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Structure and quantitative structure-activity relationship (QSAR) for (±) 3, 5-diphenyl-2-thioxoimidazolidin-4-ones as prominent cyclooxygenase-2 inhibitors

Yousery E. Sherif[1,2], Sami A. Gabr[3,4*], Elsayed A. Elmorsy[2] and Ahmad H. Alghadir[4,5]

[1]*Department of Chemistry, Faculty of Science and Arts, Ulla, Taibah University, KSA*
[2]*Clinical Pharmacology Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt*
[3]*Department of Anatomy, Faculty of Medicine, Mansoura University, Mansoura, Egypt*
[4]*Rehabilitation Research Chair (RRC), King Saud University, Riyadh, KSA*
[5]*Department of Rehabilitation Science, College of Applied Medical Sciences, King Saud University, Riyadh, KSA*

ABSTRACT

Cyclooxygenase (COX), a key enzyme playing crucial role in prostaglandin biosynthesis in Rheumatoid arthritis (RA) inflammation. For targeting COX-2 isoform, it is therefore interesting to design new molecule scaffolds with reduced side effects at gastric and renal levels. QSAR can modify the molecular structures for achieving the desired molecule with the proposed property, without experimental measurement. In the current study, we extend a published work that had been investiged the of *3, 5-diphenyl-2thioxo imidazolidin-4-ones derivatives as cyclooxygenase inhibitors. In this report, QSAR and regression analysis were used to predicate the cyclooxygenase inhibition activity of these derivatives. Moreover the cyclooxygenase inhibition activity for these molecules that was obtained experimentally is compared with the calculated ones. The cyclooxygenase inhibition activity of some of newly postulated 3, 5-diphenyl-2thioxo imidazolidin-4-ones derivatives showed a pronounced cyclooxygenase inhibition activity. QSAR and regression equations were useful in predicating the biologic activity of the old and postulated molecules with good validity.*

Key words: QSAR,2-Thioxoimidazolin-4-ones, Ovine COX-1; Human COX-2; COX inhibition

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INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory disease with polyarticular synovitis leading to formation of rheumatoid pannus and subsequent erosion of articular cartilage and bone. Prostaglandins (PGs)--a group of arachidonic acid metabolites found at elevated levels in synovial fluid and synovial membrane are considered to play a pivotal role in development of vasodilatation, fluid extravasations and pain in synovial tissues. Moreover, there is increasing evidence that PGs (especially prostaglandin E2) are mediators involved in complex interactions leading to development of erosions of articular cartilage and juxta-articular bone [1-2]. There are abundant data implicating PGE2 in the inflammatory features of RA patients [3-4]. Cyclooxygenase (COX), a key enzyme playing crucial role in prostaglandin biosynthesis, exists in at least 2 isoforms: constitutively expressed COX-1 and, inducible by many mediators of inflammation, COX-2. COX-2 is also relevant to PGE2 biosynthesis in arthritic joints; this isoenzyme is overexpressed in the synovium of RA patients, and selective COX-2 inhibitors ameliorate

RA synovitis [1, 5-6]. Besides lipoxygenases and epoxygenases, type-1 and type-2 cyclooxygenases (COX-1 and COX-2) are considered as the starting point of the metabolism of arachidonic acid, the precursor of prostaglandins (PGs) and thromboxane (TX). Contrary to COX-1, which is constitutively expressed in many organs and tissues, COX-2 expression is induced in several cell types [7-10]. Initially, the design of selective COX-2 inhibitors began with the aim to develop anti-inflammatory drugs (NSAIDs) with reduced side effects at gastric and renal levels. More recently, COX-2 over expression has been demonstrated in several types of diseases [11-14]. From a structural point of view, selective COX-2 inhibitors are divided into five classes [15-16]. Especially, vicinal diaryl carbocycles or heterocycles (coxibs). Some coxibs such as etoricoxib have a six-membered ring as central heterocycle (pyranone, pyridine and pyridazinone) [17-19]. Recently, rofecoxib was voluntarily withdrawn from the market because of an increased risk of cardiovascular adverse events with a probability linked to the dose and the duration of treatment [20-21]. For targeting COX-2 isoform, it is therefore interesting to design new molecule scaffolds different from 1, 2-diaryl heterocyclic type derivatives such as rofecoxib. The development of new cyclooxygenase inhibitors depend mainly up on molecular structures and its relation to biological activities [22]. QSAR is a mathematical relationship between a biological activity of a molecular system and its geometric and chemical characteristics. QSAR is used to find consistent relationship between biological activity and molecular properties, so that these rules can be used to evaluate the activity of new compounds. The purpose of developing a QSAR model is to reduce the cost of the target designing by modifying the molecular structures for achieving the desired molecule with the proposed property, without experimental measurement [23]. Subsequently, an ideal QSAR model should be capable of accurately predicting the desired property of a newly synthesized or a hypothetical molecule [24]. In the current study, we applied the QSAR and regression analysis for prediction the anti- inflammatory activity and prominent cyclooxygenase inhibitor activity of 3, 5-diphenyl-2thioxo imidazolidin-4-ones derivatives.

