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Research Article

QSTR AND POM STUDIES OF PROPIONIC ACID DERIVATIVES AS NON STEROIDAL ANTI INFLAMMATORY DRUGS

Taibi Ben Hadda[1]

Université Mohammed Premier, Faculté des Sciences, Laboratoire de Chimie des Matériaux, Oujda-60000, Morocco.

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Abstract

A quantitative structure-toxicity relationship (QSTR) analysis of nineteen structurally diverse Propionic acid derivatives reported as Non Steroidal Anti-Inflammatory Drugs (NSAID) has been performed using 2D and 3D descriptors. This investigation revealed several important physico-chemical and structural requirements for toxicity of these molecules. The QSTR models reported, herein, provide interesting insights in understanding the hydrophobic, steric, electronic and structural factors that are responsible for the toxicity of this individual set of compounds. Best model derived from 3 descriptors, using stepwise regression analysis, is with $R^2 = 0.876$ and $R^2(\text{pred}) = 0.810$. $R^2_{(\text{LOO})}$ and PRESS are used to validate the model. These results can be used for further design and development of new Non Steroidal Anti Inflammatory compounds with lesser toxicity along with ease of synthesis. A supplementary correlation of structure with toxicity of these compounds with respect to molecular modeling, Lipinski rule of five, drug-likeness, toxicity profiles and other physico-chemical properties of drugs are described.

Keywords: Profens, QSTR, toxicity, Petra/Osiris/Molinspiration (POM).

Introduction

Inflammation is an unwanted process affecting many parts of body, characterized by excessive heat, swelling, minor pain and redness [1]. Anti-inflammatory agents are drugs which are used to counteract inflammation and to manage edema. Anti-inflammatory agents are of two types: Steroidal and Non-Steroidal. Now a day, non-steroidal anti-inflammatory agents like Profens, Salicylates etc. are widely used to treat inflammation. In present-day medication, profens are routinely prescribed by medical practitioners, albeit most of them are strong organic acids (*pKa* = 3.0-5.0) and lipophilic with high toxicity. Thence, search for profen with high activity but low toxicity is still continue [2]. Discovery of new drug is a great challenge that particular drug has to surpass so many phases. Drug designing could be achieved by using modern techniques of drug designing like QSAR, Docking, Homology Modelling [3-5] and Petra/Osiris/Molinspiration (POM) [6-12].

In Quantitative Structure–Activity/Toxicity Relationships (QSAR/QSTR) efforts are made to correlate molecular structure with chemical properties or biochemical activities. The QSTR studies are playing a crucial role in present-day drug design. In QSTR, molecular descriptors are used which effectively characterize steric, hydrophobic, electronic characters. These descriptors are then used to get a reasonable correlation between structure and toxicity.

The objectives of this work are:

(1) To determine the best variables which afford the most significant linear QSTR models correlating the structure of these compounds with their toxicity.

(2) To understand the various characters responsible for toxicity especially for Profens.

(3) To find new ibuprofen derivatives which will be more effective than ibuprofen and easy to synthesize.

(4) To carry out POM calculations to understand properties of Profens such as asoociated

toxicity risks, Drug-likeness etc .

Experimental protocol / Computational approach

Data set: The data set of nineteen structurally diverse profens selected for the study along with their LD_{50} related to toxicity was collected from literature [13]. Table 1 contains names and values of descriptors for the various Profens. For the sake of convenience we have converted LD_{50} values into pLD_{50} or $-logLD_{50}$ values.

Table 1. LD_{50} of Propionic Acid Derivatives **1-19** as Non Steroidal Anti-Inflammatory.

