Biological Activities of 2-Styrylchromones

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Abstract: 2-Styrylchromones (2-SC) are chromone derivatives characterized by the attachment of a styryl group to the 2-position of the chromone structure. The 2-styrylchromone structure has been demonstrated to bear important biological activities such as antiallergic, antitumor, affinity and selectivity for A_3 adenosine receptors, antiviral, antioxidant and anti-inflammatory. The aim of the present paper was to review the available information on this field.

Keywords: 2-Styrylchromones, biological activity.

INTRODUCTION

2-Styrylchromones (2-SC) (Fig. (**1**)) are a group of chromone (1-benzopyran-4-one; 1,4-benzopyrone; 4-oxo-4*H*-1-benzopyran) derivatives characterized by the attachment of a styryl group to the 2-position of the chromone structure. Until very recently, only two natural compounds were known, hormothamnione (**1**) and 6-desmethoxyhormothamnione (**2**) (Fig. (**2**)). These compounds were extracted from the marine cryptophyte *Chrysophaeum taylori*, although this alga had been identified in the first place as cyanobacterium *Hormothamnion enteromorphoides* [1,2]. Recently, Yoon *et al.* [3] isolated 5-hydroxy-2-styrylchromone (**3**) (Fig. (**2**)) from *Imperata cylindrica*, although the synthesis of this compound had been previously described [4].

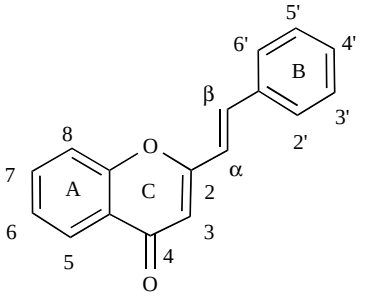

Fig. (1). Molecular scaffold of 2-styrylchromone.

Although scarce in nature, a considerable number of 2-styrylchromone derivatives has been synthesized even before the isolation of first natural compounds. The reports found in literature deal with improvements of the most promising approaches, such as: aldol condensation/oxidative cyclization and Baker-Venkataraman rearrangement (see [5] for review).

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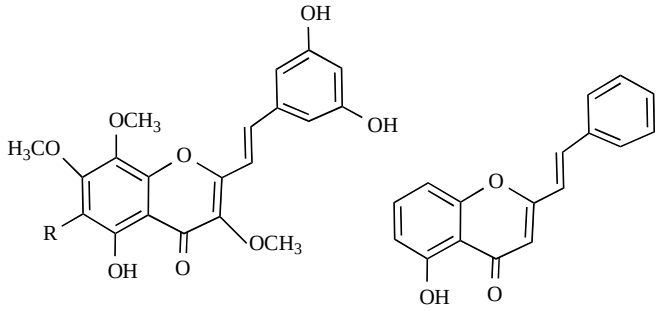

1: R=OCH_3
2: R=H

3

Fig. (2). Chemical structure of the 2-styrychromone natural derivatives: hormothamnione (**1**), 6-desmethoxyhormothamnione (**2**), and 5-hydroxy-2-styrylchromone (**3**).

Natural and synthetic 2-SC have been demonstrated to bear important biological activities. The aim of the present work is to review the available information on this field.

ANTIALLERGIC ACTIVITY

The first biological activity shown by synthetic 2-SC was reported by Doria *et al.* [6]. In this study, some of the tested 6-carboxilic acid-substituted 2-SC (Fig. (**3**)), orally administrated, were able to display antiallergic activity in the passive cutaneous anaphylaxis test in the rat, which consists of a sensitization test using rat serum rich in homocytotropic antibodies. These antibodies attach to cells of the species in which they originate and trigger the release of pharmacological mediators of anaphylaxis from those cells. Moreover, the compounds **4**, **5**, **6**, and **8** (Fig. (**3**)), when administrated parenterally, were significantly more potent than disodium cromoglycate (DSCG), an antiallergic drug used in clinical practice, in the passive cutaneous anaphylaxis test (the potency ratios of test drugs to the standard DSCG were 1.78, 2.89, 4.79, and 6.79, respectively) and in the inhibition of histamine release from rat peritoneal cells passively sensitized with IgE-antibodies (the potency ratios of test drugs to the standard DSCG were 18.64, 73.46, 26.91, and 32.72, respectively). Since many different molecules were tested in