MATERIALS AND METHODS

This work is based on previous investigations of 3, 5-diphenyl-2thioxo imidazolidin-4-ones derivatives. The synthesis, properties, and inhibitory potency of these derivatives were reported earlier [25].The inhibitory potency of 2-thioxoimidazolidin-4-ones was studied on isolated hCOX-2 as previously demonstrated on COX-2 and COX-1 isoforms in human blood cells[26]. Marie et al [25] mentioned that the new synthesized derivatives of 3, 5-diphenyl-2thioxo imidazolidin-4-ones strongly or completely inhibit recombinant hCOX-2 at 50 lM. Hence we speculated new derivatives and derived the cyclooxygenase inhibition activity for our speculated ones and compared the calculated activity with the experimental activity for their compounds using QSAR and regression analysis.

Quantitative structure activity relationship (QSAR)

The descriptors obtained from hyperchem version 8 programs at the semi-empirical theoretical method using AM1 method [27].

Semi-empirical method

The calculation method for commands was placed on the compute menu to semi-empirical quantum mechanics rather than molecular mechanics or ab-initio quantum mechanics. These calculations solve the Schrödinger equation, with certain approximations, to describe the electron properties of atoms and molecules. In semi-empirical method, the calculations can be simplified by calculating the valence electrons only, neglecting the integrals for certain interactions using standard, non-optimized, and electron orbital basis functions. Experimental parameters eliminate the need to calculate certain quantities and to correct for errors resulting from approximations. This method is applicable and appropriate for all atoms in the periodic table, where the variables are saved in the parameter files. The choice remains until one chooses the molecular mechanics or Ab-Initio module. If a file is saved after a semi-empirical calculation, the HIN file will contain the calculated atomic charges [28].

AM1

AM1 is a semi-empirical SCF and a developed MNDO method for chemical calculations [29]. It is useful for molecules containing elements from long rows 1 and 2 of the periodic table, but not transition metals. Together with PM3, AM1 is generally the most accurate semi-empirical method included in Hyperchem., it calculates the electronic properties, optimized geometries, total energy, and heat of formation.

Statistical analysis

Multiregression analysis was used for correlating physicochemical descriptors to the biological activity through QSAR using winks program [30, 31].

RESULTS AND DISCUSSION

Many of imidazolinone derivatives constitute an important class of therapeutic activities [32-34]. Recently, some new imidazoli-none derivatives have been reported for their biological activity [35-36]. Marie et al [25] mentioned that the new synthesized derivatives of 3, 5-diphenyl-2thioxo imidazolidin-4-ones strongly or completely inhibit recombinant hCOX-2 at 50 lM. Hence we speculated new derivatives and derived the cyclooxygenase inhibition activity for our speculated ones and compared the calculated activity with the experimental activity for their compounds using QSAR and regression analysis. It is well known that the work of Marie et al [25] was based on constructing and preparing the chemical compounds and testing each one individually as cyclooxygenase inhibitors, in which trials and errors method was followed. Because the preparations of cyclooxiginase inhibitors are very expensive, tedious, time consuming and require lengthy procedures. Accordingly, QSAR equations using physicochemical parameters can help in this situation. In the current study, QSAR equations have been elaborated to predict new 3, 5-diphenyl-2thioxo imidazolidin-4-ones derivatives with potential cyclooxygenase inhibition activity. In our work, the data obtained from QSAR are based on their chemical structures of 3, 5-diphenyl-2thioxo imidazolidin-4-ones derivatives (Table 1). The physicochemical properties (descriptors) of the investigated chemical compound**s** are illustrated in table 2. These descriptors include the area, volume, hydration energy, logarithm of partition coefficient, high occupied molecular orbital, low unoccupied molecular orbital, difference between LUMO, dipole moment on X directions dmx, net dipole moment, gradient charge by K Cal/mole angstrom on carbon atom [C (9)], oxygen atom [O (10)], charge on oxygen atom [O(12)], charge on nitrogen atom [N(20)], [O(9)], charge on keto oxygen [O(10)], and charge on nitrogen atom [N(12)].

