Chalcones and their Potential Role in Inflammation

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Abstract: Chalcones are a group of phenolic compounds which possess a wide variety of cytoprotective and modulatory functions.

They have been shown to possess antioxidant, oxygen scavenging and anti-inflammatory properties in a variety of experimental systems and can trigger the intracellular cascade of protective pathways offering a promising stratagem for therapeutic applications.

In this research we will review the anti-inflammatory effect of chalcone derivatives and new approaches.

Key Words: Natural/synthetic chalcones, inflammation, anti-inflammatories, antioxidants.

INTRODUCTION

Chalcone is a generic term for the compounds bearing the 1, 3-diphenyl-2-en-1-one [1] framework. They are a group of phenolic compounds that belongs to the flavonoids family widely occuring in nature as pigments.

Chalcones are highly distributed in nature and a large number has been synthesized in the laboratory. Many papers have been presented in the literature with references to structural modifications of the chalcone template [2]. The natural compounds are isolated from flavonoid biosynthesis in plants, but they do not necessarily accumulate to any appreciable degree unless the enzyme chalcone isomerase, which catalyses the cyclisation of chalcone to flavone, is absent [1].

Two conformational analyses of chalcones were reported in which the bonds about the α,β-unsaturated carbonyl (enone linkage) were rotated to identify the minimum energy conformation [3,4]. Both investigations confirmed overall planarity and rigidity of the extended π-system in chalcones, in agreement with X-ray structures of chalcones found in the Cambridge database. An interesting observation was that rings A and B had different energy barriers to rotation [3]. The semi-empirical AM1 method indicates that ring A had greater rotational flexibility, as seen from its lower energy barrier to rotation compared to ring B.

The biological activities of chalcones are equally wide-ranging. In fact, not many structural templates can claim association with such a diverse range of pharmacological activities, among, which cytotoxicity, antitumour, anti-inflammatory, antiplasmodial, immunosuppression and antioxidant are widely cited [5-11].

Several useful structure-activity relationships (SAR) on chalcones have been reported in the recent literature. However, many of the reports have neglected to assimilate their findings with the "bigger SAR picture" for a specific biological profile [12-15].

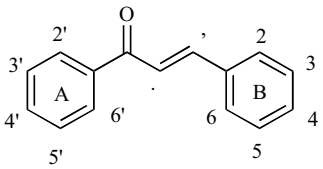

Fig. (1). General structure of chalcone derivatives.

A series of chalcones, natural and synthetic, have been already tested for their possible role as anti-inflammatory agents. Inflammation is a complex stereotypical reaction of the body expressing the response to damage of its cells and vascularized tissues. A number of various mediators are implicated in this phenomenon.

In this paper we will review the anti-inflammatory effect of chalcones derivatives and we will try to discuss this effect in terms of SAR.

RESULTS

2'-Hydroxychalcone Derivatives

Alcaraz *et al*. synthesized two new series ofchalcone derivatives [16].

The new series of chalcone derivatives were found to be inactive on nonenzymatic lipid peroxidation and unable to interact with superoxide or hydroxyl radicals. In Table **1** are indicated the most potent representatives. Both compounds **3a** and **3b** strongly inhibited LTB_4 generation in human polymorphonuclear leukocytes (PMNs). Moreover compound **3b** was found to strongly inhibit synovial human recombinant phospholiase A_2 (hr-PLA_2) as well as TxB_2 generation. The overall good *in vitro* anti-inflammatory profile of compound **3b** was confirmed with the good activity in the *in vivo* anti-inflammatory test, referring to the topical administration of compound on mouse ear edema induced by 12-O-tetradecanoylphorbol 13-acetate (TPA).

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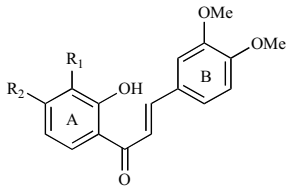
Table 1. Per Cent Inhibition of a) LTB_4 Generation in Human PMNs, b) Synovial Human Recombinant (h) Phospholipase A_2, c) Thromboxane B_2 (TXB_2) Induced by 100 µM of Chalcones



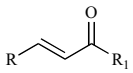
Compounds [21]	R_1	R_2	% h-PLA_2	% TXB_2
3a	Me	Me	27.5	28.1
3b	OMe	OMe	55	77.2

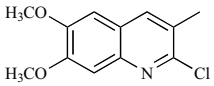
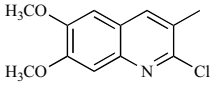
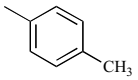
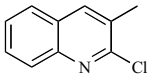
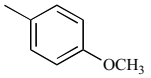
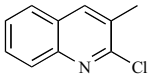
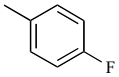
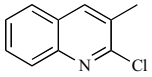
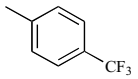
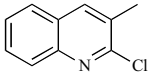
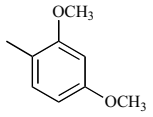
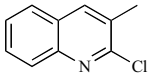
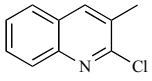
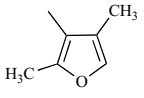
In terms of structure activity relationships, the presence of two methoxy groups is correlated with higher biological responses. It seems that substituents R_1 and R_2 with low π values (hydrophobic contribution, $\pi_{OCH3} = -0.02$, $\pi_{CH3} = 0.56$) support higher activity.

2-Chloroquinolinyl Chalcone Derivatives

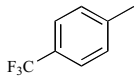
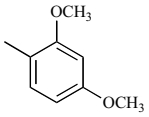
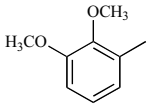
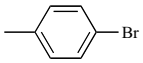
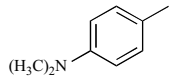
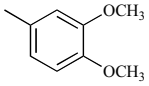
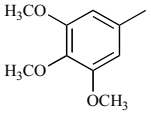
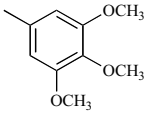
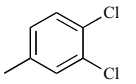
Herencia *et al.* [13] reported a new series of 2-chloroquinolinyl derivatives indicated in Table **2**. These compounds have been evaluated for their *in vitro* anti-inflammatory ef-

Table 2. *In Vitro* Results from: Elastase Release, LTB_4 Biosynthesis (Human Neutrophils), 5-LOX Activity (Cytosolic Fractions of Human Neutrophils) and COX-2 Activity (Human Monocytes). Percentages of Inhibition at Concentration of 10 µM [22]



Compounds	R *(B ring)*	R_1	Elastase %	LTB_4 %	5-LOX %	COX-2 %
1			0	42.2	42.0	0
2			40.7	9.8	61.0	0
3			0	30.2	42.3	30
4			3.0	6.2	3.9	36.3
5			0	36.9	32.9	35.6
6			0	10.7	27.	41.8
7			0	25.4	30.2	46.6
8			8.4	53.5	3.5	0

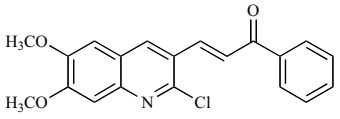
(Table 2. Contd….)

