Available online at www.derpharmachemica.com

Scholars Research Library

Scholars Research Library

Der Pharma Chemica, 2014, 6(2):1-6
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Quantitative structure structure-activity relationship (QSAR) for 2-amino-5-selenothiazole derivatives as anti-inflammatory and analgesic agents

Yousery El-Said Sherif[1,2*] and Moustafa A. Gouda[2, 3]

[1]*Department of Clinical Pharmacology, Faculty of Medicine, Mansoura University, Mansoura, Egypt*
[2]*Department of Chemistry, Faculty of Science and Arts, Ulla, Taibah University, KSA*
[3]*Department of Chemistry, Faculty of Science, Mansoura University, Mansoura, Egypt*

ABSTRACT

*Long-term clinical usage of NSAIDs is associated with significant side effects of gastrointestinal lesions, bleeding, and nephrotoxicity. Therefore the discovery of new safer anti-inflammatory drugs represents a challenging goal for such a research area. 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. In the current study, we extend a published work that had been investigated the selenothiazole derivatives as anti-inflammatory activity and analgesic agents. In this report, One equation was predicted using quantitative structure activity relationship (QSAR) and regression analysis for the anti-inflammatory activity with a regression correlation (R) close to unity(R^2~0.97, R adj.>0.84). One technique was used to investigate the validity of this equation and collagen adjuvant arthritis model in rats (in vivo).. In the pain scoring, a compound **14** was found to be more effective than Meloxicam.*

Keywords: Thiazole / QSAR / Anti-inflammatory activity / Analgesic effect

---

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used therapeutics, primarily for the treatment of pain and inflammation in arthritis for decades. However, long-term clinical usage of NSAIDs are associated with significant side effects of gastrointestinal lesions, bleeding, and nephrotoxicity. Therefore the discovery of new safer anti-inflammatory drugs represents a challenging goal for such a research area [1-4]. It is evident from the literature that thiazole moiety is a prevalent scaffold in a number of naturally occurring and synthetic molecules with attractive biological activities such as antiviral, anticancer, antibacterial, antifungal, anticonvulsant, antiparkinsonian and anti-inflammatory activities that is well illustrated by the large number of drugs in the market containing this heterocyclic moiety [5-11]

In our ongoing medicinal chemistry research program we have demonstrated that thiazoloquinoxaline exhibited good anti-inflammatory and analgesic activities [12].On the other hand, organic compounds containing selenium are of considerable interest since they exhibit diverse biological activities with numerous therapeutic applications [13,14]. In addition, the presence of aheterocyclic ring as the organic moiety in these compounds alters their properties to a great extent[15].

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 [7]. Subsequently, an ideal QSAR model should be capable of accurately predicting the desired property of a newly synthesized or a hypothetical molecule [8]. In the current study, we applied the QSAR for prediction of newly 2-amino-5-selenothiazole derivatives with pounced anti-inflammatory, analgesic activities.

MATERIALS AND METHODS

This work is based on previous investigations of thiazoles **1-5**, dexamethasone, rofecoxib and ibuprofen (Figure 1 and Table 1). The synthesis and properties of these thiazole derivatives were reported earlier [18]. Franklina et *al.* [18] mentioned the anti-inflamatory activities for their compounds. Hence we speculated new 2-amino-5-selenothiazole derivatives and derived the anti-inflamatory activity for our speculated ones and compared the calculated activity with the experimental activity for their compounds [18] and 2-amino-5-selenothiazole derivatives [19].

