quad \%EV = 73.54 \quad R_A^2 = 0.720 \quad F_{(2,34)} = 47.252 \quad p<0.0001 \quad SEE = 0.297 \quad (5)$$
$$PRESS = 3.007 \quad SSY = 11.367 \quad R^2_{cv} = 0.735 \quad S_{PRESS} = 0.297 \quad PSE = 0.285$$

Eq. (5) explains up to 73.54% of variances in the affinity and selectivity of CBRs. The model suggests that with increasing the value of S_6, the affinity and selectivity of CBRs towards 2–phenylimidazo[1,2–α]pyridineacetamides increase and with increasing the value of R_{17} the affinity and selectivity of compounds decrease. The CBR affinity and selectivity of compounds involve not only electrostatic interactions but also local dispersive forces. The stepwise deletion of compounds **6** and **2** which might act through a different mode of action gives a better QSAR model, Eq. (6).

$$pC_1 = 1.174\ (\pm0.323) + 7.342\ (\pm0.592)\ S_6 - 0.124\ (\pm0.034)\ R_{17}$$
$$n = 35 \quad \mathbf{DC = 6, 2} \quad R = 0.931 \quad \%EV = 86.76 \quad R_A^2 = 0.859 \quad F_{(2,32)} = 104.82 \quad p<0.0001 \quad (6)$$
$$SEE = 0.216 \quad PRESS = 1.490 \quad SSY = 11.248 \quad R^2_{cv} = 0.868 \quad S_{PRESS} = 0.216 \quad PSE = 0.206$$

Eq. (6) explains up to 86.76% of variances in the affinity and selectivity of CBRs. Another model was developed taking qC_1 and qC_{16}.

$$pC_1 = 7.099\ (\pm1.119) - 25.049\ (\pm1.700)\ qC_1 + 21.839(\pm8.604)\ qC_{16}$$
$$n = 37 \quad R = 0.933 \quad \%EV = 87.11 \quad R_A^2 = 0.864 \quad F_{(2,34)} = 114.89 \quad p<0.0001 \quad SEE = 0.208 \quad (7)$$
$$PRESS = 1.465 \quad SSY = 11.367 \quad R^2_{cv} = 0.871 \quad S_{PRESS} = 0.208 \quad PSE = 0.199$$

Eq. (7) explains 87.11% of variances of the binding affinity. Eq. (7) indicates the importance of atomic charge of atom numbers 1 and 16 for binding affinity and selectivity towards CBRs. The stepwise deletion of compounds **6** and **9** that are outliers gives Eq. (8).

$$pC_1 = 7.141\ (\pm 0.679) - 29.749\ (\pm 1.170)\ qC_1 + 23.171\ (\pm 5.238)\ qC_{16}$$
$$n = 35 \quad \mathbf{DC} = \mathbf{6}, \mathbf{9} \quad R = 0.977 \quad \%EV = 95.41 \quad R_A^2 = 0.951 \quad F_{(2,32)} = 332.76 \quad p<0.0001 \qquad (8)$$
$$SEE = 0.122 \quad PRESS = 0.476 \quad SSY = 10.377 \quad R^2_{cv} = 0.954 \quad S_{PRESS} = 0.122 \quad PSE = 0.117$$

Eq. (8) has much better statistical quality and explains up to 95.41% of variances in affinity. Eq. (8) suggests that the binding affinity and selectivity towards CBRs decrease with the increase in the negative charge of atom number 1, which may be influenced by substituents in heterocyclic ring. On the other hand, it is found that the increase of the atomic charge on atom 16 enhances the affinity and selectivity towards CBRs.