No	Name	LD_{50}	$-logLD_{50}$	Mor02e	HATS1m	Mor26e
1	Naproxen	360	-2.5563	30.158	0.136	-0.470
2	Ketoprofen	360	-2.5563	31.592	0.089	-0.038
3	Ibuprofen	740	-2.8692	27.316	0.125	-0.493
4	Flurbiprofen	640	-2.8061	33.868	0.058	-0.159
5	Tiaprofenic	690	-2.8388	28.835	0.116	-0.450
6	Fenoprofen	1400	-3.1461	27.863	0.093	-0.190

7	Fenbufen	795	-2.9003	35.498	0.061	-0.615
8	Oxaprozin	1210	-3.0827	30.175	0.070	0.124
9	Bermoprofen	212	-2.3263	37.962	0.064	-0.291
10	Indoprofen	700	-2.8451	32.113	0.087	-0.368
11	Benoxaprofen	800	-2.9030	30.650	0.079	-0.312
12	Pranoprofen	447	-2.6503	30.283	0.123	-0.289
13	Pirprofen	1350	-3.1303	29.276	0.094	-0.350
14	Suprofen	590	-2.7708	32.419	0.093	-0.210
15	Miroprofen	570	-2.7558	30.807	0.086	0.070
16	Isoprofen	1050	-3.0211	28.599	0.101	0.018
17	Zoliprofen	660	-2.8195	27.771	0.119	-0.242
18	Orpanoxin	2460	-3.3909	27.184	0.093	-0.295
19	Carprofen	282	-2.4502	26.782	0.152	-0.118

Molecular Descriptors and computer programs

Chem Sketch software (ACD labs 12. freeware) was used to draw 2D and 3D structures of the molecules. 2D and 3D descriptors like WHIM, GATEAWAY, and TOPOLOGICAL INDICES etc available in e-Dragon were used to get a pool of descriptors. Weka 3.6 was used to perform the regression analysis and other statistical analyses.

Optimum Number and set of Descriptors to be used:

The most important consideration in developing any successful QSAR model to breed performance is the correct number and set of descriptors in the model. This procedure involves:

1. All descriptors with same values for all molecules were omitted.

2. As far as possible, the independent variables in Multiple Linear Regression (MLR) must not be highly correlated. Therefore, one of the two descriptors that has the pair wise correlation coefficient above 0.9 (R >0.9) and has a large correlation coefficient with the other descriptors in each class was eliminated.

In multiple regression analysis, the independent variables must be orthogonal. Consequently the autocorrelation among the descriptors was checked and is given in the correlation matrix in Table 2. The correlation matrix shows that there is good correlation of –logLD_{50} with 3D descriptors like Mor02e. Moreover the correlation between descriptors is absent which is essential for statistical stability.

.**Table 2.** Correlation matrix for –logLD50 and used descriptors.

	-logLD50	**Mor02e**	**HATS1m**
Mor02e	0.433	-----	-----
HATS1m	0.238	-0.703	-----
Mor26e	-0.019	-0.138	-0.148

MLR equation

The best MLR equation derived using multi linear regression analysis along with various statistical parameters is as follows:

pLD_{50} = - 7.538 + 12.379 HATS1m + 0.119 Mor02e + 0.462 Mor26e

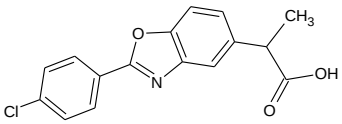
s = 0.099, R^2 = 87.6%, R^2(adj) = 85.1%, PRESS = 0.229, R^2(pred) = 81.0%

Table 3 show the observed and calculated –logLD_{50} for Profen derivatives.

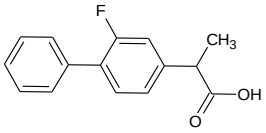
Validation

For a data set of 19 molecules, we might have derived a 3 parametric equation by chance. Therefore, in order to prove that the models are not inadvertent, we have calculated R^2_{pred}, and PRESS also.

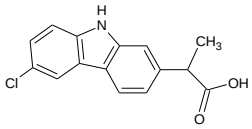
The extensive validation indicates that the derived equation is stalwart enough and can be used for prediction of –logLD_{50} values for new Profen derivatives.



