QSAR Study of ORL1 Agonist Analgesic Effect of Some Imidazoles with Molecular Descriptors

OCTAVIAN ISTRATOAIE[1], LUCIANA TEODORA ROTARU[2]*, RENATA MARIA VARUT[3], MARIUS CIPRIAN VARUT[3], MIRCEA CATALIN FORTOFOIU[4], MARIA FORTOFOIU[5], ROXANA KOSTICI[6]

[1] Univesity of Medicine and Pharmacy Craiova, Cardiology Discipline, Clinical Emergency Hospital Craiova, 2-4 Petru Rares Str., 200349,Craiova, Romania

[2]Univesity of Medicine and Pharmacy Craiova, Emergency & First Aid Department, Emergency Department-SMURD, University County Hospital Craiova, 1 Tabaci Str. 200642, Craiova, Romania

Univesity of Medicine and Pharmacy Craiova, Pharmacy Department I, 2-4 Petru Rares Str., 200349, Craiova, Romania

[4]Univesity of Medicine and Pharmacy Craiova, Department III, Medical Specialties I, Discipline of Internal Medicine-Medical Semiology, 2-4 Petru Rares Str., 200349, Craiova, Romania

[5]Univesity of Medicine and Pharmacy Craiova, Department VII, Emergency Medicine Discipline, Emergency Department-SMURD, University County Hospital 1 Tabaci Str. Str., 200642, Craiova, Romania

[6]Univesity of Medicine and Pharmacy Craiova, Pharmacy Department I, 2-4 Petru Rares Str., 200349, Craiova, Romania

Imidazole and its derivates represent an interesting source of study for researchers for more than a century and was recently studied for their analgesic effect by ORL-1 receptor agonist effect on. In the theoretical study we used molecular mechanics programs and we characterized the structural properties for a series of ten imidazoles. The selected physico-chemical descriptors were: the HOMO and LUMO frontier orbitals, the dipole moment, the heat of formation, the total energy of the molecule, the ionization energy, the surface area and the molecular volume. From the correlation study we noticed the dependence between the analgesic effect and the total energy, the area of the molecular surface and the molecular volume.

Keywords: imidazole, ORL1, QSAR

Imidazoles occupy a unique position in heterocyclic chemistry, and its derivatives have attracted considerable attention in recent years for their versatile properties in chemistry and pharmacology. Imidazole is formed from a nitrogen-containing heterocyclic ring having biological and pharmaceutical effects. Imidazole derivates possess a wide range of biological activities such as antibacterial, anticancer, antitubercular, antifungal, analgesic and anti-HIV activities [1].

Imidazole derivates have been studied for their agonist effect on ORL 1 receptors, acting as modulators in pain therapy [2].

Information obtained using molecular modeling programs and calculation of physicochemical parameters are used extensively in the pharmaceutical industry today. The utility is to improve the therapeutic activity of drugs, namely the design and synthesis of new compounds with improved pharmaceutical properties. The QSAR technique, both classical and modern - that uses a multitude of descriptors - has taken on an important scale, with impressive results in designing new drugs, benefiting from the advances of quantum chemistry and molecular modeling, boosted by the impressive avant-garde computing techniques. Numerous research shows that there has been a high correlation between experimental and estimated values, indicating the validation and good quality of QSAR models [3].

For exemple molecular modeling programs help researchers in neuroscience to adopt new approaches in the development of neuroprotective molecules for Alzheimer's disease [4].

A group of Brazilian researchers reported the antitumor activity of rutaercapine and its analogs in cancers of the central nervous system. The chemical structures were modeled using the Hyperchem program, then a number of molecular descriptors were determined for each substance. Based on the selected electronic descriptors, it is possible to suggest new compounds to be synthesized with activity against CNS cancer [5].

Molecular modeling studies *in silico* allowed determination of the interaction of the hydroxyl terminal groups of DG0 and DG1 dendrimer with the active sites of inducible enzymes of nitrogen synthase and cyclo-oxygenase-2 (COX-2) resulting in inhibition of both iNOS and COX-2 enzymes. Predictive studies correlated very well with in vitro biological data, resulting in anti-inflammatory effects of dendrimer comparable to ibuprofen and celecoxib [6].

Molecular modeling was used for testing the cellular antiproliferative effect of Kelin compared with erlotinib as a positive control. Kelin is a natural furocromone that has shown significant inhibitory activity on the epidermal growth factor receptor (ECFR) in the MCF-7 and HeLa cell lines. Molecule simulation of the therapeutic principle in the ECFR active site was performed to determine the probable binding pattern [7].

Using molecular mechanics studies, it was possible to calculate the optimal geometries and vibrational properties of the Tlln4Se16 cluster representing the local structure of the investigated crystal [8].