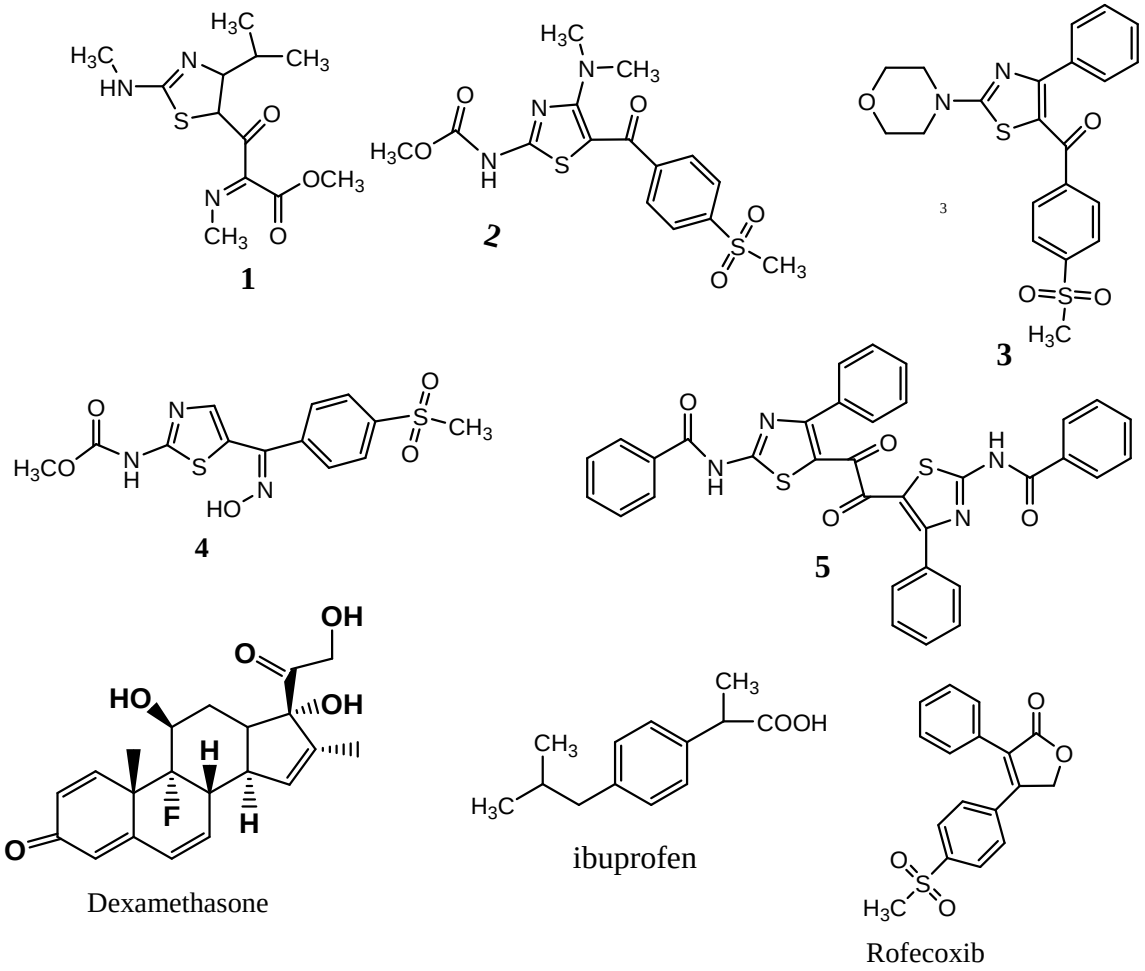

Figure 1: thiazoles 1-5, dexamethasone, rofecoxib and ibuprofen as anti-inflammatory agents

Quantitative Structure Activity Relationship (QSAR)

The physicochemical properties (descriptors) of the investigated chemical compounds obtained from Hyperchem version 8.1 program at the semi empirical theoretical method using PM3 method [20]. These descriptors include the area, volume, binding energy; heat formation, refractivity, polarizability. Multiregression statistical equation is based on the chemical descriptor data obtained from QSAR investigation.

