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STRUCTURE ACTIVITY RELATIONSHIP (SAR) ANALYSIS OF ANTI-INFLAMMATORY ACTIVITY OF SOME SUBSTITUTED CHROMONES

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Heterocyclic compounds like thiazole acetic acids and pyrazole derivatives phenylbutazone and oxyphenylbutazone (Tanderil) are good anti-rheumatic factors. Though, oxyphenylbutazone is less toxic than phenylbutazone, but still there is need for better alternatives. Hence, thiazole ring was created on chromone nucleus and other heterocyclic systems were developed on thiazole ring of thiazolylchromones with a view to study their anti-inflammatory activity and establish structure activity relationship (SAR). This paper studies SAR in them. Among these compounds 3-[2-(morpholinyl)thiazol-4-yl)-6-chloro-2-methylchromone [1] and 6-(2-methylaminothiazol-4-yl)-2,3-dimethylchromone [2] have shown good anti-inflammatory activities equal to 49 and 47 as compared to 53 for phenylbutazone standard. It is important to mention here that chromone ring is comparatively safer moiety as it is present in a number of fruits, vegetables and plants. Their safer nature is also evident by their ALD_{50} values.

KEYWORDS : Substituted chromones, thiazoles, pyrazoles, anti-inflammatory activity.

INTRODUCTION

Inflammation is characterized by pain along with swelling. Interleukin-1 induces acute inflammation response producing swelling (edema and erythema). It is responsible for rheumatic arthritis; a fatal disorder which may culminate in cancer too. Therefore, drugs for it's effective cure need to be discovered.

Chromone is an important scaffold responsible for a number of biological activities. For instance, they are associated with diuretic [1-2], antimicrobial [3, 4], central nervous system (CNS) [5, 6] and coronary vasodialator [7] activities. They are anti-inflammatory [8] and anti-complementary [9, 10] too. Pyrazoles and thiazoles also show anti-inflammatory activity. For example, phenylbutazone is anti-rheumatic factor [11]. Oxyphenylbutazone is anti-inflammatory [12] with the additional non-toxicity as compared to phenylbutazone. Thiazoles and their derivatives are anti-inflammatory to various extent [13-15].

In last century a number of natural as well as synthetic compounds and their analogues have been tested for biological and pharmacological activities. It has been found that a

particular structural unit in them is responsible for that particular activity. This structural unit is known as pharmacophore. To enhance activity of the compound containing pharmacophore or decrease its toxicity certain alkyl or aryl group or functional groups are introduced on particular position of the pharmacophore. Effect of a certain group on potential of pharmacophore is related to structural changes in the molecule and is known as structural activity relationship (SAR); whereas effect of structural changes on quantitative value of activity potential is known as quantitative structural activity relationship (QSAR) [16]. The relationship between structural changes and activity of series of compounds containing lead is actually SAR [17]. It is important to mention here that lead is basic structure responsible for a particular activity *i.e.* it is synonymous to pharmacophoric unit.

Table 1. Effect of Substitution on Anti-inflammatory activity of 2-Methylchromones

S. No.	Name of compound	Activity	ALD_{50}
1.	3-[2-(morpholinyl)thiazol-4-yl]-6-chloro-2-methylchromone	49	825
2.	6-(2-methylaminothiazol-4-yl)-2,3-dimethylchromone	47	> 1000
3.	6-(2-aminothiazol-4-yl)-2,3-dimethylchromone	14	> 1000
4.	3-(2-aminothiazol-4-yl)-2,6-dimethylchromone	18	> 1000
5.	3-(2-aminothiazol-4-yl)-6-chloro-2-methylchromone	14	316
6.	3-(2-aminothiazol-4-yl)-6-chloro-2,7-dimethylchromone	27	1000
7.	3-(6-phenyl imidazo[2,1-b]thiazol-3-yl)-6-chloro-2-methylchromone	24	1000
8.	3-(6-phenyl imidazo [2,1-b]thiazol-3-yl)-6-chloro-2,7-dimethylchromone	25	316
9.	3-(6-(p)-bromophenyl imidazo [2, 1-b] thiazol-3-yl)-6-chloro-2, 7-dimethylchromone	17	> 1000
10.	3-[2-(3, 5-dimethyl substituted-1H-pyrazol-1-yl)-4-thiazolyl]-6-chloro-2-methylchromone	19	> 1000
11.	3-[2-(3, 5-dimethyl substituted-1H-pyrazol-1-yl)-4-thiazolyl]-2, 6-dimethylchromone	35	681
12.	3-(2-benzimidazolyl)chromone	35	1000
13.	Phenylbutazone	53	-------

In recent past SAR studies have been done on various systems for different types of biological and medicinal activities. A few to mention are : Antibacterial activity and structure activity relationship studies of 4-substituted-5-(diphenylmethyl)-2, 4-dihydro-3H-1,2,4-triazole-3-thiones [18]; Synthesis and structure activity relationship studies of 4-arylthiosemicarbazide as topoisomerase IV inhibitors with Gram-positive antibacterial activity: search for molecular basis of antibacterial activity of thiosemicarbazides [19] and; Pharmacological and structural-activity relationship evaluation of 4-aryl-1-diphenylacetyl (thio) semicarbazides [20]. Studies on synthesis and structure activity relationship of some indole derivatives as potential anti-inflammatory agents have been carried out by Fatahala *et al*. [21]. NSAIDs exhibit anti-inflammatory activities through COX [cyclooxygenase] inhibitors [22-24].