3.2 QSAR Models for the PBR Affinity

In the similar way, QSAR models were developed using pIC_{50} of binding affinities of 2–phenylimidazo[1,2–α]pyridineacetamides for peripheral benzodiazepine receptors from cerebral cortex cells of the brain (pC_2) and ovarian membranes (pC_3) as the biological activity parameter. The model obtained for binding affinities of 2–phenylimidazo[1,2–α]pyridineacetamides for the peripheral benzodiazepine receptors from cerebral cortex cells (pC_2) is shown in Eq. (9).

$$pC_2 = 18.189\ (\pm 2.269) + 218.893\ (\pm 38.596)\ qC_6 + 52.948\ (\pm\ 11.343)\ qC_{19} + 2.043\ (\pm 0.470)\ I_1$$
$$- 0.284\ (\pm 0.107)\ \mu + 42.196\ (\pm 13.596)\ E_T$$
$$n = 37 \quad R = 0.811 \quad \%EV = 65.80 \quad R_A^2 = 0.603 \quad F_{(5,31)} = 11.926 \quad p<0.0001 \quad SEE = 0.800 \qquad (9)$$
$$PRESS = 19.858 \quad SSY = 58.056 \quad R^2_{cv} = 0.658 \quad S_{PRESS} = 0.800 \quad PSE = 0.733$$

Eq. (9) explains up to 65.80% of variances in the binding affinity data. The equation reveals that atom numbers 6 and 19 are important for the activity and substituents at this positions/next to these positions have valuable role in changing the activity. The positive coefficient of I_1 indicates that disubstitution on carboxamide nitrogen favors the affinity and selectivity towards PBRs. The equation also suggests that the polarity of compounds increases the affinity and selectivity towards PBRs; this can be concluded from the negative coefficient of μ. The contribution of dipole moment illustrates the non–covalent, electronic interactions between 2–phenylimidazo[1,2–α]pyridineacetamides and the peripheral benzodiazepine receptors. Another electronic descriptor, total energy plays an important role in binding affinity of these compounds. The higher value of the total energy increases the binding affinity and selectivity towards PBRs. The stepwise deletion of compounds **21**, **11**, **31** and **1** gives a more significant model, (Eq. 10).

$$pC_2 = 16.891\ (\pm 1.871) + 230.120\ (\pm 30.607)\ qC_6 + 50.463\ (\pm\ 9.068)\ qC_{19} + 2.139\ (\pm 0.364)\ I_1 -$$
$$0.260\ (\pm\ 0.087)\ \mu + 32.828\ (\pm 11.466)\ E_T$$
$$n = 33 \quad \mathbf{DC} = \mathbf{21}, \mathbf{11}, \mathbf{31}, \mathbf{1} \quad R = 0.884 \quad \%EV = 78.10 \quad R_A^2 = 0.740 \quad F_{(5,\,27)} = 19.256 \quad p<0.0001 \qquad (10)$$
$$SEE = 0.607 \quad PRESS = 9.935 \quad SSY = 45.364 \quad R^2_{cv} = 0.781 \quad S_{PRESS} = 0.607 \quad PSE = 0.549$$

Eq. (10) explains up to 86.76% of variances in PBR affinity and selectivity and reveals characteristics of different variables discussed before to express their importance in binding affinity towards PBRs. This equation has significant statistical predictivity as shown by its R^2_{cv} value (>0.7).

For binding affinities of 2–phenylimidazo[1,2–α]pyridineacetamides towards the peripheral benzodiazepine receptors from the ovary membranes, the following equation was obtained:

$$pC_3 = 16.355\ (\pm 2.342) + 2.290\ (\pm 0.584)\ I_2 + 65.960\ (\pm 11.296)\ qC_{19} + 43.203\ (\pm 14.956)\ E_T$$
$$n = 35 \quad R = 0.763 \quad \%EV = 58.16 \quad R_A^2 = 0.541 \quad F_{(3,31)} = 14.363 \quad p<0.0001 \quad SEE = 0.929 \qquad (11)$$
$$\text{PRESS} = 26.775 \quad SSY = 63.992 \quad R^2_{cv} = 0.582 \quad S_{PRESS} = 0.929 \quad PSE = 0.875$$

Eq. (11) explains up to 58.16% of variances in the affinity data. By removing compounds **29**, **11**, **21** and **4** that have large residuals and that might act through a different mechanism of action, the following QSAR model was obtained:

$$pC_3 = 13.778\ (\pm 1.629) + 2.662\ (\pm 0.362)\ I_2 + 66.643\ (\pm 7.257)\ qC_{19} + 21.705\ (\pm 10.591)\ E_T$$
$$n = 31 \quad \mathbf{DC} = \mathbf{29}, \mathbf{11}, \mathbf{21}, \mathbf{4} \quad R = 0.896 \quad \%EV = 80.26 \quad R_A^2 = 0.781 \quad F_{(3,27)} = 36.599 \quad p<0.0001 \qquad (12)$$
$$SEE = 0.569 \quad PRESS = 8.740 \quad SSY = 44.283 \quad R^2_{cv} = 0.803 \quad S_{PRESS} = 0.569 \quad PSE = 0.531$$