The descriptors obtained from hyperchem at semiemperical theoretical method [28, 37]. Fruitful descriptors are gained using multi-regression statistical calculations in winks program [31] feeding with these descriptors together with the biological activities previously measured. It is noted that, the data obtained from multi-regression calculated by winks include equations used for calculating the biological activity (cyclooxygenase inhibition activity) of the compounds in concern as well as focusing on the most chief descriptors affecting the biological activity. Accordingly, two equations had been obtained from multi-regression statistical calculations. Equation one and two are concerned with calculating the ability of the 3,5-diphenyl-2-thioxoimidazolidin-4-ones derivatives to act as cyclooxygenase inhibitors for COX-2 and COX-1 respectively.

Equation one: %INH COX2=SUM **(**579.57252+0.1712864*Area-0.330892*Volume- 7. 489595log P-6.853842*R.I. +12.330752 Polarizaed+0.34909 MW-0.5180724Total Energy +0.0476124 Bending Energy-0.0284105Heat Formation +8.1562298 HOMO 1.714134 LUMO-11.85709DM+18.275554Dmx-2.922502Dmy+2.0478183 Dmy**).**

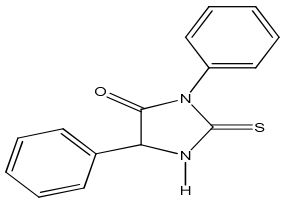
Equation two: %INH COX1= SUM **(**570.48483+0.4825072Area -0.3453402Volume-1.631416 log P-4.018702Rerfactive index -1.456209Polarizability+0.3388084Molecular Weight-0.3399199 Total Energy +0.0605661 Bending Energy +0.1356815Heat Formation+1.1924269HOMO-10.91844 LUMO-8.880187DM +12.790518Dmx-3.365335Dmy+1.5305295Dmz**).**

The degree of the validity of the two equations obtained from multi-regression statistical calculations was measured via different tools. One of such is based on calculating the biological activity and applying our proposed equations. The data obtained are monitored with that obtained from the work of Marie et al [25] and tabulated in table 3 for comparison purposes. Reading such table, one can easily notice that the great concordance between the results obtained experimentally by Marie et al and that calculated by using our equations. As shown from the results presented in table three, the value of R is close to unity reflecting more validity of the proposed equations. Through reading the data in table three especially the F and P-values (Table 4), one can touch the highly proximity of calculated values to the experimentally measured biological activities. Also, the proposed equations reported that the area of 3,5-diphenyl-2-thioxoimidazolidin-4-ones derivatives plays a significant role in the biological activity of these compounds which interns displayed the importance of QSAR analysis(Table 5).

Based on the experimental results of Marie et al, (Table 3), each compound of 3, 5-diphenyl-2-thioxoimidazolidin-4-ones derivatives 5– 9 and 11-23 was assayed for inhibition of ovine COX-1 (oCOX-1) and human recombinant COX-2 (hCOX-2). The inhibitory potency of each molecule (50 µM) is expressed as the decrease of PGF2a obtained by chemical reduction of PGH2 produced by COXs using arachidonic acid as substrate (Table 3). Except for the iodo (11) and the aminosulfonyl derivatives (15), the introduction of a substituent in para position of the phenyl (6–15) increases the hCOX-2 inhibitory potency. For the meta-substituted molecules (16–23), a similar trend is observed, except for the 3-methyl (16), the 3-chloro (19) and the 3-iodo (21) derivatives which are as or less active on hCOX-2 than their unsubstituted parent 5. Within the halo-substituted compounds, the fluoro (8, 18) and bromo (10, 20) derivatives are the most active on hCOX-2 whatever their position on the phenyl ring (meta or para). The methyl sulfonyl moiety (14, 23) increases the inhibitory potency on hCOX-2 particularly when placed in meta-position (23). Both CF3-substituted compounds (12, 22) are among the most active compounds on hCOX-2. When compared to 5, the introduction of a substituent in meta position (16–23) reduces the inhibitory potency on oCOX-1, except for the fluoro derivative (18) which is also the most active on oCOX-1 in the para series (8). In the para series, the methyl (6) compounds are more active on oCOX-1 than their parent compound (5). As expected, celecoxib, chosen as COX-2 selective inhibitor, was more potent on hCOX- 2 than on oCOX-1. At 50 lM, celecoxib completely inhibited hCOX-2 and is less potent on oCOX-1.