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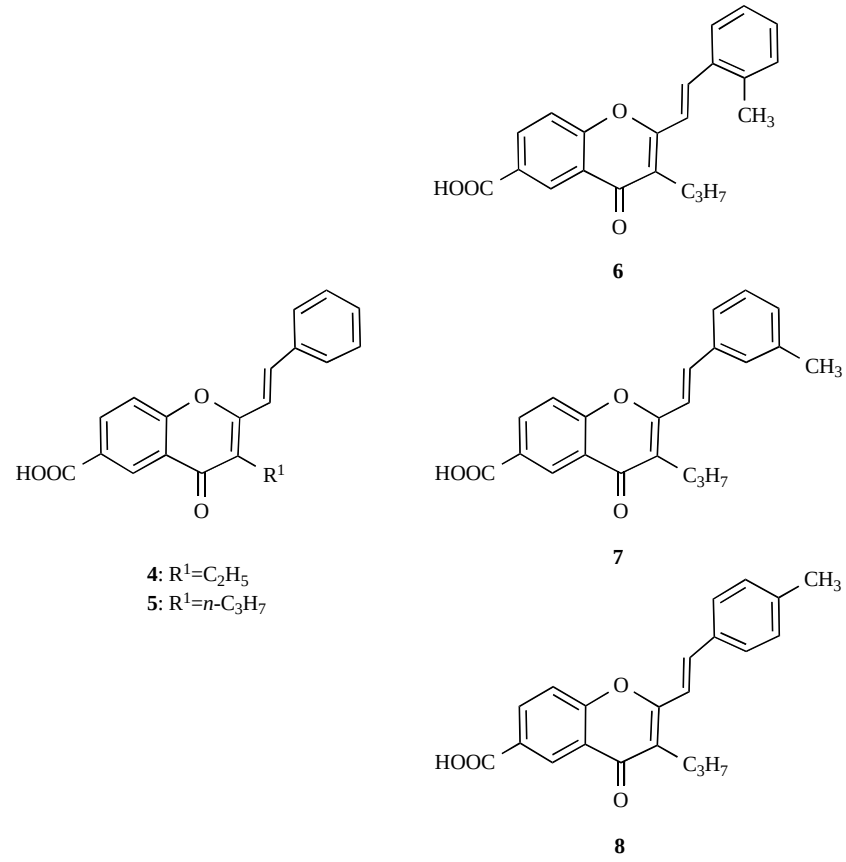


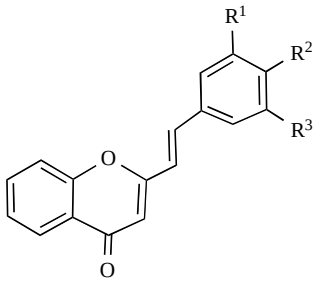
Fig. (3). Chemical structures of 2-styrylchromones studied for antiallergic activity.

this study, beyond those referred here, some structure-activity relationships were postulated. Thus, the substitution at the 3-position with lower alky groups, ethyl (**4**) and *n*-propyl (**5**), increases the oral activity. A further improvement of biological responses can be obtained in the 3-*n*-propyl series by introducing a single methyl into the aryl moiety of the styryl group (**6** and **8**). The vinyl moiety of the styryl group seems to be essential for significant antianaphylatic activity.

ANTITUMOR ACTIVITY

The antitumor potential of 2-SC was first described with the natural derivatives hormothamnione (**1**) and 6-desmethoxyhormothamnione (**2**). Hormothamnione was shown to be a potent cytotoxic agent to P388 lymphocytic leukemia and HL-60 human promyelocytic leukemia cell lines, through the inhibition of RNA synthesis [1], and 6-desmethoxyhormothamnione showed good cytotoxicity to 9 KB cells, derived from a human epidermoid carcinoma of the nasopharynx [2].

Since the isolation of the natural derivatives, other 2-SC, obtained by synthesis, were shown to produce cytotoxicity in tumor cell lines. Six newly-synthesized 2-SC (Fig. (**4**)) showed tumor-specific cytotoxic activity when tested in normal oral human cells (HGF, HPC, and HPLF) and tumor human cell lines (HSC-2, HSC-3, HSG, and HL-60) [7]. Compounds **11** and **13** showed the highest tumor specificity with selectivity indexes of 13.8 and 27.3, respectively. These compounds induced apoptosis characterized by internucleosomal DNA fragmentation and caspase 3-activation. The methoxy groups were suggested to be involved in the induction of tumor-specific cytotoxicity by the formation of cytotoxic quinones or orthoquinones due to enzymatical demethylation of those groups. Recently, Marinho *et al.* [8] verified that 4'-methoxy-2-styrylchromone (**11**), previously



9: R^1, R^2, R^3=H
10: R^1, R^3=H; R^2=CH_3
11: R^1, R^3=H; R^2=OCH_3
12: R^1=H; R^2, R^3=OCH_3
13: R^1, R^2, R^3=OCH_3
14: R^1=O-CH_2-O=R^2; R^3=H

Fig. (4). Chemical structures of 2-styrylchromones studied for antitumor activity.

identified as a potent growth inhibitor of tumor cell lines, was less efficient in inhibiting the growth of normal cells, which confirmed the higher sensitivity of tumor cell lines to the toxicity of the tested compound. In fact, this compound was shown to inhibit the growth of the tumor MCF-7 and NCI-H460 cells in a dose dependent manner (GI_{50} = 4.4 ± 0.8 and 5.2 ± 0.3 μM), respectively, while growth of the non-tumor MRC-5 cell line (GI_{50} value of 26.9 ± 3.2 μM) was six times less potent. The mechanism underlying the tumor cell