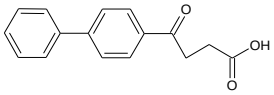
Benoxaprofen (11)



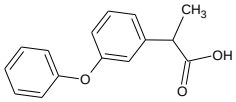
Bermoprofen (9)



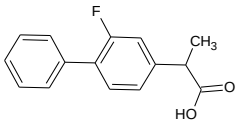
Caprofen (19)



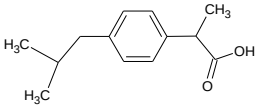
Fenbufen (7)



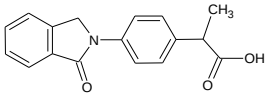
Fenoprofen (6)



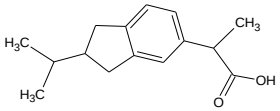
Fluribiprofen (4)



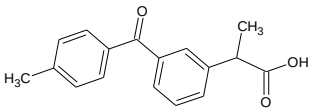
Ibuprofen (3)



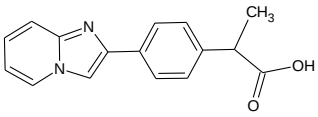
Indoprofen (10)



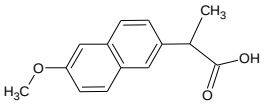
Isoprofen (16)



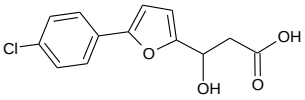
Ketoprofen (2)

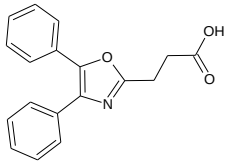


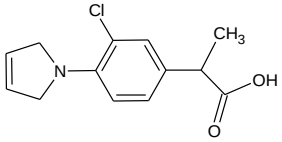
Miroprofen (15)



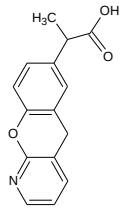
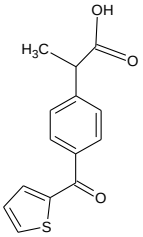
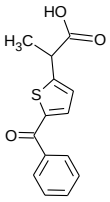
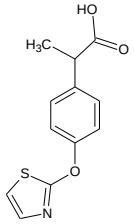
Naproxen (1)







Orpanoxin (18) **Oxaprozin (8)** **Pirprofen (13)**

Pranoprofen (12) **Suprofen (14)** **Tiaprofenic (5)** **Zolioprofen (17)**

Figure 1. Structure of some Profen derivatives **1-19** classified by alphabetic order.

Table 3. Observed and calculated –logLD50 for different Profen derivatives **1-19**.

No	Name	-logLD$_{50}$ (Obs.)	-logLD$_{50}$ (Calc.)	Residual
1	Naproxen	-2.55630	2.4890	-0.0673
2	Ketoprofen	-2.55630	2.7010	0.1447
3	Ibuprofen	-2.86923	2.9734	0.1041
4	Flurbiprofen	-2.80618	2.8703	0.0641
5	Tiaprofenic	-2.83885	2.8845	0.0456
6	Fenoprofen	-3.14613	3.1646	0.0185
7	Fenbufen	-2.90037	2.8500	-0.0503

8	Oxaprozin	-3.08279	3.0298	-0.0530
9	Bermoprofen	-2.32634	2.3706	0.0443
10	Indoprofen	-2.84510	2.8163	-0.0288
11	Benoxaprofen	-2.90309	3.0632	0.1601
12	Pranoprofen	-2.65031	2.5515	-0.0988
13	Pirprofen	-3.13033	3.0583	-0.0720
14	Suprofen	-2.77085	2.6327	-0.1382
15	Miroprofen	-2.75588	2.7816	0.0257
16	Isoprofen	-3.02119	2.8822	-0.1390
17	Zoliprofen	-2.81954	2.8777	0.0582
18	Orpanoxin	-3.39094	3.2938	-0.0972
19	Carprofen	-2.45025	2.5295	0.0792

4. Results and discussion

4.1. Previous QSAR analysis

Rustaman et al [13] derived MLR equation using MM2 based descriptors for same set of molecules which gave very good statistics for n= 19, R^2 = 0.929, R^2_{adj} = 0.883 with s = 0.088. But the equation is based on seven descriptors. It is a well known fact that use of large number of descriptors (in analysis of Rustaman, seven are used) may lead to "Over Fitting" which is certainly a demerit [5]. In contrast, the equation proposed in present work is based on only three descriptors and the statistical quality (R^2 = 0.876, R^2(adj) = 0.851, s = 0.0999, PRESS = 0.229, R^2(pred) = 0.810) is very good. Therefore the equation based on 3D descriptors is more useful for further drug designing.