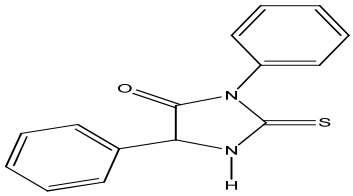
In view of the aforementioned discussion and according to the facts obtained from applying Hyperchem programs, the descriptors of the newly postulated structures are examined (Table 6). Taking into account these data and applying our equations obtained from Hyperchem, the biological activity of these compounds is calculated and illustrated (table 7). These compounds are speculated taking into account that they having 3, 5-diphenyl-2-thioxoimidazolidin-4-ones moiety and the rest of their structures are completed by active sites complementing the best descriptors obtained from our Hyperchem investigation. Thus the newly 3, 5-diphenyl-2-thioxoimidazolidin-4-ones derivatives remain to be synthesized and investigated experimentally for their inhibition activity to cyclooxygenase-2. Finally, our data may be exhibited a potential interest for investigators attempting to find new prominent cyclooxygenase-2 inhibitors.

Table (1); 18 derivatives of (±)3,5-diphenyl-2-thioxoimidazolidin-4-ones was prepared by awide variety of substituents placed on the 3-aryl residue including the aminosulfonyl present in the structures of celecoxib and valdecoxib and the methylsulfonyl present in the position para of the aryl rings of rofecoxib and etoricoxib. Each compound was obtained as a racemate since none of them exhibited optical rotation (c = 5, CHCl3) [25]



Compound No.	Ar
5	Phenyl
6	4-CH_3-phenyl
7	4-C_2H5-phenyl
8	4-F-phenyl
9	4-Cl-phenyl
11	4-I-phenyl
12	4-CF3-phenyl
13	4-NO-phenyl
14	4-CH_3SO_2-phenyl
15	4-NH_2SO_2-phenyl
16	3-CH_3-phenyl
17	3-CH_3O-phenyl
18	3-F--phenyl
19	3-Cl--phenyl
20	3-Br-phenyl
21	3-I-phenyl
22	3-3CF_3-phenyl
23	3-CH_3SO_2-phenyl

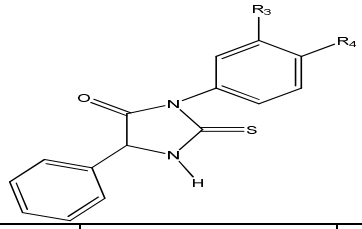
Table (2) Calculated descriptors by HyperChem for the 3, 5-diphenyl-2-thioxoimidazolidin-4-ones derivatives presented in table one [27,31]