New copper (I) [CuCl (PPh3) (L)] (1: L = 4-carboxyphenyl) bis (3,5-dimethylpyrazolyl) methane complexes; (2: L = 3-carboxyphenyl) bis (3,5-dimethyl-pyrazolyl) methane) were characterized by elemental analyzes and by various spectroscopic techniques such as FT-IR, NMR, UV-Vis and ESI-MS. The molecular structures of complexes 1 and 2 were analyzed by the B3LYP / DFT theoretical method. In addition, the potential of complex 1 interaction with DNA and enzymes (Topoisomerases I and II) was analyzed by molecular modelinh [9].

Various structural descriptors that may contribute to the biological analgesic activity of selected imidazole

* email: lucianarotaru@yahoo.com

All authors have equally contributed to this work

derivatives have been calculated in the present study. The calculated descriptors were the HOMO and LUMO orbitals, MSA (surface area of the molecule), CMV (Cosmo molar volume), μ (dipole moment), ΔHf (heat of formation) E_{tot} (total energy of the molecule) and ionisation energy (EI). We determined physicochemical parameters and found a correlation between biological activity and descriptor values.

Experimental part

The QSAR study was conducted following the steps:

- Molecular modeling of structures was performed using the HyperChem 8 program [10] (Semi-Semitic Optimization PM 3 / SCF) [11].

-Molecular quantum calculations of molecular geometries were performed using the MOPAC 2016 program. The output data contains physico-chemical information about selected molecules [12].

-Correlation between molecular descriptors and analgezic effect, using Regression Excel function from Microsoft Office package.

Results and discussions

The structure of imidazoles studied had the following common structure (fig. 1):

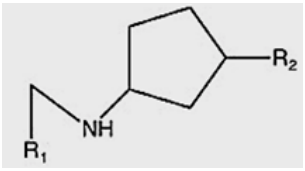


Fig.1. The common structure of the studied imidazoles

The study of molecular areas for the two types of molecular orbitals shows the contribution of atomic orbitals to their formation. The difference in energy between HOMO and LUMO levels ($\Delta E = E_{LUMO} - E_{HOMO}$) is a chemically important molecular descriptor explaining the stability of the molecule, a low value indicating that the molecule is highly reactive [13]. Another molecular parameter resulting from quantum chemical calculations is the electrical dipole moment (μ), which reflects the partial separation of the electrical charge in the molecule. This molecular descriptor is also a predictor of the chemical reactivity of molecules, expressing the polarization of the molecular system [14]. MSA and CMV are geometric descriptors that effectively characterize the form of the ligand, that plays an essential role in the interaction of the ligand (drug) - biological receptor [15]. Heat of formation is an important parameter which reveals the molecular reactivity, a high heat forming characterizing a stable molecule. The ionization potential

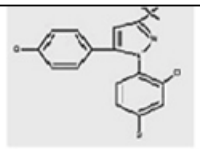
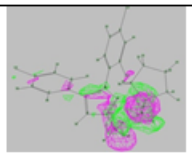
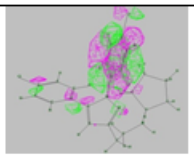
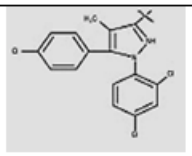
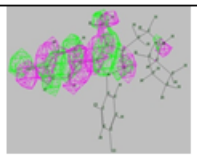
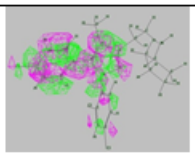
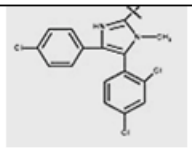
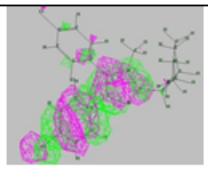
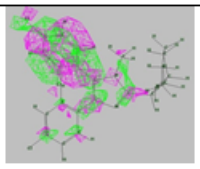
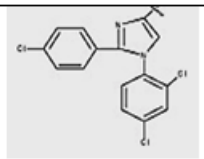
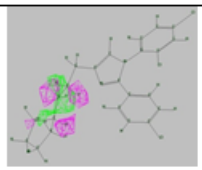
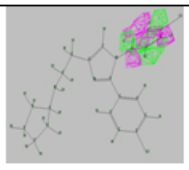
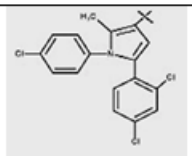
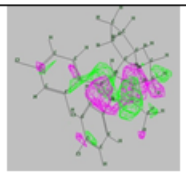
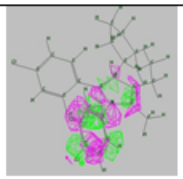
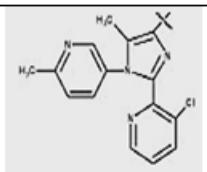
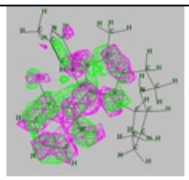
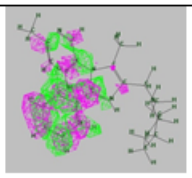
Nr.	R_1	R_2			Biological activity
1		H			6.886
2		H			7.553
3		H			6.284
4		H			6.208
5		H			6.699
6		H			7.585