Compounds	R *(B ring)*	R_1	Elastase %	LTB_4 %	5-LOX %	COX-2 %
9			0	35.4	21.7	0
10			2.2	6.7	6.1	0
11			0	0	37.9	0
12			0	21.1	14.6	0
13			5.4	4.8	4.1	0

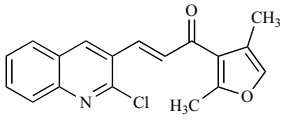
fects. They have been tested on the elastase release assay, LTB_4 biosynthesis (using human neutrophils), on the inhibition of 5-lipoxygenase (with cytosolic fractions of human neutrophils) and on the inhibition of cyclooxygenase-2 derived from human monocytes. Furthermore compound **11** was evaluated for its inhibitory effect on superoxide anion generated by a) human neutrophils or b) the hypoxanthine/ xanthine oxidase system. Human leukocytes synthesize a series of bioactive metabolites of arachidonic acid upon inflammatory stimulation, with participation of enzymes such as phospholipase A_2 (PLA_2), cyclooxygenase (COX) and 5-lipoxygenase (5-LOX), which catalyzes the first step in the synthesis of leukotrienes (LTs).

Compounds **2**, **4**, **8**, **10** and **13** were found to strongly inhibit degranulation, while compounds **4**, **5**, **6** and **7** were found to be the most potent cyclooxygenase-2 inhibitors. Chalcones seemed to strongly inhibit the release of TNF-a, a cytokine relevant to the inflammatory process. Their anti-inflammatory effect on the *in vivo* test of the mouse air pouch model (at a dose of 100 nmol/pouch) was also potent for the most of the samples. The researchers thought that inhibition of leukocyte functions and/ or lipid mediator biosynthesis could be important thereapeutic intervention in inflammatory diseases and it may lead to the discovery of new drugs as alternative approaches.

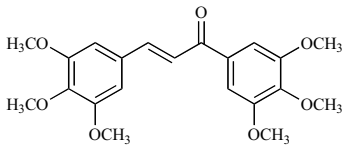
Table 3. Effect of Chalcone Derivatives on NOS and COX Activity in Peritoneal Macrophages at 10 μM. Nitrite and PGE_2 Release (%)



CH1



CH8



CH12

Compounds	A[a]		B[b]	
	NO_2^- (%)	PGE_2 (%)	NO_2^- (%)	PGE_2 (%)
CH1	58.9	7.1	17.9	5.1
CH8	50.6	7.4	10.8	3.2
CH12	51.3	7.5	6.2	2.2

[a]: Cells stimulated firstly with LPS (lipopolysaccharide) and then treated with tested compounds (ng/ml), [b]: Cells co-incubated with LPS (lipopolysaccharide) and tested compounds (ng/ml).

According to the SAR studies, derivatives with R = chloroquinolinyl group present the most potent anti-inflammatory effect. Introduction of a lipophilic group at R increases 5-LOX inhibitory activity. Replacement of 2-chloroquinolinyl group by other substituents lowers 5-LOX inhibition. The nature of the heteroaromatic group R_1 affects also the percentages of LTB_4 biosynthesized (compounds **7**, **8**). Substituents in the A ring (especially halogen), or the presence of a pyridinyl group increases the anti-inflammatory effect. The existence of a quinoline moiety in B ring increases also the COX-2 inhibitory effect *in vitro* and *in vivo*.

Chalcone Modulation of NO and/of Prostaglandins (PGs)

Herencia *et al.* [17] reported the synthesis of some new analogues with anti-inflammatory activity. Three chalcone derivatives have been evaluated as NO and prostaglandins (PGs) modulators. NO has been found to be an important inflammatory mediator [18].

Chalcone derivatives were found to inhibit dose-dependently NO and PGE_2 production *in vitro*, in mouse peritoneal macrophages and *in vivo* in the mouse air pouch. They do not seem to have direct effect on iNOS or COX-2 activities. It seems that the *in vivo* results of compounds **CH12** and **CH8** are correlated to their *in vitro* results, while compound **CH1** was found to be the most potent inhibitor. These chalcone derivatives werecabable to control NO production. No results in terms of SAR could be derived.

4-Dimethylamino-3',4'-dimethoxychalcone

4-dimethylamino-3', 4'-dimethoxychalcone was found to be a potent anti-inflammatory agent. It scavenges superoxide anion generated by stimulated human neutrophils or by the hypoxanthine/xanthine oxidase system [17, 19]. It inhibits: a) the chemiluminescence induced by zymosan in mouse peritoneal macrophages, b) the cytotoxic effects of superoxide anion and c) the nitric oxide synthase (iNOS). The exerted potent scavenging activities could explain partly the anti-inflammatory activity.

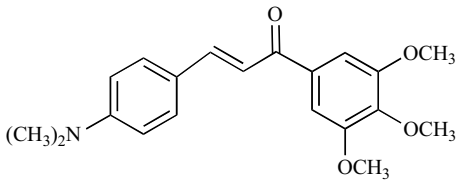


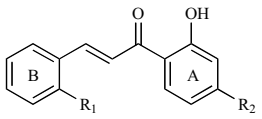
Fig. (2). Structure of compound 4-Dimethylamino-3',4'-dimethoxychalcone.

Hydroxy-Substituted Chalcones

Chalcones **1**, **2** and **3** were tested for their antioxidant and antistressful potency (Table **4**). The heme oxygenase-1 HO-1 test was used [20]. Heme-oxygenase-1, an endogenous agent in mammalians, can be stimulated by a variety of agents, such as oxidative stress, radiations and cytokines. The activation of HO-1 leads to iron release and production of carbon monoxide (CO) that, in return, activates soluble guanylyl cyclase and interestingly participates in similar events to these of nitric oxide (NO).

All three compounds were found to increase HO-1 after 6 h of incubation and provoke cytotoxicity at a concentration of 50 μM. 2′-Hydroxychalcone (compound **1)** had little effect on HO-1 at concentrations of 5-10 μM. The results are significantly increased at 20-30 μM. On the contrary, 2,2′ -dihydroxychalcone (compound **2**) showed higher antioxidant effect at 10-20 μM, whereas 2, 2′, 4′-trihydroxychalcone (compound **3**) exhibited a 3-fold increase at concentration of 20 μM.

Table 4. Structural Modifications of the Studied Chalcones



	Compounds	R_1	R_2
1	2′-Hydroxychalcone	H	H
2	2,2′-Dihydroxychalcone	OH	H
3	2, 2′,4-Trihydroxychalcone	OH	OH

It seems that the number and the site of substitution of hydroxyl groups on both the phenyl rings of chalcones, highly influence their action upon heme oxygenase-1.

3′, 4′, 5′, 3, 4, 5- Hexamethoxy-Chalcones

The synthetic 3′,4′,5′,3,4,5- hexamethoxy-chalcone was studied as a cytoprotective and anti-inflammatory agent, able to reduce nitric oxide (NO) *in vitro* and *in vivo* and to induce the production of heme oxygenase-1 (HO-1) in RAW 264.7 macrophages [21].

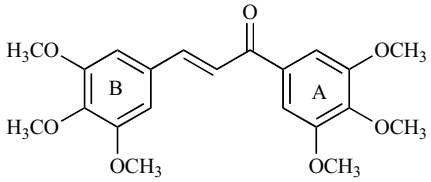


Fig. (3). Structure of 3′,4′,5′,3,4,5- hexamethoxy-chalcone.

Chalcone inhibited directly NF-κB-proteins. DNA binding was examined and the researchers concluded that DNA can interact with NF-κB proteins irreversibly.

The HO-1 induction was found to be concentration-dependent. Maximal levels of HO-1 protein were observed between 4 and 8 h and were decreased after 24 h.