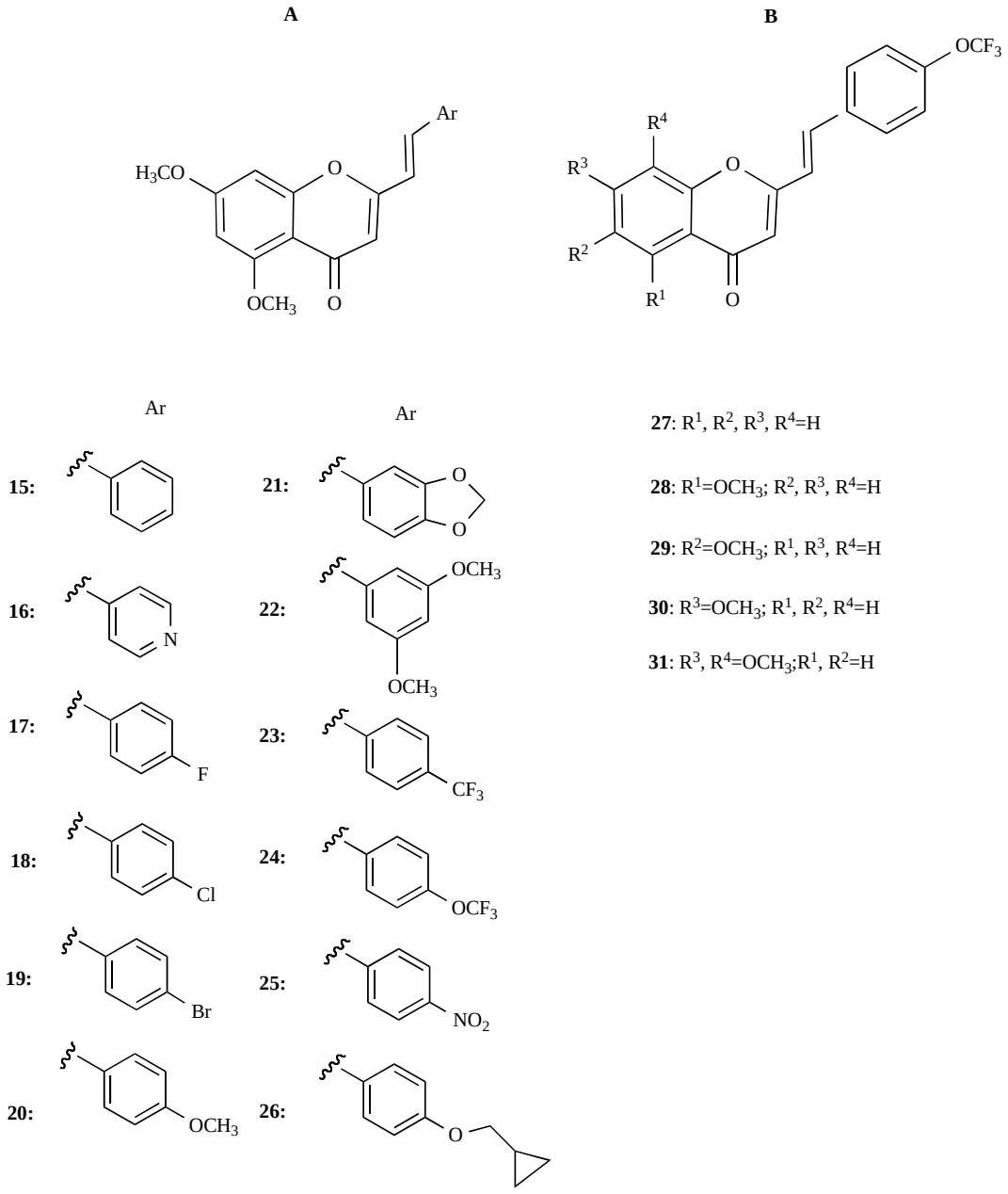


Fig. (5). Chemical structures of 2-styrylchromones studied for antitumor activity. (**A**) Analogues modified in the B-ring. (**B**) Analogues modified in the A-ring.

growth inhibitory effect involves a blockage at the G_2/M phase of the cell cycle. On the other hand, the G_2/M arrest was not observed in the non-tumor cell line. Further results suggested that **11** affected the *in vitro* assembly of tubulin into microtubules, acting as a microtubule-stabilizing agent and, thus, blocking the mitosis.

More recently a series of 2-styrylchromone analogs was synthesized and evaluated for their antiproliferative effects on five human carcinoma cell lines: PC-3 (prostate carcinoma cell), A549 (non-small cell lung adenocarcinoma cell), BT483 (mammary gland adenocarcinoma cell), HeLa (cervical epithelioid carcinoma cell) and SKHep (hepatocellular carcinoma cell) [9]. The synthesis of the 2-stryrylchromone analogs was based on modifications of B-ring (Fig. (**5A**)) and A-ring (Fig. (**5B**)).

The results obtained with PC-3 cells showed that the compound **27** exhibited moderate antiproliferative activity (IC_{50} = 28.9 ± 0.7 μM), indicating selective sensitivity of this cell line in response to 2-SC, which could be attributed to both steric and electronic effects of A-ring rather than B-ring moiety. From the A-ring analogs, **15**, **17**, **22**, **24**, **25**, and **26** exhibited moderate antiproliferative activity against A549 cells (IC_{50} values of 21.5 ± 4.1, 18.6 ± 0.6, 15.6 ± 2.6, 24.2 ±1.5, 19.7 ± 4.6, and 20.9 ± 5.9 μM, respectively). Substitution of phenyl group (**15**) for 4-pyridinyl (**16**) abolished the effect. The same happened by changing 4'-fluoro substituent (**17**) for bulkier substituents such as 4'-chloro (**18**), 4'-bromo (**19**), 4'-methoxy (**20**) and 4'-trifluoromethyl (**23**). Among the modified A-ring 2-styrylchromone analogs, only **27** demonstrated a moderate activity (IC_{50} = 15.6 ± 1.9 μM). Results from BT483 cells showed that most compounds