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. In semiempirical method, the calculations can be simplified by calculating the valence electrons only, neglecting the integrals for certain interactions using standard, nonoptimized, and electron orbital basis functions. [21]

Synthesis of 4-(5-(2-(2-(3,4-dioxo-3,4-dihydronaphthalen-1-ylamino)-4-phenylthiazol-5-yl)diselanyl)-4-phenylthiazol-2-ylamino)naphthalene-1,2-dione (14): compound **14** was prepared according to the reported method [19]

Pharmacological testes

Animals

36 Sprague-Dawley rats (200-250 g) were obtained from the animal house of Mansoura Faculty of Medicine and fed on a standard rat chow and water ad libitum. Animal care and experiments were performed in accordance with the guidelines established by the NIH Guide to the Care and Use of Laboratory Animals, NIH publication no. 86-23. Rats were housed under similar standard laboratory conditions. The animals were divided into two main groups (non-arthritic control, arthritic group). In the arthritic group, all rats had been inoculated by the reagent of Collagen-Adjuvant arthritis into the left paw pad. Rats which developed right paw arthritic manifestations after 45 days were divided into four groups as follow, arthritic control, piroxicam treated groups. The compounds were given orally via gastric tube daily for seven days, 45 days after Collagen -Freund's injection. This is a modified form of the previous models [22]. This model of Collagen–Adjuvant Arthritis [22-24] is considered to be a representative of rheumatoid arthritis or ankylosing spondylitis in humans. Collagen II - Freund's adjuvant emulsion (0.1 mL) was injected intradermal into the left hind foot paw-pad of each rat (if no arthritis developed within 4 weeks, some of the animals were challenged by a second inoculation). After 45 days, the systemic arthritis developed in both hind paws [25]. Most of the previous tested compounds were insoluble in water. These were suspended in 0.5% sodium carboxymethyl cellulose [CMC]. The determined doses were injected intraperitoneally. The doses are calculated according to reference [26].

Measurement of joint inflammation

Measurement of joint inflammation right ankle periarticular rheumatoid index and edema scoring

Rheumatoid index was based on severity and extent of the erythema and edema of the periarticular tissue, and the enlargement, distortion or ankylosis of the joints. Its inflammation was graded from 1 to 4 [27]. Grading of 4 was when the joint was distorted and ankylosed, 3 when markedly enlarged, 2 when erythematous with edema, and 1 when normal [27]. Each of the six non-arthritic, non-treated rats had a score of 1. Right paw pad thickness and joint scoring were measured at the 7th day after starting drug treatment (45 days after complete Freund's adjuvant injection).

Edema thickness

The adjuvant induced inflammation in the contralateral paw pad (hind right paw pad) was measured by the paw edemameter (paw thickness). It was carried out 45 days after complete Freund's adjuvant injection [27, 28].

Pain tolerance measurement (Analgesic effect) by pain tolerance measurement right paw pad pressure tolerance (Analgesimeter: Ugo Basile, Italy).

For assessment of the analgesic activity of the used drugs, pressure was applied by the analgesimeter on the rat pad of the right paw. The pressure was increased gradually (a certain number of grams per second until the rat either squeaks or tries to withdraw its limb). The force of pressure was continuously monitored by a pointer moving along a linear scale. Increased pressure tolerance of drug treated rats indicates analgesic activity of the administered drug [27, 28]. This measurement of pressure tolerance was done at the 7^{th} day of drug treatment (45 days after complete Freund's adjuvant injection).

Proximal joint (right ankle) mobilization tolerance (pain scoring)

This mobilization tolerance was graded from 1 to 4. Degree 1 corresponds to tolerance of complete flexion 90^{o}; degrees 2, 3 and 4 correspond to increasing degrees of maltolerance according to a rat hind limb withdrawal, squeaking and when the flexion becomes painful. Degree 4 corresponds to squeaking with just initiation of flexion. Each of the six non-arthritic, non-treated rats had a score of 1 [27]. This measurement of mobilization tolerance was done at the 7^{th} day of drug treatment (45 days after complete Freund's adjuvant injection).