The production of reactive oxygen species (ROS) after chalcone treatment was also measured by laser cytometry and it was found able to induce HO-1 significantly augmented intracellular oxidative stress after 20 min of treatment. Especially, endogenous glutathione (GSH) levels were decreased at 2 h pro-incubation with this chalcone, while they were continuously increased up to 24 h. Finally, it was supported that chalcone augmented both DNA binding and translocation of NfE_2-related factor to HO-1 production.

3,4-dihydoxychalcones

Nakadate *et al.* [22] reported that hydroxychalcones inhibit 12-lipoxygenase and cyclooxygenase in mouse epider-

mis. Chalcones with a 3, 4-dihydroxycinnamoyl structure strongly inhibited lipid peroxidation in rat liver microsomes [12].

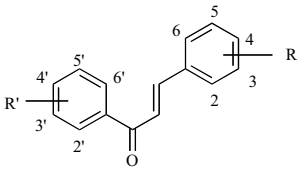
Sogawa *et al.* [12] using the above information synthesized and tested a series of 3,4-dihydroxychalcones as possible inhibitors of 5-lipoxygenase and cyclooxygenase. In Table **5** a summary is given, including the most effective compounds. Almost all compounds were found to strongly inhibit 5-LOX and COX [12]. Compounds bearing a 3, 4-dihydroxy group were especially potent inhibitors. These results were in accordance with their effect on lipid peroxidation. Structure activity relationship studies showed that the anti-5-lipoxygenase activity of 3, 4-dihydoxychalcones was not correlated with their hydrophobicity, while electron-attracting groups were not suitable for this inhibitory activity.

The substitution of hydroxy or alkoxy groups at the 2', 3' and 2', 5'-positions increases the cyclooxygenase inhibition, while the 4'-substitution remarkably reduces COX inhibition. Compound **37** (2',5'-dimethoxy-3,4-dihydroxychalcones), which presents the higher *in vivo* anti-inflammatory activity strongly inhibits COX (compared to flufenamic acid) as well as 5-LOX (compared to quercetin).

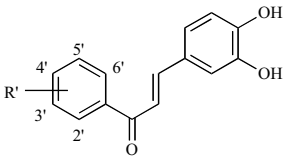
Although this study is not very recent, it is comprehensive and informative.

Compounds **10**, **11**, **12**, **45** and **52** present the higher 5-LOX inhibition due to the presence of hydroxyl groups.

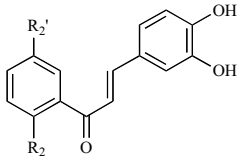
Table 5. Inhibition of 5-LOX (IC_{50}), COX (IC_{50}), % Inhibition of Lipid Peroxidation at a1 μM and of the Arachidonic Acid-Induced Mouse Ear Edema at 30 μg/ml



Compounds **10-14**



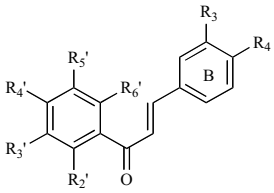
Compounds **21-37**



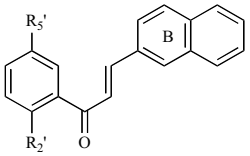
Compounds **44-53**

	Compounds		5-LOX IC_{50} (nM)	COX IC_{50} (μM)	LPOX (%) at 1 μM	AA (%) 30 μg/ear
	R'	**R**				
10	3'-OH	3,4-OH	4.2	140	24	-
11	4'-OH	3,4-OH	4.0	320	36	-
12	2',4'-OH	3,4-OH	4.6	120	40	-
14	2-thienyl	3,4-OH	22	34	56	-
	R'					
21	4'-Cl		8.5	1400	-	-
26	2'-OCH_3		27	13	-	-
27	3'-OCH_3		6.5	15	-	-
29	3'-$N(CH_3)_2$		9.8	41	-	-
30	4'-$N(CH_3)_2$		4.7	810	-	-
34	4'-OH,3'-OCH_3		9.0	14	-	-
37	2'-OCH_3,5'-OCH_3		7.8	9.2	-	77
	R_2	R_2'				
44	OH	C_2H_5	5.3	130	-	42
45	OH	$CH(CH_3)_2$	4.0	37	-	16
46	OH	$OCH(CH_3)_2$	11	140	-	67
48	CH_3	CH_3	16	44	-	58
50	OCH_3	OC_2H_5	3.8	26	-	13
52	OC_2H_5	OCH_3	27	2	-	7.4
53	OC_2H_5	OC_2H_5	2.4	24	-	-18

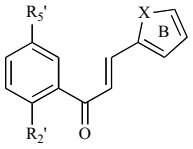
Table 6. Inhibitory effect (IC_{50}) of chalcones on the release of β-glucuronidase (β-glu) and lysozyme (Lys). Scavenging activity on superoxide anion generated from FMLP/CB (S.A.). Effect on polymyxin B-induced mouse hind-paw edema in normal and adrenalectomized mice at 30 mg/Kg.



1, 2, 6-11



3



4: X = O, 5: X = S

	R_2'	R_3'	R_4'	R_5'	R_6'	R_3	R_4	IC_{50} μM			AUC[a]	
								β-glu	Lys	S.A.[a]	Normal mice	Adrenalactomized mice
1	H	H	H	H	H	H	OH	11.4	10.5	77.5	nt	nt
2	OH	H	H	H	H	OH	H	2.0	4.2	4.8	145.1	115.9
3	OH	H	H	OH	H	-	-	5.1	1113.2	8.4	nt	nt
4	OH	H	H	OH	H	-	-	17.3	19.7	>100	nt	nt
5	OH	H	H	OH	H	-	-	9.7	23.6	>100	nt	nt
6	OH	H	H	OH	H	H	H	3.5	12.3	-	nt	nt
7	OH	H	H	OH	H	H	Cl	0.6	2.6	>100	146.1	112.1
8	OH	H	H	H	H	OCH_3	OCH_3	9.8	14.8	26.2	nt	nt
9	H	OH	H	H	H	OCH_3	OCH_3	9.7	5.9	9.4	nt	nt
10	H	OH	H	H	H	OH	OH	12.5	7.3	15.9	nt	nt
11	OH	H	H	OH	H	OCH_3	OCH_3	6.0	10.9	>100	nt	nt

[a] AUC: Area Under the Curve (time-paw swelling); S.A. superoxide anion.

Vicinal hydroxyl groups are correlated with high inhibition (**45**, **52**, **10**, **11**, **12**).

2' and 3'-Hydroxychalcones, 2',5'-dihydroxychalcones

Lin and his group [23] presented a series of chalcone derivatives (Table **6**), which were evaluated for their inhibitory effect on the release of β-glucuronidase and lysozyme from rat neutrophils [23]. All the compounds were found to be active. 2',5'-Dihydroxychalcone is a potent chemical mediator and a cyclooxygenase inhibitor [24].

Compounds **2**, **8**, **9** and **11** were found to strongly and dose-dependently inhibit degranulation of mast cells. Aromatic substitution of B ring increases their inhibitory effect.

Compounds **1, 2, 8** and **9** strongly scavenge superoxide anion as well as compounds **4**, **5** and **11**. However the two groups of compounds do not seem to follow the same inhibitory pathway.

Compounds **2** and **7** demonstrated potent activity. They present non-steroidal anti-inflammatory effect, which partly mediated through the suppression of chemical mediators released from mast cells and neutrophils.

The presence of R_2' = OH and R_3 = OH (**2**) and R_2' = OH, R_5' = OH (**3**, **5**, **6**) is correlated with higher biological response. The replacement of O (**4**) by S in compound **5** led to a more potent inhibitor of β-glucuronidase.