Table 1
RADICALS OF IMIDAZOLE DERIVATIVES AND BIOLOGICAL ACTIVITY

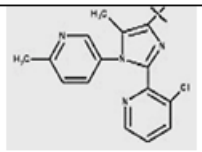
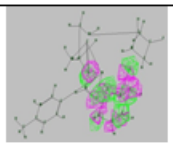
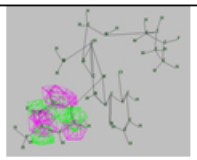
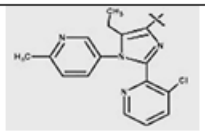
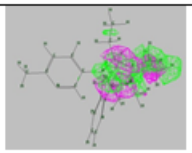
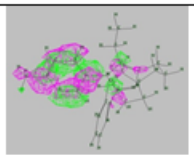
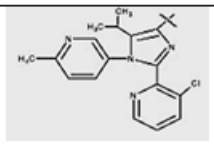
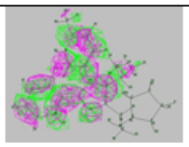
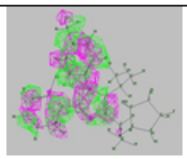
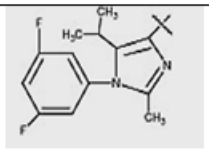
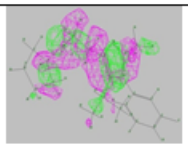
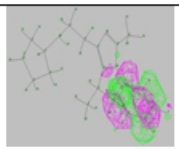
7		F			8.041
8		H			8.328
9		F			8.854
10		F			8.066

Table 1
(continuated)

Nr.	μ (D)	ΔE	ΔHf (kcal/mol)	TotE (eV)	MSA(A^2)	CMV(A^3)	IE (eV)
1	2.832	8.364	58.27	-4357.49	411.74	506.56	8.789
2	2.918	7.823	44.05	-4507.73	409.36	526.6	8.828
3	7.704	7.821	122.58	-4508.44	421.32	521.66	8.658
4	4.158	7.294	173.75	-4358.21	420.27	502.14	8.546
5	1.497	7.852	73.43	-4458.741	418.96	528.3	8.617
6	7.27	6.832	263.95	-4277.28	398.11	485.85	6.743
7	6.852	7.765	63.34	-4702.96	393.61	498.51	8.547
8	6.977	7.554	227.4	-4400.75	395.58	509.85	8.358
9	6.362	7.66	10.29	-5002.8	401.94	535.71	8.43
10	4.785	7.732	-523.83	-4763.62	363.64	448.19	8.763

Table 2
THE VALUE OF THE MOLECULAR DESCRIPTORS USED IN THE QSAR CORRELATION

	Coefficients	*Standard Error*	*t Stat*	*P-value*
Intercept	21.91244	5.326634	4.113751	0.003373
MSA(A^2)	-0.03585	0.013192	-2.71731	0.026358

Table 3
HANSCH EQUATION FOR A SINGLE DESCRIPTOR: BIOLOGICAL ACTIVITY =21.91244 - 0.03585*MSA

	Coefficients	*Standard Error*	*t Stat*	*P-value*
Intercept	20.208	8.626028	1.251557	0.250933
MSA(A^2)	-0.0767	0.001	-1.56594	0.161343
CMV(A^3)	0.0356	0.0135	-1.97782	0.088466

Table 4
HANSCH EQUATION FOR TWO DESCRIPTORS (R^2: 0.95): BIOLOGICAL ACTIVITY =20.208 0.0767*MSA+0.0356*CMV

	Coefficients	*Standard Error*	*t Stat*	*P-value*
Intercept	10.79597	8.626028	1.251557	0.250933
TotE (eV)	-0.00163	0.001044	-1.56594	0.161343
MSA(A^2)	-0.02666	0.013479	-1.97782	0.088466

Table 5
HANSCH EQUATION FOR TWO DESCRIPTORS (R2: 0.78): BIOLOGICAL ACTIVITY = 10.79597-0.00163*TOTE-0.02666*MSA

AB_T	AB_E	Differences
6.8234772	6.886	0.06252
7.72586	7.553	-0.17286
6.6310832	6.284	-0.34708
6.0104598	6.208	0.19754
7.050604	6.699	-0.3516
7.124995	7.585	0.46001
7.9248922	8.041	0.11611
8.181126	8.328	0.14687
8.6222052	8.854	0.23179
8.4160968	8.066	-0.3501