exhibited moderate activity. Nevertheless, compounds **15** and **19** were not active against this cell line. On the other hand, **22** and **26** exhibited relative higher activities than the other of compounds (IC_{50} values of 16.6 ± 2.4 and 16.6 ± 1.3 μM, respectively). Among modified A-ring analogs, most of the tested compounds exhibited moderate activities except **29**, showing no activity, which was suggested to be due to steric hindrance caused by the 6-methoxy group. Compound **27** bearing no substituent showed the most potent antiproliferative activity. HeLa cells seemed to be the most sensitive to the tested compounds among the five cell lines. Compound **31** exhibited the most potent antiproliferative activity (IC_{50} = 4.9 ± 1.0 μM) while **24** was not active among the A-ring modified analogs. SKHep cells were not as sensitive as HeLa cells. The most active compounds against this cell line were **24** and **31** (IC_{50} values of 12.5 ± 2.9 and 12.4 ± 1.5 μM, respectively). In order to examine the association between 2-styrylchromone-induced antiproliferation and cell cycle arrest the authors exposed HeLa cells to compounds **15**, **23**, and **31**. The results suggested that some of the compounds may induce the antiproliferative effect on HeLa cells through distinct mechanisms such as G_1 phase cell cycle arrest and DNA fragmentation [9].

AFFINITY AND SELECTIVITY FOR A_3 ADENOSINE RECEPTORS

Karton *et al.* [10] investigated the structure-activity relationships of a series of flavonoid derivatives concerning their affinity to adenosine receptors in an effort to develop novel A_3 adenosine receptor antagonists. Selective antagonists of A_3 receptors have potential for the treatment of allergic, inflammatory and possibly ischemic disorders [11].

One of the compounds that showed a strong affinity to A_3 receptor (K_i = 1.16 ± 0.45 μM) was a 2-styryl analogue (**32**) of the natural furanochromone visnagin (Fig. (**6**)). In addition, this compound showed a considerable selectivity for A_3 *vs.* A_1 and A_{2A} receptors. Although no functional antagonism was detected, this compound can be an interesting scaffold for developing novel molecules with improved antagonist activity and/or specificity.

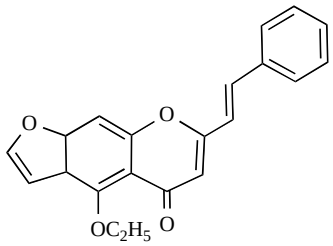


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Fig. (6). Chemical structures of 2-styryl analogue of visnagin.

ANTIVIRAL ACTIVITY

Several 2-SC (Fig. (**7**): **34**-**41**) were tested for their antiviral activity against human rhinoviruses (HRVs), which is the most frequent cause of common cold [12]. The antiviral potency was evaluated in HeLa cell cultures infected with HRV 1B and 14, selected as representative serotypes for viral groups B and A of HRV, respectively, by determining the viral plaque number and size. 2-SC **35**, **38**, **40**, and **41** displayed higher potency against serotype 14 than the others. The most active compound against both serotypes was **38** (IC_{50} value of 3.89 μM for HRV 1B and 1.33 μM for HRV 14), followed by **40** (IC_{50} value of 9.29 μM for HRV 1B and 6.41 μM for HRV 14) and **41** (IC_{50} value of 15.06 μM for HRV 1B and 13.46 μM for HRV 14). Compound **35** showed moderate activity against both serotypes. The introduction of a second chlorine atom, in position 6 (**39**), increased the potency against HRV 1B and negated the antiviral effect on serotype 14. In order to improve the antiviral effect of the first series of tested 2-SC, the authors introduced hydroxy or methoxy groups in position 3 of the C-ring (Fig. (**7**): **42**-**57**) [13]. The introduction of these

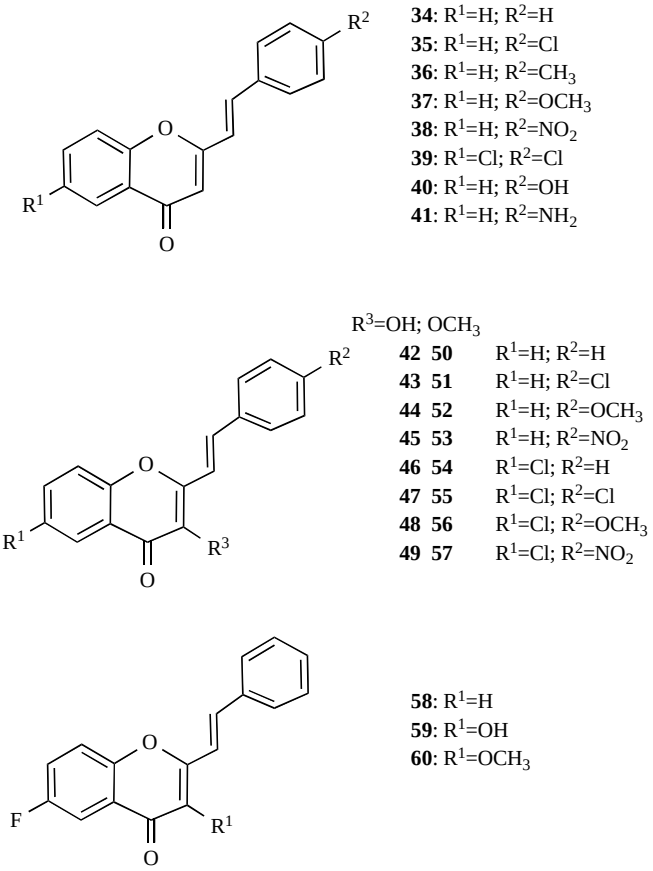


Fig. (7). Chemical structures of 2-styrylchromones studied for antiviral activity.