2'-Hydroxychalcones, 2',5'-dihydroxychalcones

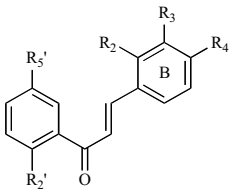
Hsieh *et al.* [25] synthesized new chalcones (Table **7**). Since degranulation of mast cells and neutrophils are highly contributed to inflammatory disorders, researchers evaluated the new chalcones *in vitro* for their inhibitory effects on macrophages and microglial cells, on mast cells and on neutrophils. Microglial cells and macrophages are believed to be involved in inflammatory diseases of the CNS.

Almost all of them exhibited potent inhibitions on the release of β-glucuronidase and lysozyme. Compound **11** was the most active. Moreover, the 2', 5'-dialkoxychalcones exhibited potent inhibitory effects on nitric oxide formation from murine microglial cell lines N9. Compound **11** was the most active.

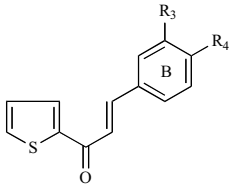
Broussochalcone (BCA)

A number of chalcone derivatives have been isolated from plants. One of the most important, chalcone derivatives according to its biological interest is *broussochalcone A* (BCA) which has been isolated from the cortex of *Broussonetia papyrifera* Vent [26]. According to traditional medi-

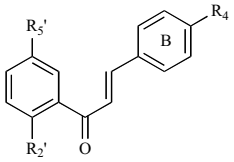
Table 7. Inhibitory Effect of Chalcones on: a) the Release of β-glucuronidase (β-glu) and Histamine (His) from Rat Peritoneal Mast Cells Stimulated with Compound 48/80, b) the Release of β-Glucuronidase (β-glu) and Lysozyme (Lys) from Rat Peritoneal Mast Cells Stimulatedwith fMLP/CB, c) Superoxide Anion Formation from rat Neutrophils Stimulated with fMLP/CB or PMA and d) Accumulation of NO_2^- from RAW 264.7 Cells and N9 Cells Stimulated with LPS



Compounds **1, 2, 4-12**



Compound **3**



Compound **13,14**

	Compounds					IC_{50} μM							
						Stimulated with 48/80		Stimulated with fMLP/CB		Superoxide anion formation		Accumulation	
	R_2'	R_3'	R_2	R_3	R_4	β-glu	His	β-glu	Lys	fMLP/CB	PMA	Raw 264.7	N9
1	OH	H	OH	H	H	45.8	54.1	1.6	1.4	>100	46.6	-	-
2	OH	H	H	H	Cl	>30	>30	>30	>20	>30	>30	>30	>30
3	-	-	-	OH	OH	>10	>10	>10	>10	>100	3.9	-	-
4	OCH_3	O CH_3	H	OH	OH	>30	>30	16.9	13.1	6.2	4.9	-	-
5	OH	O CH_3	H	O CH_3	O CH_3	65.3	80.8	5.6	7.3	2.8	>100	-	-
6	OH	O CH_3	H	H	O CH_3	81.0	>100	11.9	16.9	35.5	>100	-	-
7	OH	O CH_3	H	H	CH_3	80.1	>100	17.4	7.9	37.7	>100	-	-
8	OH	O CH_3	H	H	Cl	>30	>30	>30	>30	4.2	4.2	>30	>30
9	O CH_3	O CH_3	H	H	Cl	88.8	>100	11.9	14.7	6.3	>100	>10	5.8
10	OC_2H_5	OC_2H_5	H	H	Cl	>100	>100	>100	>100	>100	>100	>3	1.0
11	OC_3H_7	OC_3H_7	H	H	Cl	>100	>100	>100	>100	>100	>100	>3	0.7
12	OC_4H_9	OC_4H_9	H	H	Cl	>100	>100	>100	>100	>100	>100	>10	1.9

cine, the cortex of this plant was used therapeutically for diuresis, homeostasis and relief of edema and cough. *Broussochalcone* seemed to act as a potent inhibitor of platelet aggregation [27] and respiratory burst in neutrophils [28].

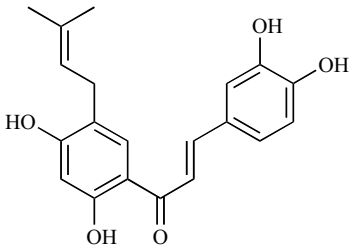


Fig. (4). Structure of *Broussochalcone A* (BCA).

By this study, it was verified that BCA is a powerful antioxidant with strong free radical-scavenging activity. Moreoever, it was found that it can suppress lipopolysaccharide (LPS)-induced iNOS protein expression. Thus, the free radical-scavenging activity in parallel with the inhibition of iNOS protein expression could be associated with its anti-inflammatory role.

2'-5'-Dihydroxy-4-chloro-dihydroxychalcone

Huang *et al.* examined the biological activity of DCDC (2',5'-dihydroxy-4-chloro-dihydroxychalcone) [29] on lipopolysaccharide (LPS)-induced responses in murine macrophage cell line RAW 264.7. DCDC (in a concentration dependent manner) inhibited NO production in LPS-stimulated macrophages. The inhibition was extended on iNOS enzyme activity. This inhibition was not proceeded in parallel with the total nitrite accumulation.

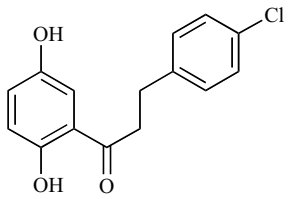
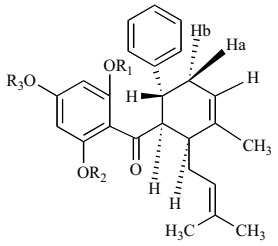


Fig. (5). Structure of 2'-5'-Dihydroxy-4-chloro-dihydroxychalcone (DCDC).

Table 8. Percent Inhibition of TPA Induced Ear Edema in Rats with Topical Application of Chalcones after 2h at a Dose 20 µg/ear



	Compounds	R_1	R_2	R_3	% Inhibition
1	*(-)-Hydroxypanduratin A*	H	H	H	53
2	(-)-panduratin A	H	H	CH_3	62

Cyclohexenyl Chalcone Derivatives

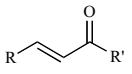
Boesenbergia pandurata (Zingiberaceae) is a common herb used widely in traditional Thai medicine. (-)-Hydroxypanduratin A and (-)-panduratin A consist cyclohexenyl chalcone derivatives with interesting *in vivo* anti-inflammatory activity [30].

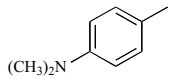
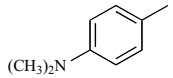
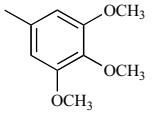
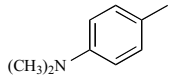
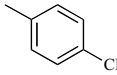
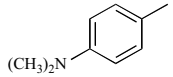
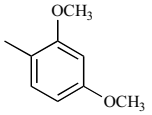
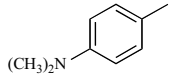
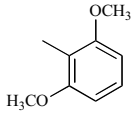
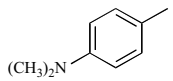
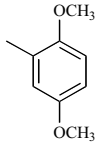
Dimethylamino-Chalcone Derivatives

Rojas *et al.* [31] reported a series of dimethylamino-chalcone derivatives (1, 2-diaryl-propenones) (Table **9**).