Statistical analysis

Results are expressed as mean standard error. Multiregression analysis (one way ANOVA, Newman-Keuls and F-test) were used for correlating physicochemical descriptors to the edema inhibition through QSAR and analysis of the pharmacological data. Mann Whitney for average S.E was used for comparing different groups; statistical difference was considered significant at *p*-value50.05 [29].

RESULTS AND DISCUSSION

In this work, QSAR equation has been elaborated to select compounds containing thiazole nucleus having anti-inflammatory, analgesic activities. Publication of Franklina et *al.*, [18] contain database for thiazoles **1-5**, dexamethasone, rofecoxib and ibuprofen (Figure 1 and Table 1) in which the biological activities were monitored at 1.0 µg/mL. The work by Franklina et al., [18] was based on preparing the chemical compounds and treating each one individually in acting as non steroidal anti-inflammatory drug (NSAID). In our work, the data obtained from QSAR are based on the chemical structures delivered from Table 1. Such data are concerned with physicochemical properties (descriptors) of the investigated chemical compounds. The descriptors were obtained from hyperchem version 8.1 calculated programs [20] at the semiemperical theoretical method (PM3) [21]. Fruitful descriptions of these descriptors are gained in using multi-regression statistical calculations in winks program 4.65 [30] feeding with these descriptors together with the biological activities, previously measured in Table 1.

Table 1: Experimental and Calculated anti-inflammatory activity in rats(% protection) by equation 1 and calculated descriptors for a: the compounds 1 to 5 , Dexmethasone, Ibuprofen and Rofecoxib (Figure 1): postulated compound 6 to 16 in Figure 2 by Hyperchem 8.1 program

Compound No.	Anti-inflammatory activity in rats (% protection)		Calculated descriptors by Hyperchem 8.1 [20]					
	Calculated data equation 1	Experimental data[18]	Area	Volume	Hydration energy	log P	Refractivity	Polarizability
1	79.92	83	578	968	-11.9	0.55	95.3	32.6
2	32.54	30	586.6	1143	-8.12	0.36	124.8	42
3	66.79	63	549	972	-15.8	0.37	96.3	32.9
4	68.07	69	695	1468	-12.5	2.13	168	59
5	71.22	73	386.7	939	-13.2	2.1	93	36
Dexamethasone	86.12	85	447	851.4	-7.5	-0.03	92	30
Ibuprofen	35.92	40	384	646	-5.5	2.36	59.5	22.2
Rofecoxib	61.72	60	517	875	-8.2	1.95	76	29
Postulated 6	-32.10	--	310	560	-11.2	1.31	51.13	19
Postulated 7	-377.42	--	289	455	-14.1	0.38	32.05	14.7
Postulated 8	-162.17	--	395	780	-10	0.9	71	28
Postulated 9	-103.50	--	499	1014	-10.9	2.62	106.7	40.6
Postulated 10	-206.11	--	526	1083	-15.7	2.42	107.7	43
Postulated 11	-319.43	--	368.5	709	-9.8	1.16	70	27.6
Postulated 12	-991.86	--	629	1277	-9.6	2.02	102.4	52
Postulated 13	-438.30	--	512	1094	-13.1	2.17	115.4	43
Postulated 14	25.46	--	457	757	3.72	0.05	68.81	27
Postulated 15	-12.26	--	401	1000	-13.6	2.1	110.6	45
Postulated 16	-513.77	--	310	560	-11.2	1.31	51.13	19

It is noted that the data obtained from multi-regression calculated by winks 4.65 program include equation 1 (Table 2) used for calculating anti-inflammatory activity in rats (% protection) of the compounds in concern as well as focusing on the degree of the validity of the equation and the most chief descriptors affecting the biological activity (% protection) (Table 2).