groups generally enhanced the antiviral potency against both tested serotypes. Only the 3-substituted 4′-nitro-2-SC (**45** and **53**) were less potent than the corresponding analogue, without substituent in position 3 (**38**). In contrast to data previously obtained, the introduction of the 6-chlorine atom generally led to reduced activity in the series of 3-substituted 2-SC. Only when a strong electron-withdrawing nitro group was present at position 4′, 6-chloro substitution resulted in analogues with higher potency against both serotypes. Thus, compounds **49** and **57** emerged as the most potent 3-hydroxy- and 3-methoxy-2-SC, respectively, but at same time they exhibited significant cytotoxicity. The authors also

tested the influence of the introduction of a fluorine atom in position 6 in 3-unsubstituted and 3-hydroxy- or methoxy-substituted 2-SC (Fig. (**7**): **58-60**) [14]. As a result, the 3-unsubstituted compound (**58**) showed a weak potency against both serotypes, while the introduction of a 3-hydroxy or a 3-methoxy substituent enhanced the activity of 6-fluoro-2-SC (**59** and **60**) against serotype 14 and led to the loss of efficacy against HRV 1B [14]. The specific activity against serotype 14 of the 3-substituted compounds can be ascribed to the presence of a fluorine atom in position 6.

ANTIOXIDANT ACTIVITY

The antioxidant properties of 2-SC have been shown in cellular [15] and non-cellular [16-19] systems. In the first case, the authors evaluated the possible protective activity of six synthetic polyhydroxylated 2-SC (Fig. (**8**): **61-63**; **65-67**) against the *tert*-butylhydroperoxide (*t*-BHP)-induced pro-oxidant hepatotoxicity in freshly isolated rat hepatocytes. All the studied 2-SC exhibited hepatoprotective activity, which was reflected on the preservation of the integrity of the plasma membrane. It was evident that the 3',4'-dihydroxy (styrylcatechol) derivatives (**61-63**) were much more potent than the 4'-hydroxy (styrylphenol) (**65-67**) derivatives. The differences between the two groups of compounds were also observed in the qualitative and quantitative preservation of biochemical homeostasis. In fact, while the hepatoprotective effect for the styrylcatechol derivatives involved the prevention of lipid peroxidation and the inhibition of reduced glutathione (GSH) depletion and oxidized glutathione (GSSG) formation, the styrylphenol derivatives only partially prevented lipid peroxidation, and had no effect on glutathione levels [15].

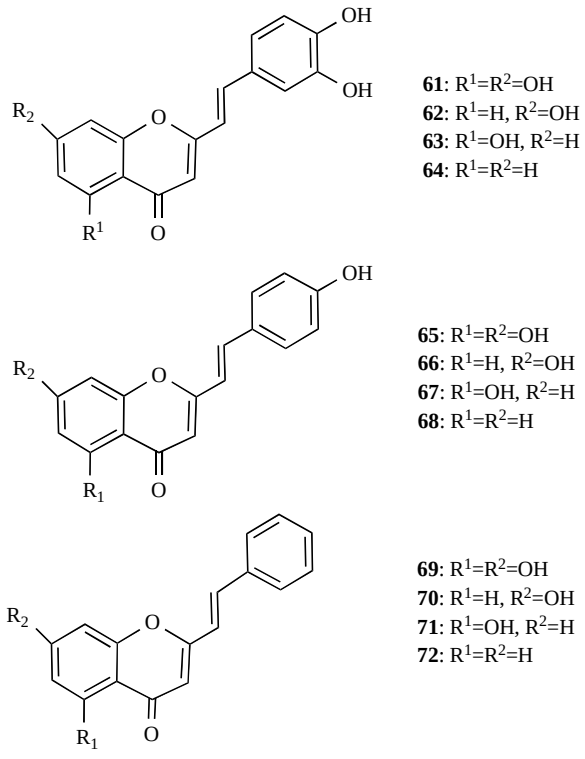


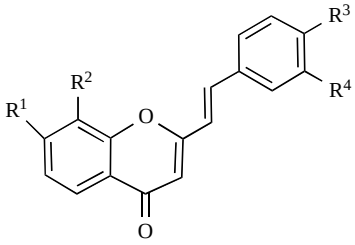
Fig. (8). Chemical structures of 2-styrylchromones studied for antioxidant and anti-inflammatory activity.

Several 2-SC (Fig. (**8**): **61-63**; **65-67**; **69-72**) were tested [16] for their inhibitory effect on xanthine oxidase (XO). XO is a highly versatile enzyme, widely distributed among species and within the various tissues of mammals [20]. In XO-catalyzed reactions, oxygen is reduced by one or two electrons giving rise to superoxide radical ($O_2^{\cdot-}$) or hydrogen peroxide (H_2O_2) [21]. Consequently, XO is considered to be an important biological source of reactive oxygen species. Furthermore, it is known that an extensive metabolism of xanthine by XO will increase body uric acid levels. Due to the low solubility of uric acid, there is a tendency for urate crystals to be deposited in the urinary tract and in the synovial fluid of joints, a process associated with painful inflammation, designated gout [22]. Fernandes *et al.* [16] found out that the tested styrylcatechol derivatives (**61-63**) are considerably more potent inhibitors of XO than the styrylphenol derivatives (**65-67**) and than the compounds with no hydroxy substituents in styryl B-ring (**69-72**). The hydroxylation pattern in the benzopyrone moiety was important for the potency of XO inhibition. The presence of 5,7-dihydroxy substituents in the benzopyrone (**61**, **65**, and **69**) lead to an increase in activity, when compared with a single hydroxy substitution. The IC_{50} values (in μM) for the most potent compounds were 0.55 ± 0.03 (**61**), 2.03 ± 0.19 (**62**), 4.36 ± 0.57 (**63**), 9.46 ± 1.08 (**65**), and 2.52 ± 0.08 (**69**).