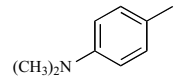
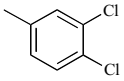
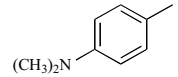
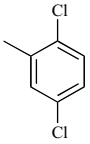
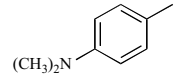
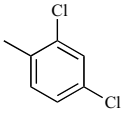
The above mentioned chalcone derivatives have been evaluated as possible inhibitors of NO release and PGE_2 pro-

Table 9. Per Cent Inhibition on the Production of NO and PGE_2 in RAW 264.7 Macrophages at a Dose 5 µM



	R	R'	NO_2^- %	PGE_2 %
1			49.9	28.7
2			49.1	36.8
3			32.2	27.9
4			17.1	34.6
5			73.2	3.5
6			63.4	73.3

(Table 9. Contd….)

	R	R'	NO_2^- %	PGE_2 %
7			25.4	36.8
8			28.2	44.9
9			39.9	44.0

duction in the RAW 264.7 macrophage cell line. It has been well documented that inhibition of production of NO and prostaglandin E_2, is contributed to the design of promising anti-inflammatory agents [32]. Chalcones were found to potentially inhibit both processes. Compound **6** was the most active. The 2', 5' – disubstituted derivatives 6 and 8 present higher inhibitory activity on the production of PGE2. Lower lipophilic contribution of 2', 5' substituents (π_{OCH3} = - 0.02) is correlated with higher activity (π_{Cl} = 0.71). Compound **6** was found to be very potent on the *in vivo* carrageenan mouse paw edema test.

Chalcone Derivatives Isolated from Millettia Leucantha

Four new chalcones and other chalcone derivatives were isolated from the stem bark of *Millettia leucantha* (Leguminosae). (Table **10**) All compounds were examined for cytotoxic, anti-inflammatory and antiviral activities [33].

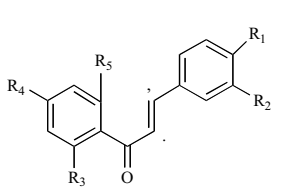
No safe observations in terms of (Q)SAR could be derived from these data, due to the small number of structural modifications and the way of presentation of the experimental results.

Novel Heteroaryl-Substituted Chalcones

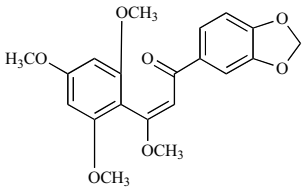
Meng *et al.* [34] tested a series of heteroayl-derivatives (Table **11**) as inhibitors of tumor necrosis factor- α (TNF-α) (induced vascular cell adhesion molecule-1 VCAM-1 expression). At the sites of inflammation, the recruitment of leukocytes is mediated, (in part), by the expression of VCAM-1 in response to various cytokines e.g. (TNF-α).

Most of these compounds were found to be very active. Thienyl or benzothienyl substitution at the meta-position of ring B helps boost potency while large subsitution at para-position on ring B is detrimental. Various substitutions are tolerated on ring A. A lipophilicity-potency relationship has been observed in several sub-series of compounds.

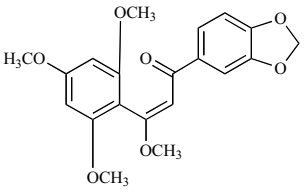
Table 10. Structure of the Examined Chalcone Derivatives



Compounds **1, 2, 10**



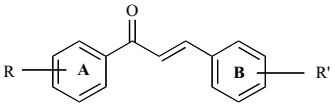
Compounds **4, 6**



Compound **7**

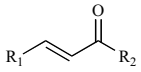
	R_1	R_2	R_3	R_4	R_5
1	OCH_2O	OCH_2O	H	OMe	OMe
2	OMe	OMe	OMe	OMe	OH
4	H	OMe	-	-	-
6	OMe	H	-	-	-
7	-				
10	OCH_2O	OCH_2O	OMe	OMe	OMe

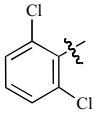
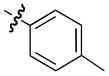
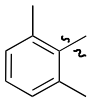
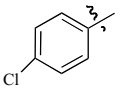
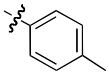
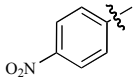
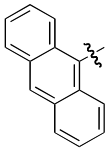
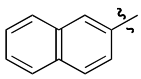
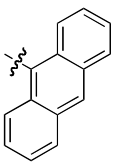
Table 11. Inhibiting Profile of Chalcones on Inducible VCAM-1 Expression



	R	R'	VCAM-1 (IC_{50} μM)
51	3,5-dimethoxy-4-(4-methoxybenzyloxy)	3,4,5-trimethoxy	1
68	3,5-dimethoxy-4-carboxymethoxy	2-methoxy-5-(thien-2-yl)	1
69	3,5-dimethoxy-4-carboxymethoxy	3,4-dimethoxy-5-(thien-2-yl)	1
71	4-carboxymethylthio	2,4-dimethoxy-5-(benzo[b]thien-2-yl)	1
72	H	2-carboxymethoxy-4-methoxy-5-(benzo[b]thien-2-yl)	1
74	3,5-dimethoxy-4-hydroxy	2,4-dimethoxy-5-(benzo[b]thien-2-yl)	1
76	3,4(dihydroxymethyl-methlenedioxy)	3,4-dimethoxy-5-(thien-2-yl)	1
78	3,4,5-trimethoxy	2-methoxy-5-bromo	1

Table 12. Percent *In Vitro* Inhibition of Endothelial Cell Proliferation (SVR) for Enone Analogues



	R_1	R_2	% SVR 1 μg/ml
1			71.6
3			73.7
6			47.7
12			48.3
28			47.6
40			54.6
41			52.5

Aromatic Enones Related to Curcumin

Curcumin, a natural product isolated from the spice *turmeric*, has been attributed with several pharmacological activities including anti-angiogenic activity [35].

This carotenoid pigment gave birth to other chalcone analogues, which seem to inhibit *in vitro* SVR endothelial cell growth in a concentration-dependent manner [35]. These chalcone derivatives have been tested at three different concentrations (1 μg/ml, 3 μg/ml and 6 μg/ml). The most promising results, except curcumin, proved to be with phenyl substitution, phenyl substitution adjusted with two chloro-atoms and, at last, anthranyl substitution. In contrast, pyridine, furan, naphthyl, biphenyl, and benzo [1,3] dioxole provoked only a slight effect, especially in minor concentrations (results not given in Table **12**, [35]).

Phenylsulphonyl Urenyl Chalcone Derivatives

Two series of phenylsulphonyl urenyl chalcone derivatives (UCH) were prepared and evaluated for their inhibitory potency on NO production and PGE_2 overproduction in RAW 264.7 macrophages [36] (Tables **13**, **14**).

The findings provide evidence that three methylated chalcones from the total of twenty methylated and chlorinated compounds reduced successfully NO generation by 50% approximately. In parallel, substitution of phenyl group by pyridinyl group in R_1 dramatically decreases the potency on PGE_2 inhibition in both **Me-UCH** and **Cl-UCH** series (Table **13**).

Compounds **Me-UCH9** and **Cl-UCH9**, **Me-UCH5** were identified for their: a) inhibitory effect on COX-2 activity in intact human monocytes, b)repulsive action concerning LTB_4 generation and 5-LOX activity from human neutrophils and c) ability as scavengers of superoxide anion without exerting results on the hypoxanthine/xanthine oxidase system.