Table 2: Regression analysis reflecting the validity of the proposed equation 1

Equation	F-Value	P-Value	R	most effective descriptor)
Anti-inflammatory activity in rats(%protection) = -2.22Area+4.0468Volume - 0.172 Hydration energy +150.98log P -130.254 Refractive index+20.303 Polarizabiability -370.54 Equation (1)	7.8	< 0.26	0.98	area P< 0.001 95% confidence

*Where F, P and R are the degree of freedom, the degree of significance and regression coefficient Analgesic activity Such data (Table 1) are concerned with physicochemical properties (descriptors) of the investigated chemical compounds. These descriptors include the area, volume, hydration energy, Log P, refractive index and polarizability. The degree of the validity of the equation was measured via different tools. One of them is based on calculating the anti-inflammatory activity. The data obtained are monitored with the data in Table 1 and figure 1. One can notice a great coincidence between the results of Franklina *et al.*, [18] and these calculated using our equation. From calculations, the most important descriptors affecting in the % protection of the chemical compound is the area descriptor. These facts are summarized in Table 2.

In view of the aforementioned discussion and according to the facts obtained from applying Hyperchem programs, [20] the descriptors of eleven postulated structures [19] are examined. Such data are presented in Table (1). Taking into account these data and applying equation 1 (table 2) obtained from Hyperchem and winks 4.6 programs, the % protection of the eleven compounds are calculated. Postulated **14** displayed good results in reduction of rheumatoid

index. In the edema thickness compound **14** also, displayed better results than Meloxicam.furthurmore, compound **14** its analgesic activity is 25.1%, accordingly its preparation will be fulfilled in the Exp. part.