In summary, an extensive QSTR analysis has been performed on a wide variety of structurally diverse set of Profen derivatives and present investigations revealed several important physicochemical and structural requirements for anti-inflammatory activity. The results derived for these completely new set of ligands could be beneficial in the

hands of medicinal chemists to further the design and development of more and better anti-inflammatory agents in the future.

4.2. Virtual screening and molecular properties calculations

4.2.1 Molinspiration Calculations [7, 19]

MiLog*P* (octanol/water partition coefficient) is calculated by the methodology developed by Molinspiration as a sum of fragment-based contributions and correction factors (**Tables 4** and **5**). The method is very robust and is able to process practically all organic and most organometallic molecules. Molecular Polar Surface Area TPSA is calculated based on the methodology published by Ertl et al. as a sum of fragment contributions [7, 18]. O- and N-centered polar fragments are considered. PSA has been shown to be a very good descriptor characterizing drug absorption, including intestinal absorption, bioavailability, Caco-2 permeability and blood-brain barrier penetration. Prediction results of compounds **1-19** molecular properties (TPSA, GPCR ligand and ICM) are valued (**Tables 4** and **5**). Lipophilicity (log*P* value) and polar surface area (PSA) values are two important properties for the prediction of per oral bioavailability of drug molecules [14, 15]. Therefore, we have calculated log*P* and PSA values for compounds **1-19** using molinspiration software programs and compared them with the values obtained for standard drugs. For all the compounds, without exception, the calculated clog*P* values were around 1.79 - 3.98 (< 5), which is the upper limit for the drugs to be able to penetrate through biomembranes according to Lipinski's rules. So, all these compounds resent good bioavailability.

The lowest degree of lipophilicity among all the compounds was exhibited by compounds **1-19**, which is an indication for good water solubility. The polar surface area (PSA) is calculated from the surface areas that are occupied by oxygen and nitrogen atoms and by hydrogen atoms attached to them. Thus, the PSA is closely related to the hydrogen bonding potential of a compound [15]. Molecules with PSA values around of 160 Å or more are expected to exhibit poor intestinal absorption [15]. Table 5 shows that all the compounds are within this limit. It has to be kept in mind that log P and PSA values are only two important, although not sufficient criteria for predicting oral absorption of a drug [16]. To support this contention, note that all the compounds have only one violations of the Rule of 5. Two or more violations of the Rule of 5 suggest the probability of problems in bioavailability [17]. All of the compounds **1-19** have zero violations of the Rule of 5. Drug-likeness of compounds **1-19** is tabulated in Table 5. Drug-likeness may be defined as a complex balance of various molecular properties and structure features which determine whether particular molecule is similar to the known drugs. These properties, mainly hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecule size and flexibility and presence of various pharmacophores features influence the behavior of molecule in a living organism, including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, metabolic stability and many others. Activity of all eight

compounds and standard drugs were rigorously analyzed under four criteria of known successful drug activity in the areas of GPCR ligand activity, ion channel modulation, kinase inhibition activity, and nuclear receptor ligand activity. Results are shown for all compounds in Table 5 by means of numerical assignment. Likewise all compounds have consistent negative values in all categories and numerical values conforming and comparable to that of standard drugs used for comparison. Therefore it is readily seen that all the compounds are expected to have near similar activity to standard drugs used based upon these four rigorous criteria (GPCR ligand, ion channel modulator, (kinase inhibitor, and nuclear receptor ligand).

