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Periodic Research

QSAR Study of Non Benzodiazepine Compounds

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Abstract

For Quantum QSAR based study of non-benzodiazepines series of non BzR have been calculated with the help of CAChe software. The parameter adopted in this calculation is the semi-empirical PM3 based.

Keywords: QSAR Study, Non Benzodiazepine Compounds.

Introduction

The non-benzodiazepines are a class of psychoactive drugs whose Pharmacological action are similar to those of the benzodiazepines, but are structurally distant or unrelated to the benzodiazepines on a chemical level. Non-benzodiazepines have demonstrated efficacy in treating sleep and emotional disorders. They act via the benzodiazepine receptor site (BzR) on the Gamma-amino butyric acid receptor (GABAA) family and have been subjected to extensive QSAR studied by Blair et al.[4], Greco et al[7], Gupta[9] and Hadjipavlou- Litina et at[10].

The various non-benzodiazepine compounds like Imidazo-benzodiazepine carboxylic Acid derivatives, Imidazo-benzodiazepine carboxylic Acid derivatives, Imidazo-benzodiazepinecarboxylic Acid, Imidazo [1, 5-a] [1, 4] benzodiazepine Esters derivatives and Imidazo [1, 5-a] [1, 4] benzodiazepine Esters also bind with BzR with a high affinity. Thus, all compounds that bind to the BzR should have certain common characteristics that allow for recognition by the receptor regardless of the type of (in vivo) activity. Molecular modeling studies have determined that all BDZ ligands share the presence of an aromatic or heteroaromatic ring, believed to undergo p/p stacking with aromatic amino acid residues within the receptor, as well as a proton-accepting group that exists in the same plane of the aromatic ring and interacts with a histidine residue on the receptor[10]. The structural diversity among non-benzodiazepine compounds makes it difficult to generalize the molecular requirements for BzR. The Quantum QSAR based study pervades better tools to explorer relationship between structures of molecules with their binding affinities. Different methods like Quantum Mechanical properties based QSAR In the present study, we have taken series of non-benzodiazepine compounds with their observed binding affinities [1, 2, 5, 6, 12, 14, 19, 20, 21]. The different QSAR models were developed to establish a generalized relation for heterogeneous data set of non-benzodiazepine derivatives. Since the drug molecules are active only when they have certain physicochemical properties with specific 3D structure in this way the physicochemical and three-dimensional aspects have equal importance for a molecule to be a medicine. The current study deals the known values of Quantum QSAR as well as 3D aspects by comparative molecular field regression analysis.

Series of nonbenzodiazepine compounds were taken with their observed affinities to BzR.

Series

The parent skeleton of series is given in Figure-1 and Table-1 contain 019 derivatives of 3-substituted Imidazo [1, 2- b] pyridazines with their observed binding affinities to the rat brain tissue[11].

Methodology

The Quantum Mechanical QSAR-

The Quantum Chemical parameter based QSAR study was performed by the following important descriptors like chemical potential (μ) Mullikan[15], Absolute hardness (η) Parr and Pearson[16], Global Softness (S) Pearson[18], Electro negativity (χ) lczkowski and Margrave[13], Eigen value of Highest occupied molecular orbital (EHOMO) Parr and Pearson[17], Eigen value of lowest unoccupied molecular orbital (EHOMO)[17]. The molecules were drawn by CACho pro software and the geometries were optimized at PM3 level in conjunction with molecular mechanics. The

EHOMO, ELUMO, values of every molecule were calculated by project leader software associated with CAChe pro. The global hardness and electronegatities were calculated using frontier orbital energies obtained from PM3 results and reported in Tables-1. Multiple liner regression analysis (MLR) is performed to establish the QSAR. Some molecules of different sets not predicted well in intitial step of regression were omitted from final model and reported as outliers

3-Substituted Imidazo [1,2-b] Pyridazines

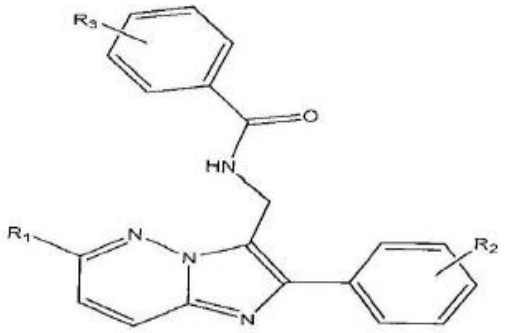

Table-1 3-Substituted Imidazo {1, 2- b} Pyridazines Derivative of Series and their Observed Activities (log 1/IC50 Affinity) [11]