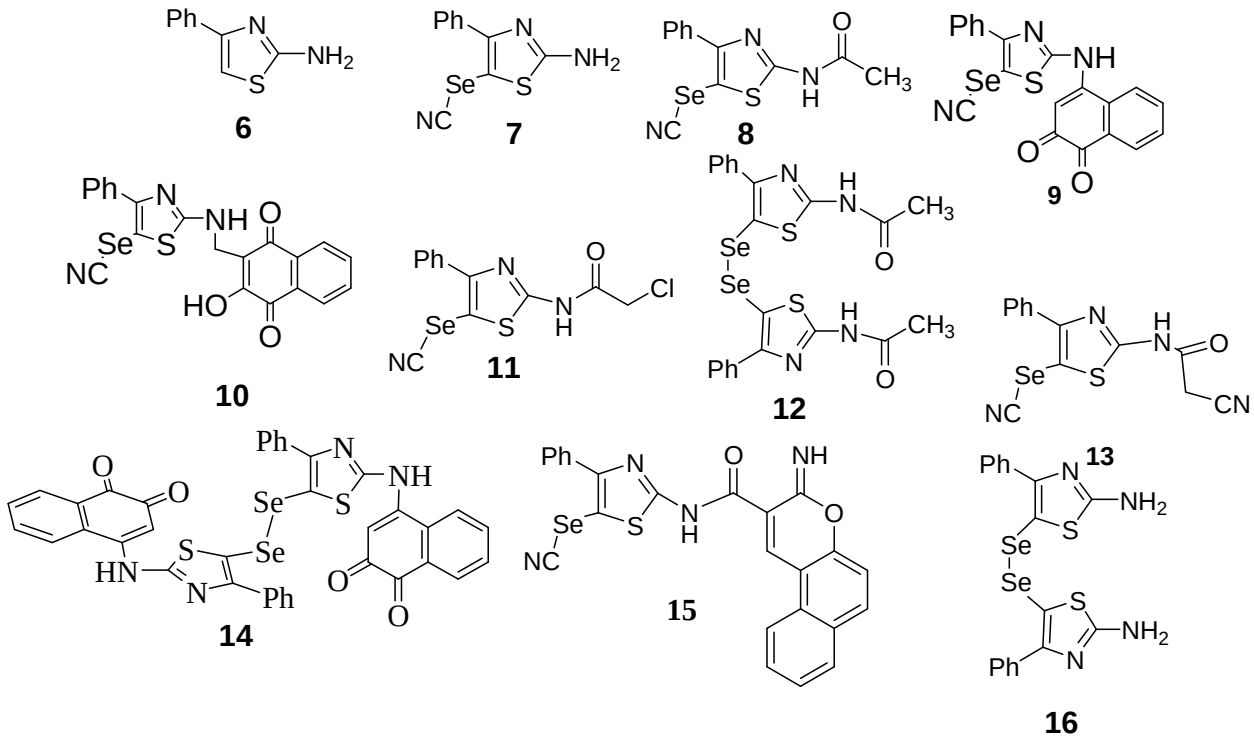

Figure 2: structure of the newly 2-amino-5-selenothiazole derivatives

Table 3 : Influence of Negative control , positive control, Meloxicam , Postulated compound 8 on Rheumatoid index, Edema thickness , Pain tolerance and Pain scoring in adjuvant induced rheumatoid arthritis model in rats (M ± S.E), n number of rats=6

Group	Dose (mg 200 g^{-1}) [31]	Inflammation		Analgesic effect	
--	--	Rheumatoid index	Edema thickness	Pain tolerance	Pain scoring
Negative control	[SCMC] Solvent	1.0±0.00	2.3±0.22	14.33±2.02	1±0.
Positive control	[SCMC] Solvent	3.67±0.22*	5.0±0.36*	1.33±0.21*	3.67±0. 21*
Meloxicam	0.36	2.67±0.22*	4.3±0.42* θ	3.33±0.84*	2.67±0. 21*θ
compound**14**	1.45	2.3±0.42* θ	2.83±0.19 θφ	3.0±0.37*	2.33±0.21*θ

SCMC 0.5% sodium carboxymethyl cellulose ¥ P < 0.001 vs. non-arthritic control. Θ P < 0.01 vs. arthritic control. φ P < 0.01 vs.Meloxicam

CONCLUSION

It is clear from the foregoing that the compound 14 is a promising compound if future pharmacological detailed studies. This is consistent with what has been predictable equation 1 in this study.

Acknowledgment
This work was supported by Taibah University, KSA, project No.433/ 1969 year: 2012

REFERENCES

[1] Kuhnert, N. **(2000).** *Pharmazie in unserer Zeit*, ,1, 32-39.
[2] Lanza,. F. L. Am. J. **(1998)**. *Gastroenterol*., 93, 2037-2046.
[3] Van Ryn, J.;Trummlitz, G.; Pairet, M, **(2000).** *Curr. Med. Chem*., 7, 1145-1161.
[4] Van Ryn, J.; *Nat. New Biol*. **(1971)**. 231, 232-235.
[5] Beuck, M.; *Angew. Chem. Int. Ed*.**(1999)**. 38, 631-633.
[6] El-Sabbagh, O.I.; Baraka, M.M.; Ibrahim, S.M.; Pannecouque, C.; Andrei, G.; Snoeck, R.J. Balzarini, A.; Rashad, A. **(2009).** *Eur. J. Med. Chem.*, 44, 3746-3753.
[7] Zaharia, V.; Ignat, A.; Palibroda, N.; Ngameni, B.; Kuete, V.; Fokunang, C.N.; Moungang, M.L.; Ngadjui, B.T. **(2010).** *Eur. J. Med. Chem*., 45, 5080-5085.
[8] Kamal, A.; Khan, M.N.A.; Reddy, K.S.; Rohini, K. **(2007)**. *Bioorg. Med. Chem*., 15 ,1004- 1013.
[9] Azam, F.; El-Gnidi, B. A.; Alkskas, I. A.; Ahmed, M. A. **(2010)**. *J. Enzym. Inhib. Med. Chem*. 25, 818-826.