Filipe *et al.* [17] studied the inhibitory effect of polyhydroxylated 2-SC (Fig. (**8**): **61-64**) on Cu^{2+}-induced oxidation of isolated human serum low density lipoproteins (LDL), an *in vitro* model of lipid peroxidation. The most active compounds were **63** and **64**. The other tested compounds **61** and **62** were thought to be less active due to different partitioning of the hydrophobic 2-SC into LDL. The electron donating properties of the compounds, tested by pulse radiolysis in different micellar solutions helped to interpret the results. Hence, the compounds were shown to be equally capable of reacting with $O_2^{\cdot-}$ and tryptophan radical ($^{\cdot}$Trp) in cationic micelles, while the superiority of compound **64** over the other three 2-SC was made clear when electron transfer reactions were carried out in neutral micelles.

The main contributing factor to the oxidative stress-related pathologies is the overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Gomes *et al.* [18] studied the scavenging activity of several 2-SC (Fig. (**8**): **61-72**) against these reactive species. Generally, the 3',4'-dihydroxy (**61-64**) derivatives were the most active compounds, although, concerning to peroxynitrite scavenging effect, 4'-hydroxy derivatives (**65-68**) were also very active. The activity of the compounds with no hydroxy substituent in the B-ring (**69-72**) was generally very low or inexistent. An exception to this rule happens with hypochlorous acid because, in this case, the hydroxy substituents in the A-ring assume high importance, more specifically when they are simultaneously positioned at C-5 and C-7. Thus, compound **69** was almost as potent as **61** and more potent than **65**. This behaviour may be related to the singular mechanism of the scavenging reaction against hypochlorous acid, which probably involves chlorination of free carbons in the A-ring. Nevertheless, a subsequent study [23] showed that, generally, the antioxidant capacity of the tested 2-SC is related to their electrochemical behaviour, since it was found that the compounds with the lowest oxidation potentials were also the most effective scavengers of ROS and RNS. Recen-

tly, the same authors tested the ROS and RNS scavenging activity of new 2-styrylchromone derivatives (Fig. (**9**)) to evaluate the effects resulting from the methylation of the



73: $R^1=R^2=R^3=R^4=OH$
74: $R^1=R^2=OCH_3$; $R^3=R^4=OH$
75: $R^1=R^2=OH$; $R^3=R^4=OCH_3$

Fig. (9). Chemical structures of 2-styrylchromones studied for antioxidant activity.

3',4'-dihydroxy group and from the changes in the position of the hydroxy groups in the A-ring as well as their methylation. The new compounds were also tested for their metal chelating activity and for their reducing capacity since these are indicators of antioxidant activity. From this study it became clear that the methylation of hydroxy groups decreases the scavenging of ROS and RNS by 2-SC, confirming the importance of hydroxyl groups for this type of effect. The decrease in the scavenging activities was, generally, more evident when the methylation occurred in B-ring (**75**). On the other hand, the introduction of a substituent, either hydroxy or methoxy, in C-8 was sometimes favorable and others unfavorable to the scavenging activities, depending on the reactive species. The methylation of the hydroxy groups in 2-SC (**74** and **75**) decreases their iron reducing capacity and also alters the spectral changes upon addition of Fe(II), indicating differences in the iron complexation ability [19].

ANTI-INFLAMMATORY ACTIVITY

The anti-inflammatory potential of hydroxylated 2-SC (Fig. (**8**)) was recently evaluated for the first time [24]. The compounds were tested for their effect in the arachidonic acid metabolic pathways, more specifically for the inhibition of cyclooxygenase-1 and -2 (COX-1 and COX-2) and for the inhibition of the production of leukotriene B_4 (LTB_4) in human neutrophils. COX-1 and COX-2 are two isoforms of an enzyme involved in the biosynthesis of prostanoids, some of them being proinflammatory mediators. One the other hand, LTB_4 is a proinflammatory eicosanoid produced by the 5-lipoxygenase pathway. The compounds with 3',4'-dihydroxy (**61**-**64**) or 4'-hydroxy substitutions (**65**-**68**) were all able to inhibit LTB_4 production by human leukocytes at the concentration of 25 μM. The pattern of substitution of the A-ring (5-hydroxy, 7-hydroxy, 5,7-dihydroxy or unsubstituted) seems to be less important for the effect. Compound **72**, with no hydroxy substitutions, was also active. The mechanism by which the compounds inhibit the production of LTB_4 probably involves the inhibition of the enzyme 5-lipoxygenase. Compounds **61** (100 and 250 μM), **62** (250 μM), **64** (100 μM), and **65** (250 μM) were able to inhibit the COX-1 activity. The mechanism through which 2-SC inhibit

Table 1. Summary of the Most Effective 2-Styrylchromones in the Studied Biological Activities. [1]When Several Compounds were Active Only the Most Potent are Referred