Therefore, thiazolylchromones were synthesized by author and various heterocyclic systems were developed on them [1, 2, 25-28]. This paper reports structure activity relationship (SAR) analysis of some substituted chromones towards anti-inflammatory activity.

MATERIAL AND METHOD

Compounds were synthesized earlier by author in the Department of Chemistry, Kurukshetra University, Kurukshetra and their synthesis are already published [1, 2, 25-28]. Anti-inflammatory activities of compounds were tested at CDRI-Lucknow on mouse. Activities were compared with phenylbutazone standard value for which is 53% inhibition of edema. Compounds studied for SAR towards anti-inflammatory activity and their ALD_{50} values are given in Table-1.

Results and discussion

Compound 3-[2-(morpholinyl)thiazol-4-yl]-6-chloro-2-methylchromone [1] has shown anti-inflammatory activity equal to 49 as compared to 53 for phenylbutazone standard. However, this compound is a bit toxic with ALD_{50} value = 825. Compound 6-(2-methylaminothiazol-4-yl)-2, 3-dimethyl chromone [2] exhibited anti-inflammatory activity 47 and this compound was non-toxic with $ALD_{50\ value} > 1000$. Additional methyl group in it decreased the activity and also reduced toxicity. [c.f. ref. 29 & 30]. Reduced activity may have been due to electron releasing effect of CH_3 group [31]. 6-(2-aminothiazol-4-yl)-2, 3-dimethylchromone [3] has anti-inflammatory activity 14, but this compound is non-toxic ($ALD_{50} > 1000$). Hence, primary amino group at C-2 of thiazole ring is detrimental for anti-inflammatory activity which is also supported by the fact that 3-(2-aminothiazol-4-yl)-2,6-dimethylchromone [4]; 3-(2-aminothiazol-4-yl)-6-chloro-2-methylchromone [5]; 3-(2-aminothiazol-4-yl)-6-chloro-2, 7-dimethylchromone [6] all have reduced anti-inflammatory activities 18, 14 and 27 respectively. Their ALD_{50} values are > 1000, 316 and 1000 due to the fact compounds [4] and [6] have greater number of methyl groups, hence, they are non-toxic. But, compound [5] with chloro substituent is toxic [ALD_{50} value = 316] [29]. In [6] effect of chloro substitution is compensated by one additional methyl group.

Compound 3-(6-phenylimidazo [2, 1-b]thiazol-3-yl)-6-chloro-2-methylchromone [7]; 3-(6-phenylimidazo [2, 1-b]thiazol-3-yl)-6-chloro-2, 7-dimethylchromone [8]; 3-(6-(p)-bromophenylimidazo [2,1-b] thiazol-3-yl)-6-chloro-2, 7-dimethylchromone [9] and 3-[2-(3, 5-dimethyl substituted-1H-pyrazol-1-yl)-4-thiazolyl]-6-chloro-2-methylchromone [10] all have reduced anti-inflammatory activities of 24, 25, 17 and 19, respectively indicating tertiary amino group in cyclic systems at C-2 of thiazole ring reduces anti-inflammatory activity. It is worth mentioning that same trend has been observed in diuretic activity too [30]. However, it increases ALD_{50} values with the exception of compound [8]. Compound [11] *i.e.* 3-[2-(3, 5-dimethyl substituted-1H-pyrazol-1-yl)-4-thiazolyl]-2, 6-dimethylchromone exhibited diuretic activity 35 due to the presence of one additional methyl group. Benzimidazole ring at C-3 of chromone *i.e.* compound [12] also favours anti-inflammatory activity [35 as compared to standard] and this system is also safe for health as ALD_{50} value for this compound is 1000.

Conclusion

Methyl group reduces activity on account of its electron releasing nature and also makes compound safer for health. Presence of alkyl amino (secondary amino group) at C-2 of thiazole in chromones bearing thiazole system makes them good anti-inflammatory agents (values 47 for [2]). Primary and teriary nitrogen at C-2 of thiazolyl chromones are detrimental for anti-inflammatory activity [compounds 3-10] and at the same time they reduce toxicity. Bromo substitution reduces diuretic activity as well as toxicity.