Eq. (12) explains up to 80.26% of variances of the affinity data. The equation suggests that the presence of acetamide group on atom number 9 favors the affinities for PBRs as demonstrated by the positive regression coefficient of I_2. The positive coefficient of qC_{19} indicates that the affinity and selectivity towards PBR increase with increase the value of atomic charge at C_{19}. The higher value of the total energy is advantageous to the interaction between these compounds and PBRs as indicated by the positive regression coefficient of E_T.

The correlation matrix of the independent parameters along with the biological activities used to build these models is presented in Table 3. The student t–values and associated probability *p*–values of all derived QSAR models are shown in Table 4.

Table 3. Correlation matrix of biological activity and parameters

	S_6	R_1	R_{17}	I_1	I_2	qC_1	qC_6	qC_{16}	qC_{19}	μ	E_T	pC_1	pC_2	pC_3
S_1	0.922	0.997	–.220	0.170	0.129	–.973	0.388	0.222	0.179	0.174	0.017	0.917	0.353	0.281
S_6	1.000	0.891	–.045	0.176	0.136	–.879	0.364	0.154	0.140	0.237	0.226	0.838	0.324	0.265
R_1		1.000	–.230	0.158	0.134	–.975	0.386	0.223	0.160	0.140	–.008	0.915	0.350	0.273
R_{17}			1.000	–.137	0.184	0.251	–.007	–.442	–.349	–.133	0.416	–.217	–.165	–.093
I_1				1.000	0.125	–.177	–.160	–.064	0.172	0.483	–.339	0.153	0.231	0.118
I_2					1.000	–.196	0.769	–.288	–.276	–.141	0.080	0.114	0.429	0.301
qC_1						1.000	–.448	–.098	–.065	–.123	–.010	–.921	–.330	–.246
qC_6							1.000	–.097	0.019	0.109	0.030	0.344	0.520	0.410
qC_{16}								1.000	0.406	–.005	–.050	0.242	0.183	0.166
qC_{19}									1.000	0.609	–.255	0.139	0.389	0.508
μ										1.000	–.202	0.118	0.225	0.280
E_T											1.000	0.066	0.117	0.199
pC_1												1.000	0.308	0.267
pC_2													1.000	0.934

Table 4. *t*–Values and *p*– values of all models

Eq. No	Intercept/ Parameters	*t*–values	*p*–values	Eq. No	Intercept/ Parameters	*t*–values	*p*–values
(1)	Intercept	74.541	0.000	(9)	Intercept	8.016	0.000
	S_1	13.628	0.000		qC_6	5.671	0.000
					qC_{19}	4.668	0.000
(2)	Intercept	291.36	0.000		I_1	4.345	0.000
	S_1	61.520	0.000		μ	–2.645	0.013
					E_T	3.103	0.004
(3)	Intercept	30.741	0.000				
	R_1	13.503	0.000	(10)	Intercept	9.028	0.000
					qC_6	7.518	0.000
(4)	Intercept	92.452	0.000		qC_{19}	5.750	0.000
	R_1	55.797	0.000		I_1	5.882	0.000
					μ	–3.003	0.006
(5)	Intercept	4.254	0.000		E_T	2.863	0.008
	S_6	9.445	0.000				
	R_{17}	–2.091	0.044	(11)	Intercept	6.984	0.000
					I_2	3.921	0.000
(6)	Intercept	3.632	0.000		qC_{19}	5.839	0.000
	S_6	14.129	0.000		E_T	2.889	0.007
	R_{17}	–3.653	0.001				
				(12)	Intercept	8.459	0.000
(7)	Intercept	6.347	0.000		I_2	7.351	0.000
	qC_1	–14.736	0.000		qC_{19}	9.184	0.000
	qC_{16}	2.538	0.016		E_T	2.049	0.050
(8)	Intercept	10.516	0.000	(9)	Intercept	8.016	0.000
	qC_1	–25.428	0.000		qC_6	5.671	0.000
	qC_{16}	4.423	0.000		qC_{19}	4.668	0.000