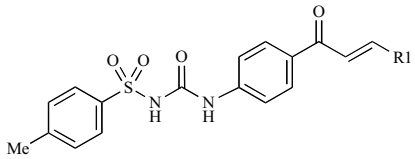
Dichlorosubstitution on phenyl ring strongly inhibited COX-2 activity (Table **14**, compound **5**). Difluoro and monofluoro substituted derivatives present lower activity than the corresponding 4 and 5 chlorosubstituted.

Cardamomin

Cardamomin, a 2′, 4′-dihydroxy-6′-methoxychalcone (Fig. **6**), has been firstly isolated from the seeds of *Amomum subulatum* [37], from *Boesenbergia pandurata* [38] and from *Alpinia henryi*, where it was found to cause vasorelaxation [39]. It was also isolated from the spicy plant *Alpinia conchigera* Griff (Zingiberaceae), a Vietnamese traditional medicinal herb used for treating inflammatory diseases. Israf *et al.* [40] isolated also c*ardamonin* from the fruits of *Alpinia raffesiana*. It was tested for its role to inhibit NO and PGE_2 production from lipopolysaccharide- and interferon-γ-induced RAW 264.7 cells and from whole blood [40]. *Cardamomin* was also examined for its anti-inflammatory and death-prolongating activity. The analysis of thromboxane B_2 (TxB_2) secretion from whole blood either stimulated by COX-1 or COX-2 pathway revealed the inhibitory role of *cardamonin* in both pathways, although it was found to be a more selective COX-2 inhibitor. It was evaluated as potent inhibitor of intracellular reactive oxygen species generation and TNF-α secretion in RAW 264.7 cells. These results led to the conclusion that *cadramonin* strongly suppresses major pro-inflammatory mediators.

Several experiments related to the expression and production of NF-κB factors that regulate the transcription of genes involved in immune, inflammatory and antiapoptotic responses were conducted in order to examine the NF-κB inhibitory potency of *cardamomin* [41]. *Cardamomin* was able to inhibit the production of nitric oxide (NO) and tumor

Table 13. Percent Inhibition of the Accumulation of NO_2^- (%) and PGE_2 in Stimulated RAW 264.7 Macrophages (IC_{50})



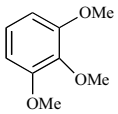
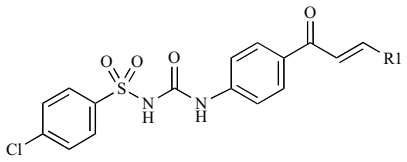
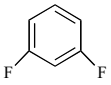
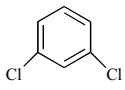
	Compound	R_1	NO_2^- % (10 μM)	PGE_2 IC_{50} (μM)
1	Me-UCH1		48.1	0.08
2	Me-UCH5		0.7	0.07
3	Me-UCH8		52.3	0.28
4	Me-UCH10		58.3	51.0

Table 14. Inhibitory Activity on the Accumulation of NO_2^- (%) and PGE_2 in Stimulated RAW 264.7 Macrophages (IC_{50}) Induced by the Tested Chalcones



	Compound	R_1	NO_2^- % (10 μM)	PGE_2 IC_{50} (μM)
1	Cl-UCH1		14.5	1.28
2	Cl-UCH6		37.7	0.19
3	Cl-UCH7		42.8	0.19
4	Cl-UCH8		38.7	0.16
5	Cl-UCH9		33.0	0.13

necrosis factor (TNFα) in RAW cells 264.7 incubated with LPS and inhibited TNFα. It was found that preincubation of macrophages with *cardamomin* significantly prevented degradation of IκBα protein and resynthesis of the same protein. In advance, the chalcone affected the LPS-induced phosphorylation of IκBα protein essential for the function of NF-κB factor. Cells treated with *cardamomin* significantly suppressed the induced DNA-binding activity of NF-κB by LPS, but *cardamomin* did not directly affect it.

However, *cardamomin* suppressed transcriptional activity of the transactivation domain of RelA/p65. Moreover, the LPS-induced phosphorylation of p38 kinase was affected by cardamomin.

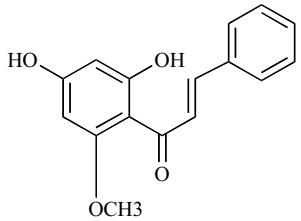


Fig. (6). Structure of *Cardamonin.*

Finally, since activation of NF-κB has been implicated in sepsis, it was observed that cardamomin protected C57BL/6 mice from LPS-induced lethality.

Hydroxy and Chloro-Hydroxy-Chalcone Derivatives

Won *et al.* [42] synthesized new chalcones as potent anti-inflammatory agents (Table **15**). The new analogues were tested on: a) the release of β-glucuronidase and lysozyme from rat neutrophils stimulated with fMLP/CB, and b) superoxide anion generation in rat neutrophils stimulated with fMLP/CB or PMA (IC_{50}). The inhibitory effect on the accumulation of nitrite in the culture media of RAW 264.7 cells in response to LPS and N9 cells in response to LPS/IFN-γ induced by the tested chalcones, was investigated.

This series of chalcone derivatives was studied *in vitro* for their inhibitory effects on chemical mediators released by inflammatory cells (mast cells, neutrophils, macrophages and microglial cells). Compounds **1-3** and **7** exhibited potent inhibitory activity on the release of β-glucuronidase or lysozyme in rat neutrophils, while compounds **1** and **3** showed potent inhibitory effects on superoxide anion generation as well as in rat neutrophils. The SAR study has showed that the 5'-OH substitution is crucial for the inhibitory activity.

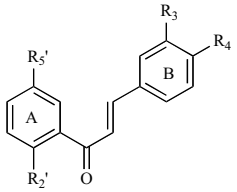
Compounds were also evaluated for their possible inhibitory effect on NO production in microglial or macrophage-like cells. Compounds **5**, **6** and **12** were found to strongly inhibit NO-production.

Lopjhirone L

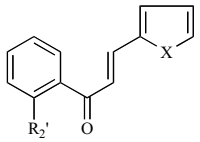
Lately a new chalcone derivative has been isolated from *Ochna squarrosa*, a plant that belongs to the family Ochnaceae and it is commonly known as "sunari" or "yerra juvvi" [43]. It has been considered as an important drug in the treatment of ulcer, sores, cancers and asthma.

The new isolated chalcone derivative has been evaluated for its analgesic and anti-inflammatory activity [44]. The analgesic activity was performed by taily-flick technique [45, 46] and the presented results were significant. Its anti-

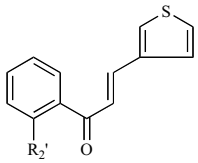
Table 15. Structure of Chalcone Derivatives



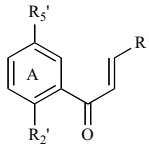
Compounds **1, 5, 12**



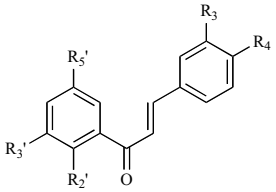
Compounds **2**(X=S), **4**(X=O)



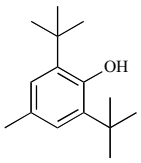
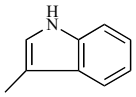
Compound **3**



Compounds **6, 7**



Compounds **8-11**

	R_2'	R_3'	R_5'	R_3	R_4	R
1	OH	H	H	H	OH	
2	OH	H	H	H	H	
3	OH	H	H	H	H	
4	OH	H	H	H	H	
5	OH	H	H	Cl	Cl	
6	OH	H	OH	H	H	
7	OH	H	OH	H	H	
8	OMe	H	OMe	Cl	Cl	
9	OH	H	OH	Cl	Cl	
10	OH	H	OCH_2CH=CH-	H	Cl	
11	OH	CH_2=CH-CH(CH_3)-	OH	H	Cl	
12	O CH_3	H	O CH_3	H	OH	

inflammatory activity was tested with the carrageenan-induced paw edema and the results were promising. The significant effect of crude extract in both experiments reveals the need for further investigation of the extract ingredients.