Comp No	R_1	R_2	R_3	Clog P
1	OCH_3	3,4-OCH_2O-	H	8.155
2	OCH_3	4-Cl	H	7.538
3	OCH_3	H	2F	6.857
4	OCH_3	$4CH_3$	2F	7.678
5	OCH_3	3,4-OCH_2O-	2F	7.854
6	OC_2H_5	H	H	6.733
7	OC_2H_5	CH3	H	7.456
8	OC_2H_5	3,4-OCH_2O-	H	7.602
9	OC_2H_5	4-Cl	H	7.194
10	OC_2H_5	H	2F	6.682
11	OC_2H_5	$4CH_3$	2F	7.292
12	OC_2H_5	3,4-OCH_2O-	2F	7.509
13	OC_3H_7	$4CH_3$	H	6.742
14	OC_3H_7	3,4-OCH_2O-	H	6.936
15	OC_3H_7	H	2F	6.623
16	OC_3H_7	$4CH_3$	2F	6.845
17	$O(CH_2)_2OCH_3$	$4CH_3$	2F	6.498
18	OCH_3	3,4-OCH_2O-	NO2	8.097
19	OCH_3	3,4-OCH_2O-	NO2	7.638

Table-2 Values Of Descriptors Predicted Biological Activities Of Series 'C'

Compound	μ	η	S	χ	ELUMO (eV)	EHOME (eV)
1	-3.73470202	3.734702	0.1338795	-4.88948304	-1.15478102	-8.62418505
2	-3.81041249	3.8104125	0.1312194	-4.99195378	-1.18154129	-8.80236627
3	-3.89900782	3.8990078	0.1282378	-4.93227592	-1.0332681	-8.83128374
4	-3.84226975	3.8422698	0.1301314	-4.85977232	-1.01750257	-8.70204207
5	-3.88489628	3.8848963	0.1287036	-4.97198384	-1.08708756	-8.85688011
6	-3.88489628	3.8848963	0.1287036	-4.97198384	-1.08708756	-8.85688011
7	-3.88392426	3.8839243	0.1287358	-4.95733786	-1.0734136	-8.84126212
8	-3.74024467	3.7402447	0.1336811	-4.86459589	-1.12435122	-8.60484055
`9	-3.81797418	3.8179742	0.1309595	-4.9678373	-1.14986312	-8.78581148
10	-3.90696211	3.9069621	0.1279767	-4.91792178	-1.01095967	-8.82488388
11	-3.85073005	3.85073	0.1298455	-4.84635073	-0.995620683	-8.69708078
12	-3.74373347	3.7437335	0.1335565	-4.94478181	-1.20104834	-8.68851528
13	-3.82276935	3.8227693	0.1307952	-4.89635946	-1.07359011	-8.7191288
14	-3.73881975	3.7388198	0.133732	-4.86649156	-1.12767181	-8.60531131
15	-3.90616833	3.9061683	0.1280027	-4.9195721	-1.01340377	-8.82574042
16	-3.84924304	3.849243	0.1298957	-4.84646363	-0.997220593	-8.69570667
17	-3.84243562	3.8424356	0.1301258	-4.8724045	-1.02996888	-8.71484011
18	-3.71079835	3.7107983	0.1347419	-5.00973384	-1.29893549	-8.72053218
19	-3.64504469	3.6450447	0.1371725	-5.1327464	-1.48770171	-8.77779108

Multiple Linear Regression (MLR) Analysis

MLR analysis were perfomed using Minitab software. The quantum mechanical descriptors were used as independent variables and the log 1/Ki and C log P values as the dependent variables. In the statistical analysis, the systematic search was performed to determine significant descriptors. The correlation matrix was developed to minimize the effect of co-linearity and to avoid redundancy and the variables physically removed from the analysis, which shows exact linear dependencies between subsets of the variables and multi-co-linearity (high multiple correlations between subsets of the variables.)

Result and Conclusion

In this model compounds μ, η, E LUMO and E HOME have been identified as are highly correlated with predictors and the reaming descriptor S and χ of these compounds are not included in deriving regression equation. The Plot of percent vs. standardized residual values for this model is given in **Figure-1.**

In this contribution the calculation of Quantum mechanical semi empirical based

descriptors is carried out and the regression models have been generated for the determine of biological activity of BzR of series of compounds. The comparison of all the models indicates that the Quantum based QSAR study is more reliable than others and has high predictive power.

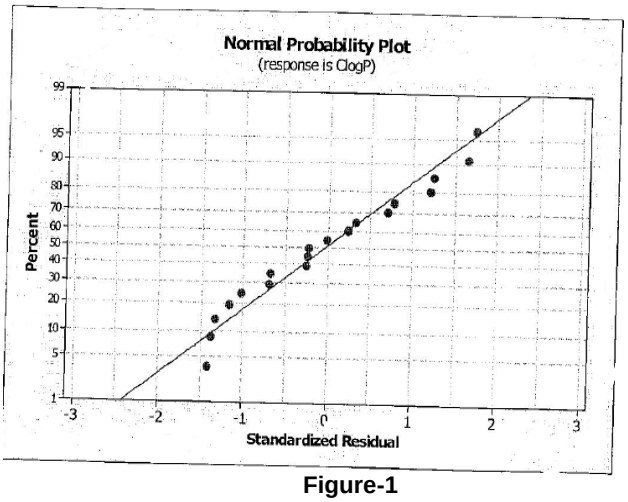

Figure-1

The regression equation is

C log P = 764-99032109μ+3141394η-2877S+81239301χ
91706455E LUMO(ev)+10467151E HOMO(ev)

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