The predictive powers of final Eqs. (2), (4), (6), (8), (10) and (12) were evaluated by the leave–one–out (LOO) cross–validation method. In this method, each compound was left out of the model and prediction of activity of that compound was done. The observed (Obs), calculated (Calc), residual (Res), LOO– predicted (Pred) and predicted residual (Pres) values of these QSAR equations are shown in Table 5, 6 and 7 respectively.

4 CONCLUSIONS

The present study suggests the importance of atom numbers 1, 6 and 17 for affinity towards CBRs. The affinity and selectivity of these compounds towards CBRs increase with the increase of the value of S_1 and S_6 as evidenced by the positive coefficients of S_1 and S_6. As the ETSA index carries electronic and topological information of the pattern of substituents, it can be concluded that atom numbers 1 and 6 may be involved in electronic interaction of 2–phenylimidazo[1,2–α]pyridineacetamides with the receptor. Similarly, the contribution of the RTSA index reveals that atom numbers 1 and 17 are important in relation to the dispersive/van der Waals interactions of these compounds with central benzodiazepine receptors. The lower negative atomic charge at C_1 position and the higher negative atomic charge at C_{16} position have valuable roles for improving the affinity and selectivity towards CBR.

Table 5. Observed, calculated (Calc.), residual (Res.), LOO–predicted (LOO Pred.) and predicted residual (Pres) activities of Eqs. (2) and (4)

Cpd	Observed	Eqn 2				Eqn 4			
	pC_1	Calc	Res	Pred	Pres	Calc	Res	Pred	Pres
1	7.040	7.037	0.003	7.035	0.005	6.902	0.138	6.836	0.204
2	5.000	5.164	–0.164	5.169	–0.169	4.998	0.002	4.998	0.002
3	5.000	5.010	–0.010	5.009	–0.009	4.978	0.022	4.977	0.023
4	5.000	5.019	–0.019	5.019	–0.019	4.960	0.040	4.959	0.041
5	7.051	6.910	0.141	6.842	0.209	6.922	0.129	6.858	0.193
6	5.481	–	–	–	–	–	–	–	–
7	5.000	5.015	–0.015	5.015	–0.015	4.994	0.006	4.994	0.006
8	5.000	4.981	0.019	4.981	0.019	4.986	0.014	4.985	0.015
9	6.133	–	–	–	–	–	–	–	–
10	5.000	5.023	–0.023	5.023	–0.023	4.988	0.012	4.987	0.013
11	5.000	4.976	0.024	4.975	0.025	4.976	0.024	4.975	0.025
12	5.000	4.913	0.087	4.910	0.090	4.999	0.001	4.999	0.001
13	5.000	4.963	0.037	4.961	0.039	5.015	–0.015	5.016	–0.016
14	5.000	4.960	0.040	4.959	0.041	4.986	0.014	4.985	0.015
15	5.000	5.012	–0.012	5.012	–0.012	5.017	–0.017	5.018	–0.018
16	5.000	5.045	–0.045	5.047	–0.047	5.026	–0.026	5.027	–0.027
17	5.000	5.048	–0.048	5.049	–0.049	5.018	–0.018	5.019	–0.019
18	5.000	5.015	–0.015	5.015	–0.015	5.010	–0.010	5.010	–0.010
19	6.725	6.845	–0.120	6.897	–0.172	6.979	–0.254	7.115	–0.390
20	5.000	4.937	0.063	4.935	0.065	5.027	–0.027	5.028	–0.028
21	5.000	4.997	0.003	4.997	0.003	4.998	0.002	4.998	0.002
22	5.000	5.028	–0.028	5.029	–0.029	5.014	–0.014	5.014	–0.014
23	5.000	4.995	0.005	4.994	0.006	5.006	–0.006	5.006	–0.006
24	5.000	5.008	–0.008	5.008	–0.008	5.007	–0.007	5.008	–0.008
25	5.000	4.975	0.025	4.974	0.026	4.999	0.001	4.999	0.001
26	5.000	4.985	0.015	4.985	0.015	5.031	–0.031	5.032	–0.032
27	5.000	4.991	0.009	4.990	0.010	5.007	–0.007	5.007	–0.007
28	5.000	5.005	–0.005	5.005	–0.005	5.005	–0.005	5.005	–0.005
29	5.000	5.039	–0.039	5.040	–0.040	5.012	–0.012	5.013	–0.012
30	5.000	4.971	0.029	4.970	0.030	5.009	–0.009	5.010	–0.009
31	5.000	5.000	0.000	5.000	0.000	4.974	0.026	4.974	0.026
32	5.000	5.008	–0.00	5.008	–0.008	4.981	0.019	4.980	0.020
33	5.000	4.973	0.027	4.972	0.028	4.985	0.015	4.985	0.015
34	5.000	4.997	0.003	4.997	0.003	4.998	0.002	4.998	0.002
35	5.000	5.035	–0.031	5.031	–0.031	5.005	–0.005	5.006	–0.006
36	5.000	4.969	0.031	4.968	0.032	5.005	–0.005	5.006	–0.006
37	5.000	4.977	0.023	4.976	0.024	4.999	0.001	4.999	0.001