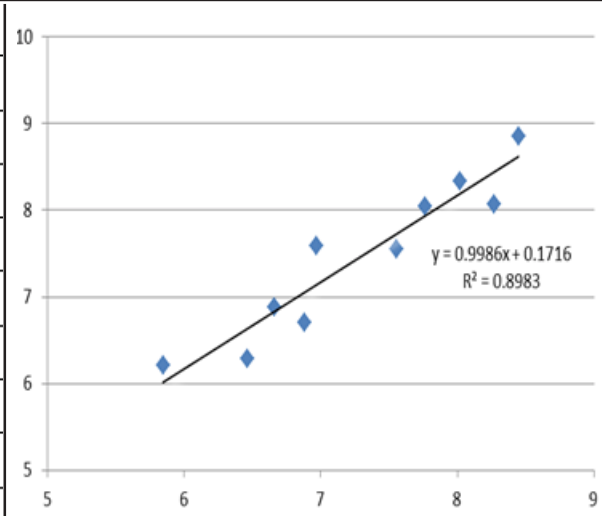


Table 6
AB_T - THEORETICAL BIOLOGICAL ACTIVITY (USING TWO DESCRIPTORS AND R^2: 0.95); AB_E - EXPERIMENTAL BIOLOGICAL ACTIVITY

may play an important role in the pharmacokinetics of compounds [16].

The best correlation with a single descriptor was observed with MSA.(R^2=0.68).

The best correlation between biological activity and two descriptors was observed in correlation with MSA and CMV (R^2: 0.95) followed by the total energy of the molecule and the area of the molecular surface (R^2: 0.78).

Conclusions

Computational chemistry is of real use in the field of drug research, helping considerably to find new therapeutic targets useful in managing various diseases.

Imidazole and its derivatives represent an interesting source of study for researchers for more than a century. Our research was therefore aimed at involving molecular descriptors in conducting QSAR / QSPR studies that would allow the molecular design to be thorough and implicitly to predict and describe the properties of chemical compounds. The calculated predictors were the HOMO and LUMO border orbitals, the molecular surface area, the Cosmo molar volume , the dipole moment, the heat of formation, the total energy of the molecule and the ionizing energy. The calculations show the dependence between the analgesic activity of the imidazole derivatives and the total energy of the molecule, the area of the molecular surface and the molecular volume.Acknowledgement

References

1.VERMA, A., JOSHI, S., SINGH, D., Journal of Chemistry, article ID 329412, 2013.
2.SRIVASTAVA, K., SHUKLA, N., Journal of Saudi chemical society, 17, nr. 3, 2013, p. 321-328.
3. ALMI, Z., ILCNAC, 18, 2014, p. 113-122.
4.Kumar, P., Pillay, V., Choonara, Y.E., Modi, G., Naidoo, D., Int. J. Mol. Sci., 12, 2011, p. 694-724.
5.MARTINS, G.R., HAMILTON B., CAMARGO, T.F.M., CAMARGO, A.J., Journal of the Brazilian Chemical Society, 23, nr. 12, 2013, p. 2183-2190.
6.NEIBERT, K., GOSEIN, V., SHARMA, A., KHAN, M., WHITEHEAD, M.A., Mol. Pharmaceutics, 10, 2013, p. 2502"2508.
7.ABDEL-SATTAR, S., ELGAZWY, H., EDREES, M.M., ISMAIL, S.M., Journal of Enzyme Inhibition and Medicinal Chemistry, 28, nr. 6, 2012, p. 1171-1181.
8.KALKAN, N., CELIK, S., BAS, H., OZEL, A.E, Journal of optoelectronics and advanced materials, 19, nr. 3 - 4, 2017, p. 234 – 245.
9.KHAN, R.A., USMAN, M., DHIVYA, R., BALAJI, P., ALSALME, A., ALLOHEDAN, H., Scientific Reports, nr. 7, 2017, p. 1-15.
10.www.filestube.com/116d34a4d3cd050403e9,g/Poetable-HyperChem-8-0-7.html
11.***http://www.4shared.com/file/E6zKU0pg/portable_hyperchem_807.html
12. *** http://openmopac.net/
13. MINSKY, A., MEYER A.Y., RABINOVITZ, M., 1, nr. 50, 1982, p. 5351-5354.
14.ERIC, J., LIEN C.T., Journal of Pharmaceutical Sciences, 71, nr. 6, 1982, p. 641-655.
15.WATERBEEMD, H., LENNERNÄS, H., ARTURSSON, P., Drug Bioavailability: Estimation of Solubility, Permeability, Absorption and Bioavailability, 2003.
16.***http://www.sciencedirect.com/topics/pharmacology -toxicology-and-pharmaceutical-science/degree-of ionization

Manuscript received: 27.03.2017