	AREA	VOLUME	LOG P	R.I	Polariz	MW	Total E.	Bending E.	Heat of Formation	HOMO	LUMO	DM	DMx	Dmy	DMz
5	407	812	1.1	88.7	31.6	270.4	-102.2	-3558	86	-8.8	-7.3	2.9	1.64	-0.64	-2.3
6	571	910	-5.7	93.6	33.5	285	-108	-3677	242	-7.7	-3.8	9.6	5.8	-1.5	-7.5
7	560	917	-6.9	98	35	298	-114.6	-4069	125	-8.2	-2.4	3.8	2.4	-0.41	-2.99
8	580	821	0.5	89	31.5	288	-118.3	-3568	42	-8.9	-2.3	4.7	2.4	-1.3	-3.8
9	528.7	855	0.88	93.4	33.6	304.8	-113.7	-3542	79	-8.8	-2.4	3.5	1.9	-0.83	-2.8
11	618.7	976	1.62	101	37	396	-112.7	-3537	80	-9.1	-2.1	3.6	2	-0.8	-2.9
12	577	927	-4.1	94.5	33.2	338	-154	-3424	395	-4.6	-2.9	3.8	1.6	30.3	23.1
13	542.3	879	-7.8	93.4	33.5	315	-129	-3687	136.8	-8.7	-1.4	7.7	1.2	-3.4	-6.8
14	668	1073	-6.4	102	34.6	348.4	-136	-3967	137	-7.7	-4.5	10.4	6.5	-1	8.3
15	690.6	1088	-4.96	101	34.1	349	-137	-3869	125	-9.1	-2.2	6.1	4.4	-1.4	-3.9
16	579	922	-6.2	93.6	33.5	284	-119	-3885	99	-9.5	-2.5	5.1	1.5	-3.1	-3.7
17	613	960	-5.9	95.1	34.1	300	-117	-3450	57	-9.03	-2.4	4	1.3	-1.9	-3.5
18	483	776	0.98	87.1	30.8	286	-113	-3541	79	-8.9	-2.3	3.3	1.6	-0.95	-2.7
19	529	855	0.88	93	33.5	304.8	-154	-3807	13	-9	-2.2	4.5	1.13	-2.5	-3.6
20	538	873	1.15	96.2	34.3	350	-115	-3455	163	-4.5	-1.2	11.7	7.1	-1.7	-9.2
21	542	890	1.6	101	36.4	396	-112.7	-3510	107	-8.9	-2.3	4.5	1.13	-2.5	-3.6
22	570	914	-4.6	94.4	33.2	338	-154	-3806	14	-9	-2.2	4.5	1.13	-2.5	-3.6
23	681	1086	-0.5	102.3	34.6	348	-136	-3877	228	-4.5	-1.2	31.3	26.6	10.8	-12.6

[9]C: charge on carbon atom 9; [10]O: charge on oxygen atom10; [11]O; charge on oxygen atom 11; [12]O: charge on oxygen atom 12; [20]N: charge on nitrogen atom 20; LUMO: low unoccupied molecular orbital; HOMO: high occupied molecular orbital; H.E: hydration energy; Log P: Log of calculated octanol-water partition coefficient; MW: molecular weight; dmx (dipole x): dipole moment in X direction.

Table (3) The biological activity (percentage inhibition of COX-1 and COX2) for 18 derivatives of 3,5-diphenyl-2-thioxoimidazolidin-4-ones as determined theoretically (by equations; 1,2) and experimentally as reported earlier [25]



No.	Compound	% INH COX1		% INH COX2	
		Exper.	Calcul.	Exper.	Calcul.
5	Phenyl	67	67.78	63	63.06
6	4-CH_3-phenyl	75	74.32	89	88.92
7	4-C_2H5-phenyl	8	11.1	81	80.87
8	4-F-phenyl	91	91.87	88	88.2
9	4-Cl-phenyl	57	50.16	70	71.5
11	4-I-phenyl	40	42.60	60	60.055
12	4-CF3-phenyl	67	66.70	98	97.99
13	4-NO-phenyl	12	15.94	68	68.40
14	4-CH_3SO_2-phenyl	61	61.8	74	74.05
15	4-NH_2SO_2-phenyl	41	41.98	42	42.025
16	3-CH_3-phenyl	33	26.1	60	59.9
17	3-CH_3O-phenyl	48	50.3	85	84.42
18	3-F--phenyl	72	75.36	88	87.26
19	3-Cl--phenyl	20	24.0	59	58.5
20	3-Br-phenyl	48	47.0	93	92.99
21	3-I-phenyl	31	29.45	48	47.6
22	3-3CF_3-phenyl	44	38.6	85	85.36
23	3-CH_3SO_2-phenyl	38	37.99	90	89.97

Table (4): Regression analysis reflecting the validity of the proposed two equations

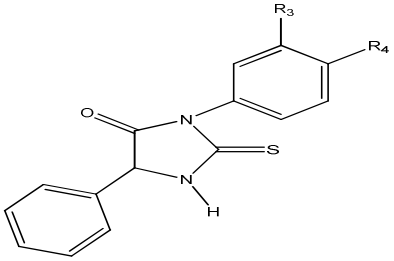
	F-VALUE	P-VALUE	R
Equation 1 at 10.0 µg COX-1	5.7	< 0.15	0.802
Equation 2 at 10.0 µg COX-2	159.6	< 0.06	0.992

Where F, P and R are respectively the degree of freedom, the degree of significance and regression coefficient