Table 6. Observed, calculated (Calc.), residual (Res.), LOO–predicted (LOO Pred.) and predicted residual (Pres) activities of Eqs. (6) and (8)

Cpd	Observed pC_1	Eqn 6				Eqn 8			
		Calc	Res	Pred	Pres	Calc	Res	Pred	Pres
1	7.040	7.156	–0.116	7.240	–0.200	6.969	0.071	6.923	0.117
2	5.000	–	–	–	–	5.236	–0.236	5.245	–0.245
3	5.000	5.205	–0.205	5.214	–0.214	5.022	–0.022	5.022	–0.022
4	5.000	5.274	–0.274	5.285	–0.285	4.760	0.240	4.748	0.252
5	7.051	6.591	0.460	6.456	0.595	6.777	0.274	6.657	0.394
6	5.481	–	–	–	–	–	–	–	–
7	5.000	4.934	0.066	4.926	0.074	4.919	0.081	4.906	0.094
8	5.000	5.013	–0.013	5.014	–0.014	5.035	–0.035	5.036	–0.036
9	6.133	6.392	–0.259	6.447	–0.314	–	–	–	–
10	5.000	4.993	0.007	4.992	0.008	4.969	0.031	4.964	0.036
11	5.000	4.985	0.015	4.984	0.016	5.071	–0.071	5.075	–0.075
12	5.000	4.586	0.414	4.546	0.454	4.975	0.025	4.974	0.026
13	5.000	4.870	0.130	4.863	0.137	5.091	–0.091	5.095	–0.095
14	5.000	4.866	0.134	4.858	0.142	5.035	–0.035	5.036	–0.036
15	5.000	5.222	–0.222	5.231	–0.231	5.164	–0.164	5.169	–0.169
16	5.000	5.146	–0.148	5.166	–0.166	5.025	–0.025	5.027	–0.027
17	5.000	5.163	–0.163	5.183	–0.183	4.965	0.035	4.962	0.038
18	5.000	5.238	–0.238	5.247	–0.247	5.104	–0.104	5.107	–0.107
19	6.725	6.100	0.624	6.021	0.704	6.859	–0.134	6.924	–0.199
20	5.000	4.722	0.278	4.701	0.299	5.104	–0.104	5.107	–0.107
21	5.000	5.129	–0.129	5.135	–0.135	5.104	–0.104	5.107	–0.107
22	5.000	5.028	–0.028	5.032	–0.032	4.912	0.088	4.901	0.099
23	5.000	5.106	–0.106	5.111	–0.111	5.058	–0.058	5.060	–0.060
24	5.000	4.897	0.103	4.884	0.116	4.965	0.035	4.962	0.038
25	5.000	4.975	0.025	4.974	0.026	5.104	–0.104	5.107	–0.107
26	5.000	4.720	0.280	4.682	0.318	4.969	0.031	4.967	0.033
27	5.000	5.069	–0.069	5.072	–0.072	5.121	–0.121	5.126	–0.126
28	5.000	5.165	–0.165	5.172	–0.172	5.091	–0.091	5.095	–0.095
29	5.000	5.089	–0.089	5.101	–0.101	4.767	0.233	4.754	0.246
30	5.000	4.930	0.070	4.926	0.074	5.091	–0.091	5.095	–0.095
31	5.000	5.147	–0.147	5.153	–0.153	5.088	–0.088	5.091	–0.091
32	5.000	5.197	–0.197	5.205	–0.205	4.909	0.091	4.894	0.106
33	5.000	4.962	0.038	4.960	0.040	4.863	0.137	4.848	0.152
34	5.000	5.122	–0.122	5.127	–0.127	4.976	0.024	4.972	0.028
35	5.000	5.047	–0.047	5.053	–0.053	4.836	0.164	4.830	0.170
36	5.000	4.923	0.077	4.919	0.081	4.952	0.048	4.947	0.053
37	5.000	4.982	0.018	4.981	0.019	4.929	0.071	4.923	0.077

