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OXAZOLE, THIAZOLE, AND IMIDAZOLE DERIVATIVES OF 2,6-DI-TERT-BUTYLPHENOL AS DUAL 5-LIPOXYGENASE AND CYCLOOXYGENASE INHIBITORS

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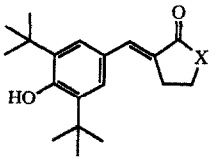
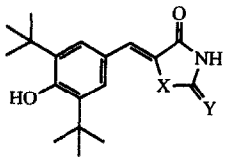
Abstract Benzylidene di-tert-butylphenols containing oxazole, thiazole, and imidazole substituents are dual inhibitors of 5-lipoxygenase and cyclooxygenase with IC_{50} values <5 μM. The oxazole and thiazole analogs exhibit oral antiinflammatory activity.

Nonsteroidal antiinflammatory drugs (NSAIDS) are widely used for the treatment of inflammatory diseases, including rheumatoid arthritis.[2] Many NSAIDS have been found to block the metabolism of arachidonic acid by inhibition of the enzyme cyclooxygenase (CO). The resulting inhibition of prostaglandin biosynthesis associated with the inhibition of this enzyme may contribute to the analgesic and antiinflammatory properties of these drugs.[3] However, long term NSAID use has also been associated with gastrointestinal ulceration. Increased production of proinflammatory leukotrienes through the 5-lipoxygenase (5-LO) enzyme pathway (an additional branch of the arachidonic acid cascade) is thought to contribute to this side effect.[4] Compounds that are dual inhibitors of 5-LO and CO are being studied as potential antiinflammatory agents with an improved safety profile in comparison to NSAIDS.[5]

Derivatives of 2,6-di-tert-butylphenol represent one chemical class that has been extensively investigated. We previously described[6] a series of antiinflammatory dual inhibitors comprised of a 1,2,4-oxadiazole or 1,2,4-thiadiazole ring directly linked to a di-tert-butylphenol. Related compounds have the phenol portion of the molecule as part of a benzylidene moiety attached to a heterocyclic ring.[7] Additional examples of this type are KME-4[8] (1a) and E-5110[9] (1b). In this communication, we describe the preparation and preliminary biological activity of a series of benzylidene oxazoles, thiazoles, and imidazoles, generically represented by 2.



1a X = O
1b X = NOMe

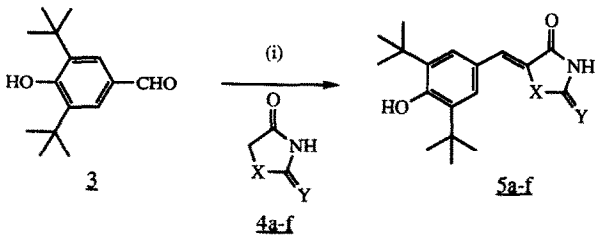


2 X = O, S, NMe
Y = O, S, NH, $NCNHNH_2$

Many di-tert-butylphenols are highly lipophilic compounds with generally poor aqueous solubility. In addition, phenolate salts of these compounds often cannot be readily obtained. We chose instead to prepare derivatives with acidic or basic functional groups on the heterocyclic ring in order to increase ionization and permit salt formation for increased water solubility.

Benzylidene derivatives are conveniently prepared by the Knoevenagel condensation in refluxing acetic acid (Scheme 1).[10]

Scheme 1



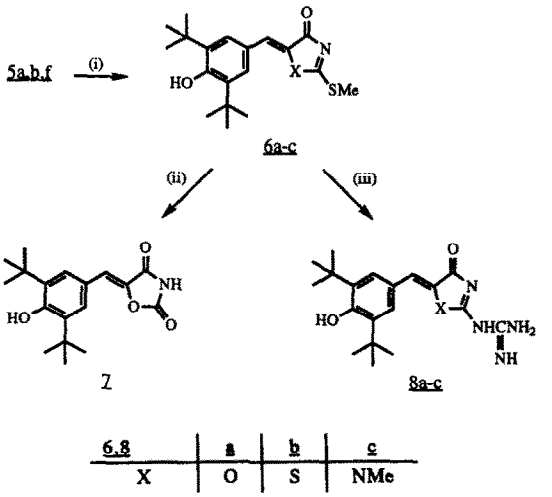
3 4a-f 5a-f

4,5	a	b	c	d	e	f
X	O	S	S	S	NMe	NMe
Y	S	S	O	NH	O	S

Reagents: (i) HOAc, NaOAc or β-alanine, 10-83%.