2.1.2. Osiris Calculations [7, 20]

Structure based design is now fairly routine but many potential drugs fail to reach the clinic because of ADME-Tox liabilities. One very important class of enzymes, responsible for many ADMET problems, is the cytochromes P450. Inhibition of these or production of unwanted metabolites can result in many adverse drug reactions. With our recent work on the drug design by combination of various pharmacophore sites by using heterocyclic structure, it is now possible to predict activity and /or inhibition with increasing success in two targets (bacteria and HIV) [7, 21]. This was done using a combined electronic/structure docking procedure and an example will be given here. The remarkably well behaved mutagenicity of divers synthetic molecules classified in data base of CELERON Company of Swiss can be used to quantify the role played by various organic groups in promoting or interfering with the way a drug can associate with DNA. The Osiris calculations are tabulated in Table 4. Toxicity risks (mutagenicity, tumorogenicity, irritation, reproduction) and physico-chemical properties (miLog*P*, solubility, drug-likeness and drug-score) of compounds **1-19** are calculated by the methodology developed by Osiris. The toxicity risk predictor locates fragments within a molecule, which indicate a potential toxicity risk. Toxicity risk alerts are an indication that the drawn structure may be harmful concerning the risk category specified. From the data evaluated in Table 4 indicates that, nine of eighteen compounds (Benoxaprofen, Bermoprofen, Fenoprofen, Indoprofen, Orpanoxin, Oxaprozin, Pirprofen, Pranoprofen and Zoliprofen), their structures are supposed to be non-mutagenic, non-irritating with no reproductive effects when run through the mutagenicity assessment system comparable with standard drugs used. The log*P* value of a compound, which is the logarithm of its partition coefficient between n-octanol and water, is a well-established measure of the compound's hydrophilicity. Low hydrophilicities and therefore high log*P* values may cause poor absorption or permeation. It has been shown for compounds to have a reasonable probability of being well absorb their log*P* value must not be greater than 5.0. On this basis, all the compounds **1-19** are having log*P* values in the acceptable criteria. Along with this, the nice compounds, which have shown good anti-inflammatory screening results, are having the best Drug-Score values (DS = 0.46 - 0.86), as compared to other compounds in the series.

4.2.2. The aqueous solubility of a compound significantly

The aqueous solubility of a compound significantly affects its absorption and distribution characteristics. Typically, a low solubility goes along with a bad absorption and therefore the general aim is to avoid poorly soluble compounds. Our estimated log*S* value is a unit stripped logarithm (base 10) of a compound's solubility measured in mol/liter. There are more than 80% of the drugs on the market have an (estimated) log*S* value greater than -4. In case of compounds **1-19**, values of log*S* are around -4. Further, the table 4 shows drug-likeness of compounds **1-19** which is in the comparable zone with that of standard drugs used for comparison. We have calculated overall drug score (DS) for the compounds **1-19** and compared with that of standard drugs Zoliprofen used as shown in Table 4. The drug score combines drug-likeness, miLog*P*, log*S*, molecular weight and toxicity risks in one handy value than may be used to judge the compound's overall potential to qualify for a drug. This value is calculated by multiplying contributions of the individual properties with the equation 1:

DS= Π (½ + ½ Si) Π ti ---------- (1)

Where; S= 1/ 1+eap+b

DS is the drug score. Si is the contributions calculated directly from of miLog*P*; log*S*, molecular weight and drug-likeness (pi) via the second equation, which describes a spline curve. Parameters a and b are (1, -5), (1, 5), (0.012, -6) and (1, 0) for miLog*P*, log*S*, molecular weight and drug-likeness, respectively. ti is the contributions taken from the four toxicity risk types. The ti values are 1.0, 0.8 and 0.6 for no risk, medium risk and high risk, respectively. The reported compounds **1-19** showed moderate to good drug score as compared with standard drugs used.

4.2.3. Petra Calculations [7, 20]

PETRA is a program package comprising various empirical methods for the calculation of physicochemical properties in organic molecules. All methods are empirical in nature and have been developed over the last 20 years in the research group of Prof. J. Gasteiger.