Table (5): The most important physicochemical descriptors affecting the % inh of COX-1 & COX-2 indicated by p- value and t-value according to Hyperchem &Winks Program [27,31]

95% CONFIDENCE USING INTERVEL AT 10UG DRUG			
COX -1		COX -2	
AREA		AREA	
t-value	p-value	t-value	p-value
<8.3	<0.001	16.5	<0.001

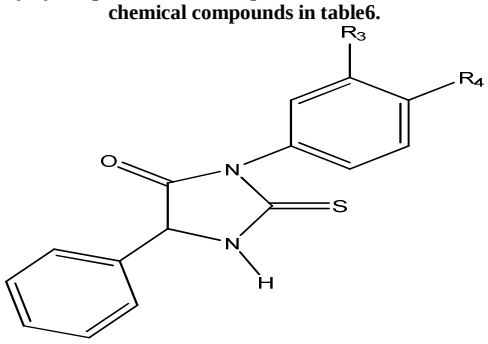
Table (6): Calculated physicochemical descriptors of newly speculated chemical compounds (10; structure) of 3,5-diphenyl-2-thioxoimidazolidin-4-ones



post			AREA	V	LOG P	R.I	Polariz	MW	Total E.	B. E.	H.F	HOMO	LUMO	DM	DMx	Dmy	DMz
	$-R_3$	$- R_4$															
1	-	pyridyl	960	1554	-1.36	127.3	43.6	425	-180	-4840	389	-8.3	-1.51	2.8	-1.28	0.94	2.3
2	-	phenyl	960	1554	-1.36	127.3	43.6	425	-177	-5002	232.8	-7.97	-1.08	7.4	-4.2	3.1	5.2
3	-	F	706	1150	-0.62	100.8	33.74	364	-164	-3807	160.4	-8.12	-1.14	9.5	-5.4	3.63	7
4	F	F	716	1161	-1.22	100.9	33.65	382.4	-181.4	-3817	117.7	-8.3	-1.18	11.5	-6.03	4.85	8.5
5	-	Cl	730	1187.5	-0.24	105.4	35.7	380	-160	-3779	198.6	-8.12	-1.137	9.5	-5.36	3.89	6.8
6		NH_2	730	1182.21	-1.74	104.2	35.18	361	-154.89	-3961	204.9	-7.59	-1.06	7.5	-3.64	4.125	5.13
7		$NHCH_3$	760	1240	-1.33	109.1	37.02	375.5	-160.6	-4232	208.8	-7.58	-1.05	7.3	-3.5	4.21	4.8
8		CH_3NHCH_3	782	1285	-0.97	114	38.9	389.5	-166.3	-4500.7	215.7	-7.5	-1.04	7.3	-3.5	4.45	4.6
9		$CH_3NHCH_2CH_3$	814	1336	-0.62	119	40.7	403.5	-172	-4780.5	210.96	-7.5	-1.05	7.7	-3.73	4.57	4.9
10		$CH_3CH_2NHCH_2CH_3$	838	1381	-0.28	123.8	42.5	417.5	-177.75	-5060.9	205.6	-7.5	-1.04	7.4	-3.35	4.77	4.6

^{9}C: charge on carbon atom 9; ^{10}O: charge on oxygen atom10; ^{11}O; charge on oxygen atom 11; ^{12}O: charge on oxygen atom 12; ^{20}N: charge on nitrogen atom 20; LUMO: low unoccupied molecular orbital; HOMO: high occupied molecular orbital; H.E: hydration energy; Log P: Log of calculated octanol-water partition coefficient; MW: molecular weight; dmx (dipole x): dipole moment in X direction; B.E.:bonding energy; V: volume; H.F. : heat of formation.

Table (7): The calculated biological activity by the predictable two equations which are concerned with the descriptors of the speculated chemical compounds in table6.



Postulated	-R_3	-R_4	%INH COX1cal	%INH COX2cal
1	-	pyridyl	-84	-128
2	-	phenyl	-70	-56
3	-	F	119	141
4	F	F	146	186
5	-	Cl	110	131
6		NH_2	92	117
7		$NHCH_3$	55	84
8		CH_3NHCH_3	22	60
9		$CH_3NHCH_2CH_3$	-11	34
10		$CH_3CH_2NHCH_2CH_3$	-49	4

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