[10]Kumar, Y.; Green, R.; Boryska, K.Z.; Wise, D. D.; Wotring, L. L.; Townsend, L.B., **(1993)**. *J. Med. Chem*., 36, 3843-3848.
[11]Sharma, R.N.; Xavier, F.P.; Vasu, K.K.; Chaturvedi, S.C.; Pancholi, S.S. **(2009)**. *J. Enzym. Inhib. Med*. Chem., 24, 890-897.
[12]Abu-Hashem, A.A.; Gouda, M.A.; Badria, F.A, **(2010)**. *Eur. J. of Med. Chem*.,45,1976–1981.
[13] Shambenger, R.J. in: Frieden E. (Ed.), Biochemistry of ‘‘Selenium”, PlenumPress, (1983).
[14]McNaughton, M.; Engman, L.; Birmingham, A.; Powis, G.; Cotgreave, I. A.; **(2004)**, *J. Med.Chem*., 47, 233-239.
[15] Bhasin, K.K.; Arora, E.; Kwak, Chee-Hun; Mehta, S.K., **(2010)** *J. of Organometallic Chem*., 695, 1065–1068
[16] Fu J, Cheng K, Zhang Z-M, Fang R-Q, Zhu H-L **(2010)**. *European Journal of Medicinal Chemistry*, 45:2638–2643
[17]Organization for Economic Co-operation and Development, Guidance Document on the Validation of (Quantitative) Structure-Activity Relationship ((Q)SAR) Models OECD series ontesting and assessment 69. OECD document ENV/JM/MONO. Organization for Economic Cooperation and Development, **(2007)**, pp 55-65.
[18] P.X. Franklin, Ajay D. Pillai, Parendu D. Rathod, Swapnil Yerande, Manish Nivsarkar, Harish Padh, Kamala K. Vasu, V. **(2008)** , *European Journal of Medicinal Chemistry* 43, 129:134
[19] M. A. Gouda, , Y. El-Sayed Sherif, and M. S. Elsherbinid, **(2004)** ID GPSS-2013-0238.R2 accepted
[20] Hyperchem Program version 8.1, available from http://www.hyperchem.com/homepage, Windows Hypercube, Inc., USA.
[21]H. Kubiny, H. Folkers, and C. Martin, 3D QSAR in Drug Design: Ligand Protein Interactions and Molecular Similarity, Kluwer Academic Publishers, New York, **(1981)**. p. 138**.**
[22]D.E. Trentham, A.S. Townes, A.H. Kang. **(1977)**, *J. Exp. Med*., *146*, 857-868.
[23]R. Halmdahal, V. Malmstrom, E. Vuorio. **(1977)**, *Med*. **(1993)**, *25*, 251-254.
[24]B.H. Waksman, C.M. Person, J.T. Sharp, **(1960)**, *J. Immunol*., *85*, 403-417.
[25]F.D. Wood, G.M. Pearson, N. Tankan, **(1969)**, *Int. Arch. Allergy*, *35*, 456-464.
[26]M.N. Ghosh, H.O. Schild, "*Fundamentals of Experimental Pharmacology*", 1st Edn, Scientific book agency, Calcutta, **(1971)**.
[27]L.O. Randall, J.J. Selitto. **(1957)**, *Arch. Intl. Pharmacol*., *111*, 409-419.
[28]J.R. Ward, R.S. Jones, **(1962)**, *Arthr. Rheum*. *5*, 557-564.
[29] H.B. Waynforth, P.A. Flecknell. Vital Statistics and Miscellaneous Compounds Information, Academic Press, London (**1992**).
[30] Winks version 4.65, available from contact Texa Soft, Web page, http//www.texasoft.com/home Page
[31]Paget and Barnes, "Evaluation of drug activities", In, Laurence and Bacharach", (eds). Pharmacometrics, New York, Academic Press, 1964, 1, quoted from M.N. Ghosh, H.O. Schild, "Toxicity studies", In, "Fundamentals of Experimental Pharmacology", Chapter 13, 1st ed., Scientific book agency, Calcutta, **(1971)**, 84-88.