Biological activity	Specific effect(s)	Active compound(s)[1]	Refs.
Antiallergic	Antiallergic activity in the passive cutaneous anaphylaxis test in the rat. Inhibition of histamine release from passively sensitized rat peritoneal cells.	4-8 4, 5, 7, 8	[6]
Antitumor	Cytotoxicity to P388 and HL-60 tumor cell lines	1	[1]
	Cytotoxicity to 9 KB tumor cells	2	[2]
	Tumor-specific cytotoxic effect	11, 13	[7]
	Tumor-specific antiproliferative effect	11	[8]
	Antiproliferative effect against human carcinoma cell lines: PC-3, A549, BT483, HeLa, SKHep	PC-3: 27; A549: 22, 27; BT483: 22, 26, 27; HeLa: 31; SKHep: 24, 31	[9]
Affinity for A_3 adenosine receptors	Binding to A_3 receptor; selectivity for A_3 vs. A_1 and A_{2A} receptors	32	[10]
Antiviral	Activity against HRV (serotypes 1B and 14)	Serotype 1B: 39 Serotype 14: 59, 60 Both serotypes: 38, 40, 41, 49, 57	[12-14]
Antioxidant	Protective activity against *t*-BHP-induced pro-oxidant hepatotoxicity in rat hepatocytes	61-63	[15]
	Inhibition of XO	61-63, 65, 69	[16]
	Inhibition of Cu^{2+}-induced oxidation of isolated human serum LDL	63, 64	[17]
	Scavenging effect against ROS and RNS	61-64	[18,19]
Anti-inflammatory	Inhibition of COX-1 activity	61, 62, 64, 65	[24]
	Inhibition of LTB_4 production in human neutrophils	61-64, 65-68, 72	[24]

COX-1 is likely to consist in the scavenging of the radical intermediates involved in COX enzyme catalysis, since the only effective 2-SC had previous shown high ROS and RNS scavenging activity [18].

CONCLUSION

This review shows that 2-SC are molecules with poly-valent properties some of which have been quite explored (resumed in Table **1**). Due to the large variety of structures that have been tested so far it is difficult to establish generic structure-activity relationships. Nonetheless, some structural specific aspects can be highlighted. For instance, lower alkyl substituents in C-3 seem important to an increased oral activity. On the other hand, the presence of methoxy substituents in the B-ring is thought to be involved in the induction of tumor-specific cytotoxicity. As for the antiviral activity, studies have brought some fruitful results with the HRVs, indicating that C-4', C-3 and C-6 are important positions for substi-tutions. Thereby, the introduction of hydroxy or methoxy groups in C-3 generally enhances the antiviral potency while the presence of a fluorine in C-6 determines the specificity of the molecule. One of the most explored properties of 2-SC has been their antioxidant activity. In this area, the presence of hydroxy substituents, especially in the B-ring, has proven to assume an essential role on the molecule's efficiency.

Recently, the anti-inflammatory potential of 2-SC started to be explored. This is a promising field of investigation considering that these compounds are vinylogues of flavones (2-phenylchromones), which have demonstrated anti-inflam-matory activity in several systems.

To conclude, some of the ascertained properties of 2-SC are fairly promising and deserve further investigation in the attempt of finding new therapeutic alternatives.

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REFERENCES

[1] Gerwick, W.H.; Lopez, A.; Van Dyune, G.D.; Clardy, J.; Ortiz, W.; Baez, A. Hormothamnione, a novel cytotoxic styrylchromone from the marine cyanophyte *Hormothamnion enteromorphoides* grunow. *Tetrahedron Lett.*, **1986**, *27*, 1979-82.

[2] Gerwick, W.H. 6-Desmethoxyhormothamnione, a new cytotoxic styrylchromone from the marine cryptophyte *Chrysophaeum taylori*. *J. Nat. Prod.*, **1989**, *52*, 252-6.

[3] Yoon, J.S.; Lee, M.K.; Sung, S.H.; Kim, Y.C. Neuroprotective 2-(2-phenylethyl)chromones of Imperata cylindrica. *J. Nat. Prod.*, **2006**, *69*, 290-1.

[4] Pinto, D.; Silva, A.M.S.; Cavaleiro, J.A.S. A convenient synthesis of new (E)-5-hydroxy-2-styrylchromones by modifications of the Baker-Venkataraman method. *N. J. Chem.*, **2000**, *24*, 85-92.

[5] Silva, A.M.S.; Pinto, D.C.G.A.; Cavaleiro, J.A.S.; Levai, A.; Patonay, T. Synthesis and reactivity of styrylchromones. *Arkivoc*, **2004**, *2004*, 106-23.

[6] Doria, G.; Romeo, C.; Forgione, A.; Sberze, P.; Tibolla, N.; Corno, M.L.; Cruzzola, G.; Cadelli, G. Antiallergic agents. III. Substituted *trans*-2-ethenyl-4-oxo-4*H*-1-benzopyran-6-carboxylic acids. *Eur. J. Med. Chem.*, **1979**, *14*, 347-51.

[7] Momoi, K.; Sugita, Y.; Ishihara, M.; Satoh, K.; Kikuchi, H.; Hashimoto, K.; Yokoe, I.; Nishikawa, H.; Fujisawa, S.; Sakagami, H. Cytotoxic activity of styrylchromones against human tumor cell lines. *In Vivo*, **2005**, *19*, 157-63.