Chalcones Isolated from Xanthoxyline

The researchers focused on the antinociceptive activity of several chalcones (Table **17**) isolated from xanthoxyline against acetic acid-induced abdominal constrictions [47].

The most effective compound proved to be the one with a carboxylic acid group adjusted at position-6 of ring B. In addition, replacement of a hydrogen atom at position-5′ of ring B by a bromo atom, eliminated writhes. When naphthalene group replaced the phenyl group, analgesic activity was also augmented. At last, nitro group in position-3 of ring B slightly ameliorated situation.

Viscolin

Hwang *et al.* [48] examined a new chalcone derivative named *viscolin* (4′, 4″-dihydroxy- 2′, 3′, 6′, 3″-tetramethoxy-1, 3-diphenylpropane), which has been isolated from the mistletoe *Viscum coloratum*, for its anti-inflammatory activity.

Table 16. IC_{50} Values of Chalcone Derivatives Tested on: a) the Release of β-Glucuronidase (β-glu) and Lysozyme (lys) from rat Neutrophils Stimulated with fMLP/CB, b) Superoxide Anion Generation in Rat Neutrophils Stimulated with fMLP/CB or PMA (IC_{50}), and c) the Accumulation of NO_2- in the Culture Media of RAW 264.7 Cells (in Response to LPS) and N9 cells (in Response to LPS/INF-γ

Compounds	IC_{50} (μM)					
	β-glu	lys	Superoxide Anion Generation		RAW 264.7 Cells	N9 Cells
			fMLP	PMA		
1	-	7.5	6.4	>30	>30	>10
2	23.5	27.4	>30	>30	>30	>30
3	8.7	13.4	8.2	>30	>30	>30
4	>30	>30	>30	>30	>30	>30
5	>30	>30	>30	>1	23.8	11.8
6	>3	>30	>1	>1	23.3	>10
7	17.1	>30	>1	>30	>10	>10
8	>30	>30	>30	>30	>30	>10
9	>30	>30	>30	>30	>1	>3
10	>30	>30	>30	>10	>30	>30
11	>3	>3	>10	24.3	>30	>30
12	-	-	-	-	14.6	17.8

The experiments provided evidence showing that *viscolin* inhibited fMLP/CB- induced $O_2^{\cdot-}$ (ROS) production and elastase release by human neutrophils in a concentration dependent manner. FMLP is consisted of formyl-L-methionyl-L-leucyl-l-phenylalanine-activated human neutrophils and was used as an assay system. Neutrophil degranulation was measured according to the extent of release of elastase, a primary granule-derived protease. *Viscolin* could not modify the basal level of elastase release under resting conditions. *Viscolin* remarkably potentiated PGE1-induced inhibition.

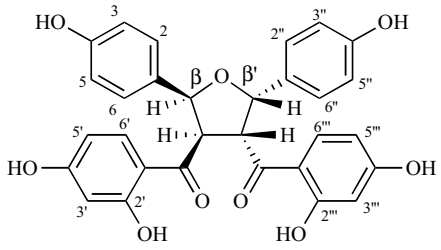


Fig. (7). Structure of *Lopjhirone L*.

Measurements of cAMP concentrations were conducted to determine whether the inhibitory effects of *viscolin* are likely to be associated with cAMP. It was detected that the chalcone increased cAMP levels in FMLP-stimulated human neutrophils in a concentration dependent manner. However, *viscolin* inhibited cAMP-specific and cGMP-specific PDEs (endotoxin-induced inhibitors), data indicating that the elevation of cAMP amounts occurs *via* inhibition of PDE activity.

1,3-Diarylprop-2-en-1-Ones

It is well known that COX-2 is the target for the design of new potent antiinflammatory agents. Selective COX-2 inhibitors frequently belong to a class of diarylheterocycles that possess vicinal diaryl moieties attached to a central heterocyclic ring scaffold in conjuction with a COX-2 pharmacophore such as *para*-SO_2NH_2, or a *para*-SO_2Me, substituent on one of the phenyl rings.

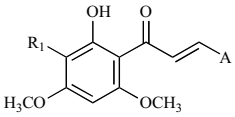
Zarghi *et al.* [14] presented recently a new group of 1,3-diarylprop-2-en-1one regioisomers possessing a COX-2 SO_2Me pharmacophore at para-position of one phenyl ring in conjunction with a substitiuent (H, Me, F and OMe) at *para*-position of the other phenyl ring (Table **18**).

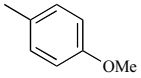
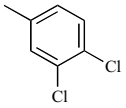
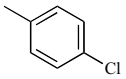
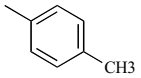
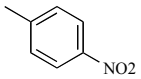
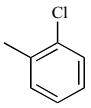
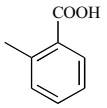
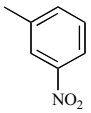
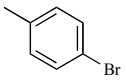
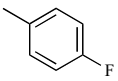
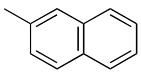
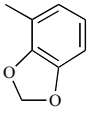
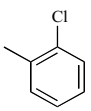
The compounds are tested for their inhibition on COX-1 and COX-2 and for their selectivity.

Compound **9f** ((E)-1-(4- methanesulfonylphenyl)-3-(4-methylphenyl)prop-2-en-1-one) was found to be the most potent and selective COX-2 inhibitor. Docking studies of compound **9f** at COX-2 active site shows that it is bound in the primary binding site and that *para*-SO_2Me substituents on the C-1 phenyl ring is oriented in the vicinity of the secondary pocket present in COX-2. The computational study showed that the sterochemical disposition of substituted aryl rings about the C=C bond controls the optimal protein-ligand binding interactions in the active site of COX-2.

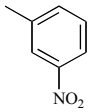
The *in vitro* enzyme inhibition structure-activity relationship studies have led to the following results: a) the propenone moiety present in a 1,3-diarylprop-2-en-1-one structure

Table 17. Analgesic Activity (%) of Chalcones (Given Intraperitoneally) Against Acetic Acid-Induced Abdominal Constrictions in Mice



Compound	R_1	A	% Analgesic Activity at 100 mg/kg
2	H		55.6
3	H		58.2
4	H		61.7
5	H		22.6
6	H		68.8
7	H		42.8
8	H		49.5
9	H		92.2
10	H		82.3
11	H		37.4
12	H		15.5
13	H		86.0
14	H		36.7
15	Br		55.3

(Table 17. Contd....)

Compound	R_1	A	% Analgesic Activity at 100 mg/kg
16	Br		76.4
17	Br		86.7

presents a suitable scaffold (template) to design COX-2 inhibitors, b) (E)-1-(4-methanesulfonylphenyl)-3-(4-methylphenyl)prop-2-en-1-one (**9f**) is a potent selective COX-2 inhibitor, and c) small lipophilic substituents (CH_3 group) in R_1 or R_2 increase IC_{50} value.