Reaction of aldehyde 3 with a series of active methylene heterocycles 4a[11], 4b-e (commercially available) and 4f[12] provided the benzylidene-type oxazoles, thiazoles, and imidazoles 5a-f. Further elaboration of these molecules is shown in Scheme 2.

Scheme 2



6,8	a	b	c
X	O	S	NMe

Reagents: (i) MeI, Et_3N, THF, 83% (6a); MeI, $(i\text{-}Pr)_2NEt$, EtOH, 55% (6b), 70% (6c); (ii) HCl, H_2O, EtOH, 53%; (iii) guanidine, t-BuOK, EtOH, 55% (8a), 31% (8b), 47% (8c).

Alkylation of the thione portion of 5a, 5b, and 5f with iodomethane in THF gave the intermediate thioethers 6a-c. The oxazole dione 7 could not be prepared by a direct Knoevenagel condensation with 3, but was instead obtained by acidic hydrolysis of 6a. Earlier work[6] in related chemical series indicated that a guanidino substituent was useful for salt formation and to impart dual inhibitor activity. The guanidino derivatives 8a-c were accordingly prepared by reaction of intermediates 6a-c with guanidine in refluxing EtOH.

Test compounds were evaluated for inhibition of LTB_4 (a product of 5-LO) and $PGF_{2\alpha}$ (a product of CO) formation in rat basophilic leukemia (RBL-1) cells stimulated with the calcium ionophore A23187. The rat carrageenan footpad edema (CFE) test was used to assess antiinflammatory activity.[13] Table 1 depicts the biological test results for the synthetic compounds and compares them to the corresponding data for KME-4 and sodium meclofenamate, a standard NSAID.

Table 1. Biological Data for Benzylidene Derivatives

Compound	IC_{50}, μM[a]		IC_{50} ratio:	CFE[b]: % inhib ± SEM
	5-LO	CO	5-LO/CO	
5a	0.84	1.7	0.49	40 ± 2.9
5b[c]	0.38	0.012	31.7	36 ± 5.0[d]
5c	1.4	0.35	4.0	59 ± 4.6[d]
5d	1.2[e]	0.11[e]	10.9	61 ± 4.5[e]
5e	0.78	4.6	0.17	N[f]
5f	0.17	0.79	0.22	N[f]
7	2.8[d]	0.65[d]	4.3	51 ± 2.7[d]
8a	1.2[e]	0.34[e]	3.5	48 ± 3.3[e]
8b	0.91[g]	0.083[g]	11.0	40 ± 3.1[g]
8c	1.3	2.1	0.62	N[f]
KME-4	2.5	0.15	16.7	28 ± 5.1
Sodium Meclofenamate	24.0	0.10	240	41 ± 5.3

[a] Concentration (μM) of test compound causing 50% inhibition of LTB_4 (5-LO) or $PGF_{2\alpha}$ (CO) formation in RBL-1 cells. The standard errors average 11% for 5-LO and 8% for CO.

[b] Percent inhibition ±SEM of edema in the carrageenan footpad edema test. Dosed at 30 mg/kg po.

[c] See Reference 14.

[d] Data from the choline salt.

[e] Data from the methanesulfonate salt.

[f] Inactive (N) is defined as <25% inhibition.

[g] Data from the hydrochloride salt.

The test compounds inhibit the 5-lipoxygenase and cyclooxygenase pathways with varying degrees of selectivity toward the two enzymes. Four compounds, 5a, 5e, 5f, and 8c, show greater inhibitory potency against 5-LO (IC_{50} ratio of 5-LO/CO < 1). The remaining six compounds (5b-d, 7, 8a, 8b) are more potent inhibitors of CO, a profile similar to the reference dual inhibitor KME-4. However, these six compounds also contain a potent 5-LO inhibitory component, unlike sodium meclofenamate, which is predominantly a CO inhibitor.

Except for the three imidazole compounds 5e, 5f, and 8c, all of the test compounds also displayed oral antiinflammatory activity in the CFE assay; the thiazole dione 5c and the amino analog 5d were especially potent in this model. Selected compounds are currently being evaluated for ulcerogenic potential and in additional models of inflammation.

We have described a novel series of oxazole, thiazole, and imidazole derivatives of 2,6-di-tert-butylphenol. Several of these compounds are relatively balanced dual inhibitors of the 5-lipoxygenase and cyclooxygenase enzyme pathways, and exhibit substantial inhibitory activity in an in vivo model of inflammation.

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