The following chemical effects can be quantified: heats of formation, bond dissociation energies, sigma charge distribution, □-charge distribution, inductive effect, resonance effect and delocalization energies and polarizability effect. The series compounds **1-19** have been subjected to delocalised-charge calculations using Petra method of the non-hydrogen common atoms, obtained from the partial pi-charge of the heteroatoms, have been used to model the bioactivity against bacteria. It is found that the negative charges of the oxygen atoms and the partial pi positive charges of oxygen atoms contribute positively in favor of an antibacterial activity, more, and this is in good agreement with the mode of antibacterial action of the compounds bearing ($X^{□-}$---$Y^{□+}$) pharmacophore(s) site(s). It

was hypothesized that difference in charges between two heteroatoms of the same pharmacophore site ($X^{\delta-}$---$Y^{\delta+}$) may facilitate the inhibition of bacteria, more than viruses. This hypothesis was rationalized as follows [7, 20].

The structure of clinical anti-inflammatory agents **1-19** for ease of analysis can be divided into three parts, Viz., terminal carboxylate skeleton, substituted-phenyl or aromatic heterocyclic ring and another phenyl ring or alkyl group as side chain attached to first aryl moiety. We have fixed the former carboxylate skeleton part and varied the latter two by substituting with several functional groups in case of all compound **1-19**. Compound Orpanoxin is among the least toxic substance to have been evaluated as anti-inflammatory agents in this series. In case of compound Bermoprofen, where there is a meta-substitution with fluoro on the central phenyl ring. Accordingly, we remarked an effort was initiated to establish a pharmacophore hypothesis to delineate the requirements of the active site via a comprehensive program of analogue synthesis and evaluation of the effects of structural modification(s) on anti- inflammatorily activity of Ibuprofen. We then set out to determine the resultant *in vitro* effects of chemical alterations in this region. The modulating inflammatorily effect(s) of substituent having different electronegative properties, located at different positions of phenyl ring sites have been ascertained (Figure 1).

5. Conclusion

In practical medicine, Moroccan Doctors usually recommend their patients (both children and adult) to start with ibuprofen - this is marketed in Morocco as Brufen. The important thing about anti-inflammatory medications is that they are hard on the stomach but this one (Brufen) is not the best one of anti-inflammatory agents- if you start having heartburn or acid reflux when you try to increase the dosage, you've hit the maximum your body will tolerate. The National Moroccan Ministry of Health should take in consideration the side effects of commercialized Brufen (Mutagenic and Reproductive Effective, Table 4) and try –as soon as possible- to commercialize Orpanoxin or any other less toxic one, instead Brufen in Morocco.

Although Nonsteroidal anti-inflammatory drugs (NSAIDs) are popular and important for the treatment of inflammation and pain, some necessary precautions should be taken.

In fact, conventional NSAIDs are not only and intrinsically toxic to the gastroduodenal (GD) mucosa but they are able to represent a real danger. The bioinformatics can, and should, guide us towards safer prescribing of NSAIDs. Factors known to increase the risk of GD toxicity include: history of peptic ulcer disease; advanced age; high doses; and co-administration of aspirin, anticoagulants or corticosteroids. Patients with any one of these risk factors, with the possible exception of age alone, should receive gastroprotective prophylaxis with proton pump inhibitors or misoprostol. Standard dose H2 antagonists do not protect against NSAID-induced gastric ulcers and are unsuitable for prophylaxis. Awareness of risk factors and appropriate prophylactic agents will minimize the risk to patients.

Whether the new generation of highly selective COX-2 inhibitors and nitric oxide-donating NSAIDs are safer drugs in long-term, use be remains to be proven, though initial clinical trial data are positive [22, 23].

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Table 4. Osiris calculations of compounds.