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REFERENCES

1. Garg, C.P., Sharma, V.P. and Kapoor, R.P., *Indian J. chem*., **24B**, 1197-2000 (1985).
2. Sharma, V.P., *Asian J. Chem.,* **17**, 887-894 (2005).
3. Ellis, G.P., "*Heterocyclic Compounds: Chromones, Chromanes and Chromanones*", John-Wiley & Sons, New York (1977).
4. Kumara, K.O. and Kondo,K., *Jap. Kokai,* **72**, 25181 (1972); Chem. Abstr., *78*, 4122 (1973).
5. Milli, A., Mazzei, M., Roma,G., Cuttica, A. and Passerini, N*., Farm. Ed. Sci.,* **30,** 870 (1975): *Chem. Abstr***., 84**, 43766f (1976).
6. Sharma, V.P., *Ph. D. Thesis*; "Heterocyclic Compounds: Studies on the Synthesis of Substituted Chromones of Potential Medicinal Interest", Kurukshetra University- Kurukshetra (1986).
7. Barsoum, G.S. and Kenawy, M.R., *Am. Heart*, **47,** 297 (1954).
8. Gupta, V. and Mishra, U., *Indian J. Heterocyclic Chem.,* **17**, 281-282 (2008).
9. Singh, O.V., Sangeeta, Khanna, M.S., Garg, C.P. and Kapoor, R.P., *Indian J. Chem*., **32B**, 1241-1248 (1993).
10. Singh, O.V., Garg, C.P.,. Kapoor, R.P., Moza, N. and Kapil, A., *Indian J. Chem***., 31B**, 248-253 (1992}.
11. Whitehouse, M.W., *Prog. Drug. Res*., **8,** 321-429 (1965): *Chem. Abstr*., **63**, 13854h (1965).
12. Burns, J.J., Rose, R.K., Goodwin, S., Reichenthal, H., Horning, E.C. and Brodic, B.B*., J. Pharmacol. Expt. Therap.*, **113**, 481 (1955): *Chem. Abstr*., **49**, 9810f (1955).
13. Chandak, N., Kumar, P,. Kaushik, P., Varshney, P., Sharma, C., Kaushik, D., Jain, S., Aneja, K. and Sharma, P.K., *J. Enzyme Inhib. Med. Chem*., **29(4),** 476-484 (2014).
14. Patel, A.D. and Patel, C.N., *Int. J. Drug Dev. and Res*., **4(1),** 106-111 (2012).
15. Fatima, A., Kulkarni, R. and Mantipragada, B., *Der Pharma Chemia*, **7(3**), 212-220 (2015).
16. Patrick, G.L., "*An Introduction to Medicinal Chemistry*", Oxford University Press, New York, p-128 (1995).
17. Thomas, G., "*Medicinal Chemistry: An Introduction*" (Second edition), Wiley-India Pvt Ltd, New Delhi, p-76 (2011).
18. Kusmeiz, E., Siwek, A., Kosikowska, U., Malm, A., Stefanska, J., Dzitko, K. and Wujee, M., *Lett. Drug Design Discov.* , **10** , 95-101 (2013).
19. Siwek, A., Staczek, P. and Stefanska, J., *Eur. J. Med. Chem.*, **46**, 5717-5726 (2011).
20. Wujee, M., Kedzierska, E., Kusmeiz, E., Plech, T., Wrobel, A., Paneth, A., Urzelska, J., Fidecka, S. and Paneth, P., *Molecules*, **19**, 4745-4759 (2014).
21. Fatahala, S.S., Mohammed, A.K. and Mohamed, M.S., *Acta Chim. Slov.*, **64**, 865-876 (2017).
22. Bang, J.S., Oh, D.H., Choi, M., Sur, B.J., Lim, S-J., Kim, J.Y., Yang, H-I., Yoo, M.C., Halm, D.H. and Kim, K.S., *Arthritis Res. Ther.*, **11**, R49 (2009).
23. El-Nezhawy, A.O.H., Gaballah, S.T., Radwan, M.A.A. and Abdel-Salam, A.R.B., *Med. Chem.* (Los Angeles), **202**, 558-569 (2009).
24. Rainford, K.D., *Inflamm. Pathog. Chronic Dis.*, **42**, 3-27 (2007).
25. Kapoor, R.P., Sharma, V.P., Singh, O.V. and Garg, C.P., *Indian J. Chem***., 30B**, 1152-1155 (1991}.
26. Sharma, V.P., Sunita and Surjeet, , *Indian J. Heterocyclic Chem.*, **14**, 31-34 (2004).
27. Garg, C.P., Sharma,V.P., Chhabra, V. and Kapoor, R.P., *Indian J. Chem***., 27B**, 469-471 (1988).
28. Sharma, V.P., *Indian J. Heterocyclic Chem.* , **13**, 171-172 (2003).
29. Gupta, A.L., *Medicinal Chemistry*, p-40 (2013).
30. (a) Sharma, V.P., *JPDS*, **7(7)**, 605-606 (2015). ; (b) Sharma, V.P., *JPDS*, **8(8)**, 421-422 (2016).
31. Silvermann, R.B., "*Organic Chemistry of Drug Design and Drug Action*" (Second Edition), Academic Press, London, p-21 (2004).

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