[8] Marinho, J.; Pedro, M.; Pinto, D.C.G.A.; Silva, A.M.S.; Cavaleiro, J.A.S.; Sunkel, C.E.; Nascimento, M.S.J. 4 '-Methoxy-2-styrylchromone a novel microtubule-stabilizing antimitotic agent. *Biochem. Pharmacol.*, **2008**, *75*, 826-35.

[9] Shaw, A.Y.; Chang, C.Y.; Liau, H.H.; Lu, P.J.; Chen, H.L.; Yang, C.N.; Li, H.Y. Synthesis of 2-styrylchromones as a novel class of antiproliferative agents targeting carcinoma cells. *Eur. J. Med. Chem.*, **2009**, *44*, 2552-62.

[10] Karton, Y.; Jiang, J.L.; Ji, X.D.; Melman, N.; Olah, M.E.; Stiles, G.L.; Jacobson, K.A. Synthesis and biological activities of flavonoid derivatives as A3 adenosine receptor antagonists. *J. Med. Chem.*, **1996**, *39*, 2293-301.

[11] Linden, J. Cloned adenosine a(3) receptors - pharmacological properties, species-differences and receptor functions. *Trends Pharmacol. Sci.*, **1994**, *15*, 298-306.

[12] Desideri, N.; Conti, C.; Mastromarino, P.; Mastropaolo, F. Synthesis and anti-rhinovirus activity of 2-styrylchromones. *Antivir. Chem. Chemother.*, **2000**, *11*, 373-81.

[13] Desideri, N.; Mastromarino, P.; Conti, C. Synthesis and evaluation of antirhinovirus activity of 3-hydroxy and 3-methoxy 2-styrylchromones. *Antivir. Chem. Chemother.*, **2003**, *14*, 195-203.

[14] Conti, C.; Mastromarino, P.; Goldoni, P.; Portalone, G.; Desideri, N. Synthesis and anti-rhinovirus properties of fluoro-substituted flavonoids. *Antivir. Chem. Chemother.*, **2005**, *16*, 267-76.

[15] Fernandes, E.; Carvalho, M.; Carvalho, F.; Silva, A.M.S.; Santos, C.M.M.; Pinto, D.C.G.A.; Cavaleiro, J.A.S.; Bastos, M.L. Hepatoprotective activity of polyhydroxylated 2-styrylchromones against *tert*-butylhydroperoxide induced toxicity in freshly isolated rat hepatocytes. *Arch. Toxicol.*, **2003**, *77*, 500-5.

[16] Fernandes, E.; Carvalho, F.; Silva, A.M.S.; Santos, C.M.M.; Pinto, D.C.G.A.; Cavaleiro, J.A.S.; Bastos, M.L. 2-Styrylchromones as novel inhibitors of xanthine oxidase. A structure-activity study. *J. Enzyme Inhib. Med. Chem.*, **2002**, *17*, 45-8.

[17] Filipe, P.; Silva, A.M.S.; Morliere, P.; Brito, C.M.; Patterson, L.K.; Hug, G.L.; Silva, J.N.; Cavaleiro, J.A.; Maziere, J.C.; Freitas, J.P.; Santus, R. Polyhydroxylated 2-styrylchromones as potent antioxidants. *Biochem. Pharmacol.*, **2004**, *67*, 2207-18.

[18] Gomes, A.; Fernandes, E.; Silva, A.M.S.; Santos, C.M.M.; Pinto, D.C.G.A.; Cavaleiro, J.A.S.; Lima, J.L. 2-Styrylchromones: novel strong scavengers of reactive oxygen and nitrogen species. *Bioorg. Med. Chem.*, **2007**, *15*, 6027-36.

[19] Gomes, A.; Neuwirth, O.; Freitas, M.; Couto, D.; Ribeiro, D.; Figueiredo, A.G.P.R.; Silva, A.M.S.; Seixas, R.S.G.R.; Pinto, D.C.G.A.; C., T.A.; Cavaleiro, J.A.S.; Fernandes, E.; Lima, J.L.F.C. Synthesis and antioxidant properties of new chromone derivatives. *Bioorg. Med. Chem.*, **2009**, *17*, 7218-26.

[20] Parks, D.A.; Granger, D.N. Xanthine-Oxidase - Biochemistry, Distribution and Physiology. *Acta Physiol. Scand.*, **1986**, *126*, 87-99.

[21] Hille, R.; Nishino, T. Flavoprotein structure and mechanism .4. xanthine-oxidase and xanthine dehydrogenase. *FASEB J.*, **1995**, *9*, 995-1003.

[22] Pascual, E. Gout update: from lab to the clinic and back. *Curr. Opin. Rheumatol.*, **2000**, *12*, 213-8.

[23] Gomes, A.; Fernandes, E.; Garcia, M.B.; Silva, A.M.; Pinto, D.C.; Santos, C.M.; Cavaleiro, J.A.; Lima, J.L. Cyclic voltammetric analysis of 2-styrylchromones: relationship with the antioxidant activity. *Bioorg. Med. Chem.*, **2008**, *16*, 7939-43.

[24] Gomes, A.; Fernandes, E.; Silva, A.M.S.; Pinto, D.C.G.A.; Santos, C.M.M.; Cavaleiro, J.A.S.; Lima, J.L.F.C. Anti-inflammatory potential of 2-styrylchromones regarding their interference with arachidonic acid metabolic pathways *Biochem. Pharmacol.*, **2009**, *78*, 171-7.

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