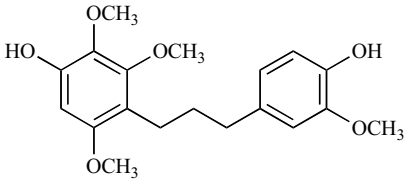


Fig. (8). Structure of *Viscolin.*

Chalcones as Interleukin-5 Inhibitors

A series of chalcone derivatives have been synthesized and evaluated as IL-5 inhibitors (Table **19**) [15]. Eosinophilic inflammation is histologically correlated to airway hyperresponsiveness and tissue injury in the pathogenesis of bronchial asthma [49, 50]. It has been estimated that cytokines have been implicated in this disease and interleukin (IL)-5 appears to be one of the main proinflammatory mediators that induce eosinophilic inflammation [51]. Compound **22** was found to be the most active. The necessary structural requirements derived from the SAR study are: 1) the hydrophobic group e.g. cyclohexylmethoxy group at 2-position of A ring, 2) the existence of phenolic hydroxyl at 6-position of A ring, 3) a propenone motif as α,β unsaturated ketone and 4) electron withdrawing groups with hydrogen acceptor property at 4-position of B ring (three-atom size).

For these compounds a quantitative structure activity relationship study has been performed, where the inhibitory effect on IL-5 is related to the electronic σ_p Hammett parameter (for carboxylate anion value (0) was used) [49].

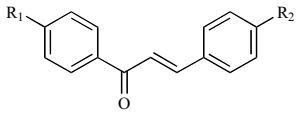
$$\log 1/IC_{50} = 0.763\ \sigma_p - 0.86\ (n = 8, r^2 = 0.86)$$

Carboxylated, Heteroaryl-Substituted Chalcones

Meng *et al.* [52] presented a new series of carboxylated, heteroaryl-substituted chalcones (Table **20**). This group of compounds were evaluated as inhibitors of vascular cell adhesion molecule – 1 (VCAM-1), which is a key regulator of leukocyte trafficking to sites of inflammation and it has been implicated in numerous inflammatory diseases such as asthma, rheumatoid arthritis and atherosclerosis.

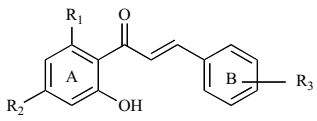
The biological data have shown that the α,β-unsaturated ketone moiety of the chalcone, is the pharmacophore of this series of compounds for inhibition of VACM-1 expression.

Table 18. ***In Vitro*** **COX-1 and COX-2 Enzyme Inhibition Data (IC_{50}) for 1,3-Diarylprop-2-en-1-ones**

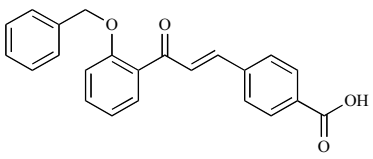


			IC_{50} (μM)	
	R_1	R_2	COX-1	COX-2
9a	H	SO_2Me	1.1	0.8
9b	Me	SO_2Me	1.0	0.3
9c	F	SO_2Me	4.2	10.0
9d	OMe	SO_2Me	3.2	4.9
9e	SO_2Me	H	21.5	1.0
9f	SO_2Me	Me	32.0	0.3
9g	SO_2Me	F	31.6	0.6
9h	SO_2Me	OMe	3.3	3.2

Table 19. Inhibitory Activity of Chalcone Analogues Against IL-5



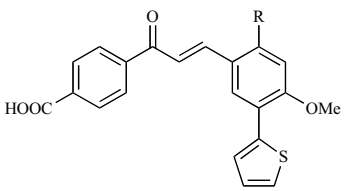
Compounds **1-24**



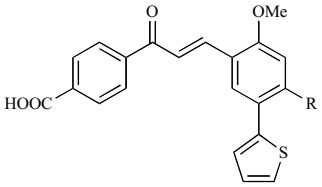
Compound **25**

	R_1	R_2	R_3	IC_{50} (μM)
11	Cyclohexylmethoxy	H	4-$COOCH_3$	3.9
17	Cyclohexylmethoxy	H	Cl	7.1
19	Cyclohexylmethoxy	H	4-$NHCOCH_3$	6.4
20	Cyclohexylmethoxy	H	4-CH_2CH_3	6.4
21	Cyclohexylmethoxy	H	4-CH_2OH	4.5
22	Cyclohexylmethoxy	H	4-CHO	1.8

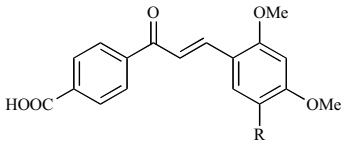
Table 20. Inhibiting Profile of 4-[3E-(2-Substituted-4-Methoxy-5-Thien-2-yl)Acryloyl]Benzoic Acids on TNF-α Induced VCAM-1 Expression



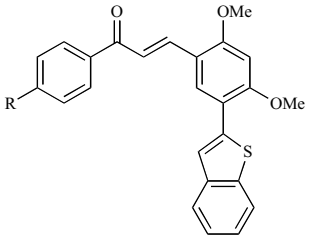
Compounds **23-29**



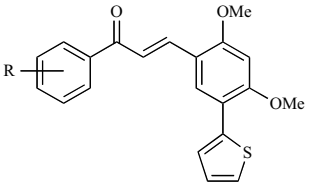
Compounds **30-33**



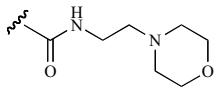
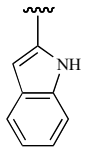
Compounds **19, 34-39**



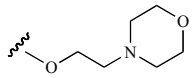
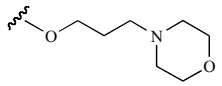
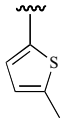
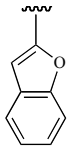
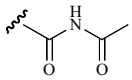
Compounds **5, 6, 40-44**



Compounds **45, 46**

	R	VCAM-1 IC_{50} (μM)
5	-COOH	0.6
6		0.8
19		0.9

(Table 20. Contd....)

	R	VCAM-1 IC_{50} (μM)
26		0.8
27		0.9
35		1.0
37		0.3
41	-$CONH_2$	0.2
42	-CONHOMe	0.5
43		0.8

No discussion can be done for the rest of the structural characteristics of the compounds. Compound **19** has been further studied for its antiiflammatory activity in a mouse model of allergic inflammation and it has been presented potent inhibitory activity, indicating the possible therapeutic role of such compounds in human asthma and other inflammatory disorders.

CONCLUDING REMARKS

From the above review the following are concluded:

- Naturally occurring chalcones isolated from plants extracts e.g. *cardamomin, viscolin, lophirone, (-)-hydroxypanduratin A and (-)-panduratin A, broussochalcone A*, were found to significantly suppress the induced DNA-binding activity of NF-κB by LPS and to be potent against inflammation and edema as well as against enzymes and chemical mediators implicated in the phenomenon of inflammation.

- Several synthetic derivatives simple or more complicated were found to be potent antiinflammatories/antioxidant agents. The propenone moiety present is a suitable scaffold (template) to design COX-2 inhibitors.

- The enone moiety is required for the inhibition of mast cell degranulation, as well as for the inhibition of neutrophil degranulation and superoxide anion formation from rat neutrophils.

- The mono- and poly- hydroxyl-aromatic substituted derivatives seem to be potent inhibitors of lipoxygenase.

- The number and the position of hydroxyl groups on both A and B phenyl rings of chalcones influence their action upon heme oxygenase-1

- The 2', 6'-dimethylamino substituent seems to be correlated with selective and potent inhibition of nitric oxide synthase.

These results and observations could be used in computer-assisted drug design in order to find out new synthetic chalcones with better and selective antiinflammatory activity.

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