Table 7. Observed, calculated (Calc.), residual (Res.), LOO–predicted (LOO Pred.) and predicted residual (Pres) activities of Eqs. (10) and (12)

Cpd	Observed	Eq. 10				Observed	Eq. 12			
	pC_2	Calc	Res	Pred	Pres	pC_3	Calc	Res	Pred	Pres
1	8.230	–	–	–	–	7.980	8.251	–0.271	8.292	–0.312
2	8.104	8.161	–0.057	8.169	–0.065	7.646	8.004	–0.358	8.031	–0.385
3	8.284	7.630	0.654	7.581	0.703	7.731	7.890	–0.159	7.902	–0.171
4	6.424	7.224	–0.800	7.405	–0.981	5.584	–	–	–	–
5	8.485	8.489	–0.004	8.490	–0.005	8.172	7.937	0.235	7.920	0.252
6	8.292	8.316	–0.024	8.320	–0.028	7.312	7.692	–0.380	7.729	–0.417
7	7.939	7.631	0.308	7.616	0.323	8.337	7.571	0.766	7.534	0.803
8	7.876	8.047	–0.171	8.059	–0.183	8.319	7.857	0.462	7.813	0.506
9	8.824	8.993	–0.169	9.014	–0.190	7.936	8.104	–0.168	8.117	–0.181
10	7.616	8.517	–0.901	8.638	–1.022	7.047	7.779	–0.732	7.869	–0.822
11	5.464	–	–	–	–	4.740	–	–	–	–
12	7.566	6.835	0.731	6.294	1.272	7.157	7.374	–0.217	7.471	–0.314
13	7.701	8.058	–0.357	8.236	–0.535	7.599	8.368	–0.769	8.459	–0.860
14	8.092	8.370	–0.278	8.395	–0.303	8.252	8.142	0.110	8.132	0.120
15	6.668	7.139	–0.471	7.222	–0.554	0.400	6.217	–0.143	6.230	–0.156
16	5.907	6.686	–0.779	7.040	–1.133	0.406	5.930	–0.901	6.124	–1.095
17	6.804	6.938	–0.134	6.964	–0.160	–0.807	6.119	–0.282	6.160	–0.323
18	8.301	7.415	0.886	7.303	1.000	0.248	6.405	0.631	6.364	0.672
19	7.454	7.663	–0.209	7.714	–0.260	0.766	5.978	0.542	5.903	0.617
20	6.845	7.118	–0.273	7.238	–0.393	0.527	5.864	–0.267	5.937	–0.340
21	4.682	–	–	–	–	3.139	–	–	–	–
22	7.412	7.070	0.342	7.030	0.382	6.636	5.863	0.773	5.787	0.849
23	8.313	7.420	0.893	7.301	1.012	7.449	6.083	1.366	5.956	1.493
24	5.663	6.173	–0.510	6.247	–0.584	5.296	5.750	–0.454	5.800	–0.504
25	6.046	6.814	–0.768	6.959	–0.913	5.294	6.036	–0.742	6.118	–0.824
26	5.677	5.707	–0.030	5.720	–0.043	5.387	5.784	–0.397	5.843	–0.456
27	6.409	5.908	0.501	5.788	0.621	6.538	6.336	0.202	6.319	0.219
28	6.640	5.653	0.987	5.385	1.256	5.977	6.194	–0.217	6.209	–0.232
29	5.878	6.671	–0.793	6.879	–1.001	5.884	–	–	–	–
30	6.772	7.081	–0.309	7.170	–0.398	–	–	–	–	–
31	5.920	–	–	–	–	5.572	5.306	0.266	5.172	0.400
32	5.288	4.966	0.322	4.688	0.600	5.513	5.242	0.271	5.107	0.406
33	5.005	5.364	–0.359	5.616	–0.611	4.937	5.473	–0.536	5.744	–0.807
34	9.347	8.599	0.748	8.509	0.838	8.481	8.257	0.224	8.233	0.248
35	8.456	8.417	0.039	8.408	0.048	8.638	7.971	0.667	7.872	0.766
36	9.481	8.534	0.947	8.442	1.039	8.770	8.291	0.479	8.243	0.527
37	8.623	8.585	0.038	8.581	0.042	–	–	–	–	–