Compd.	Toxicity Risks				Osiris calculations				
	MUT	TUMO	IRRI	REP	MW	CLP	S	DL	D-S
Benoxaprofen					301	3.98	-5.69	0.68	0.46
Bermoprofen					296	3.77	-5.34	1.11	0.53
Carprofen					273	3.79	-4.72	1.21	0.36
Fenbufen					254	3.16	-4.4	-0.19	0.33
Fenoprofen					242	3.13	-4.26	0.48	0.62
Flurbiprofen					244	3.46	-4.36	-0.74	0.29
Ibuprofen					206	3.20	-2.89	3.97	0.31
Indoprofen					267	1.79	-3.56	3.57	0.85
Isoprofen					266	2.78	-5.02	2.5	0.40
Ketoprofen					254	2.99	-4.06	-0.41	0.20
Miroprofen					266	2.78	-5.02	2.5	0.40
Naproxen					230	2.80	-3.59	0.89	0.26
Orpanoxin					252	1.92	-3.24	2.05	0.83
Oxaprozin					293	3.50	-4.15	3.05	0.39

Pirprofen					251	2.51	-3.19	3.58	0.86
Pranoprofen					257	2.50	-2.72	2.06	0.84
Suprofen					260	2.84	-4.07	1.53	0.26
Triaprofenic					260	2.97	-4.18	074	0.39
Zoliprofen					249	2.66	-3.99	2.41	0.78

MUT: mutagenic, TUMO : tumorigenic, IRRI : irritant, REP : reproductive effective, MW: mol weight, CLP: cLog*P*, S: solubility, DL: drug-likeness, D-S: drug-score.

Table 5. Molinspiration calculations of compounds **1-19**.

	Molinspiration calculations						**Drug-likeness**			
Compd.	MW	cLog*P*	TPSA	*OH--NH* Interract.	N viol.	Vol.	GPCR ligand	ICM	KI	NRL
Benoxaprofen	452	63	302	1	0	251	0.04	-0.69	-1.06	0.30
Bermoprofen	378	64	296	1	0	266	0.05	-0.36	-0.64	-0.01
Carprofen	432	53	273	2	0	231	0.25	0.01	-0.09	-0.29
Fenbufen	304	54	235	1	0	254	0.12	0.03	-0.50	-0.07
Fenoprofen	389	47	225	1	0	242	0.13	-0.07	-0.30	0.26
Flurbiprofen	405	37	244	1	0	221	0.37	0.18	-0.14	0.13
Ibuprofen	346	37	206	1	0	211	0.28	0.06	-0.58	0.09
Indoprofen	288	58	281	1	0	254	0.29	-0.31	-0.09	-0.22
Isoprofen	456	37	232	1	0	234	0.33	0.03	-0.68	-0.09
Ketoprofen	359	54	254	1	0	235	0.19	-0.09	-0.19	0.33
Miroprofen	320	55	266	1	0	241	0.34	0.10	-0.30	-0.72
Naproxen	338	47	230	1	0	214	0.13	-0.26	-0.38	0.08

Orpanoxin	250	71	267	2	0	219	-0.29	-0.71	-0.31	-0.87
Oxaprozin	375	63	293	1	0	265	0.20	-0.49	0.21	-0.19
Pirprofen	325	41	252	1	0	221	0.27	-0.23	-0.39	-0.38
Pranoprofen	309	59	255	1	0	227	0.08	-0.33	-0.37	-0.53
Suprofen	352	54	260	1	0	226	-0.02	-0.36	-0.31	-0.39
Triaprofenic	328	54	260	1	0	226	-0.02	-0.39	-0.44	-0.55
Zoliprofen	297	59	249	1	0	211	-0.24	-0.37	-0.97	-0.47

MW: Molecular weight, TPSA: Molecular polar surface area, Vol.: volume, ICM: Ion channel modulator, KI: Kinase inhibitor, NRL: Nuclear receptor ligand

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[22] (a) Note on side effects of ibuprofen (Brufen): Extreme allergic reaction. After drug was administered, patient experienced the following side effects: caesarean section, candidiasis, pelvic pain, plantar fasciitis, pregnancy, pubic pain.

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