The higher negative charges of atoms C_6 and C_{19} have important electronic roles and substituents at these positions/ next to these positions have valuable roles in changing the PBR affinity and selectivity. The presence of an acetamide group and double substitution on carboxamide nitrogen favors the PBR affinity and selectivity of those compounds. The negative coefficient of dipole moment indicates that the polarity of compounds increases the affinity and selectivity towards PBR receptors. The contribution of dipole moment indicates the non–covalent, electronic interactions between 2–phenylimidazo[1,2–α]pyridineacetamides and peripheral benzodiazepine receptors. The total energy of compounds has also an important role in the interaction between these compounds and the PBRs for improving the affinity and selectivity of PBRs. These observations are represented by the three dimensional iso–surface electrostatic potential map of the best active analog

(compound 36) as shown in Figure 2.

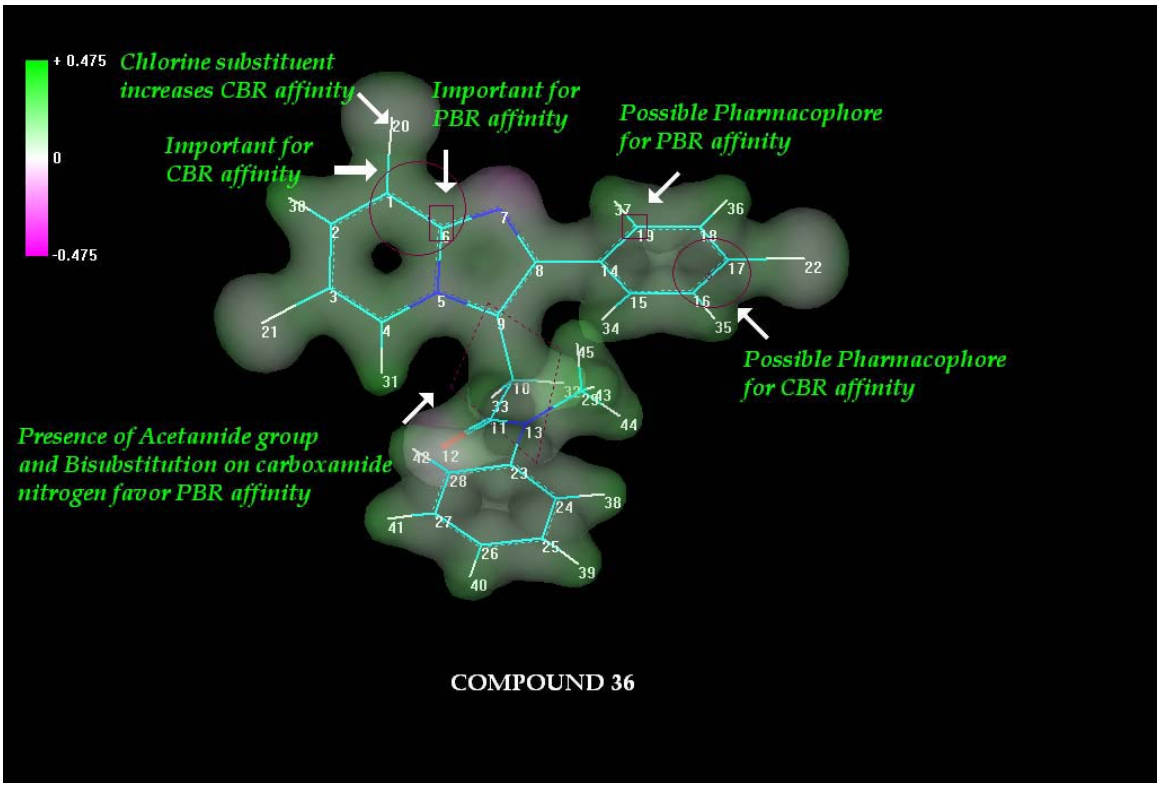

Figure 2. 3D Iso–surface electrostatic potential map of compound **36**

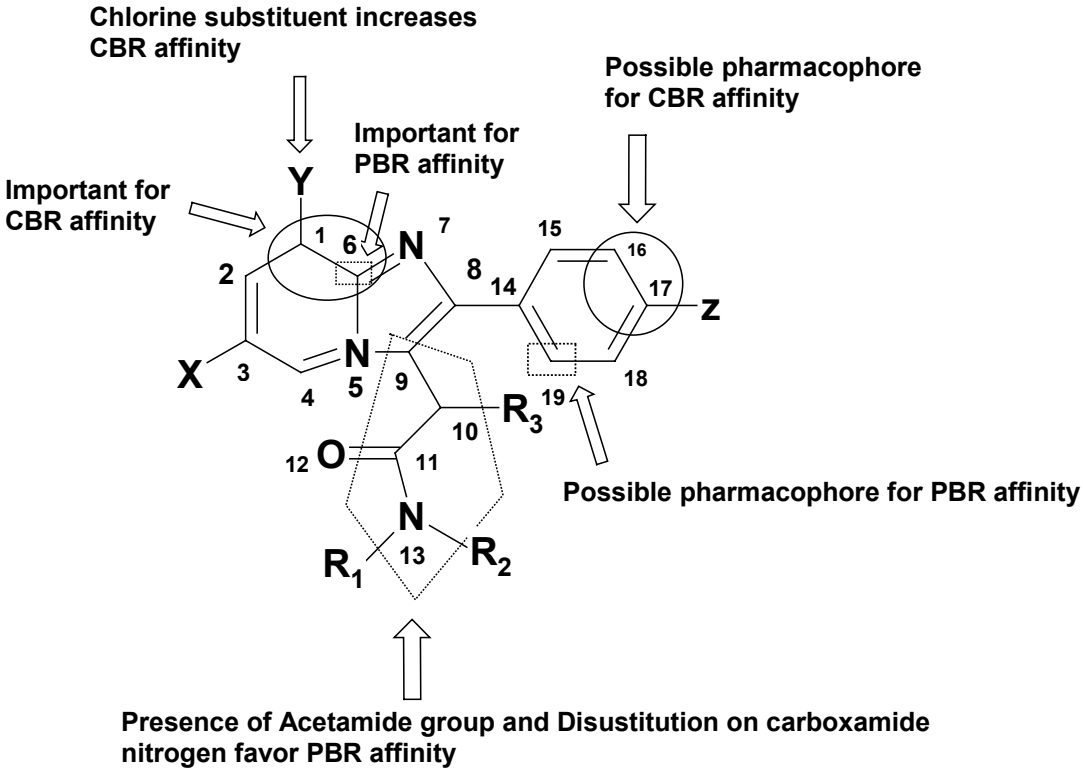

Figure 3. Pharmacophoric representation of 2–phenylimidazo[1,2–α]pyridineacetamides

The possible pharmacophoric atoms in 2–phenylimidazo[1,2–α]pyridineacetamides for the CBR or PBR affinity and selectivity are presented in Figure 3.

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