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BENZOXEPIN AND BENZOTHIEPIN DERIVATIVES AS POTENT, ORALLY ACTIVE INHIBITORS OF 5-LIPOXYGENASE

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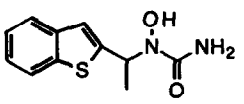
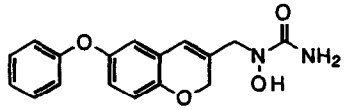
Abstract: A series of *N*-hydroxyurea derivatives based on substituted benzoxepin and benzothiepin templates was prepared and the compounds were evaluated for their ability to inhibit 5-lipoxygenase *in vitro* and *ex vivo*.

It is becoming increasingly evident that leukotrienes (LT's) are potent mediators of mammalian inflammatory reactions.[1] Since the conversion of arachidonic acid to LTA_4 by 5-lipoxygenase (5-LO) is the first committed step for the generation of LT's in the arachidonic acid cascade, it has long been hypothesized that inhibition of 5-LO could provide novel therapy for human inflammatory diseases, such as asthma, psoriasis, rheumatoid arthritis, inflammatory bowel disease, and allergic rhinitis. Recent clinical data on zileuton (A-64077) appear to support this hypothesis.[2]

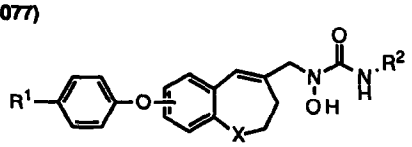
Considerable efforts have been made to identify potent, orally active and long-acting 5-LO inhibitors.[3] Especially since a report by Corey et al describing derivatives of arachidonic acid hydroxamic acid as potent 5-LO inhibitors in rat basophilic leukemia cells,[4] inhibitors containing the hydroxamic acid moiety have been subjected to intensive studies.[3,5] We recently reported that substituted chromene *N*-hydroxyureas, represented by CGS 23885, are potent and orally active inhibitors of 5-LO.[6] In the SAR study, we noted that a small substituent at the 2-position of the chromene ring system did not have detrimental effects on 5-LO inhibitory activity. This fact prompted us to design, synthesize and evaluate 7-membered analogs, namely benzoxepin and benzothiepin derivatives (**I**).



zileuton (A-64077)



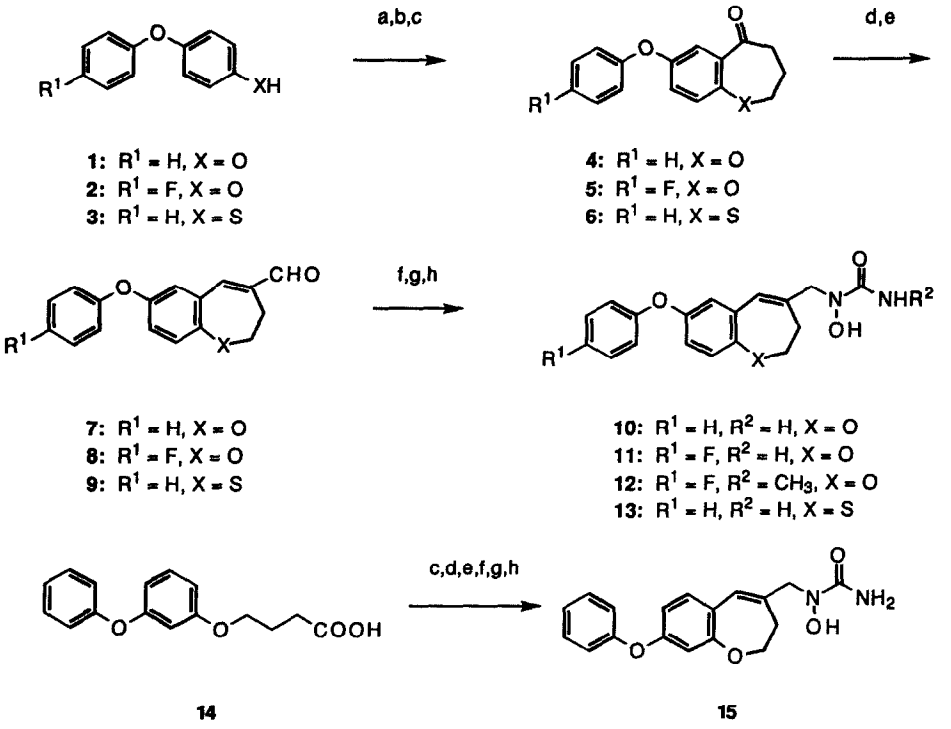
CGS 23885



X = O,S
R^1 = H, F
R^2 = H, CH_3

I

Scheme



Reagents and Conditions: [a] Br-$CH_2CH_2CH_2COOEt$, K_2CO_3, [b] NaOH, [c] PPA, [d] $HC(OEt)_3$, BF_3·OEt_2, -78 °C, then **4** - **5** or **15**, $EtNPr^i_2$, [e] $NaBH_4$, then HCl aq., [f] NH_2OH-HCl, py, [g] BH_3·pyridine, CF_3COOH, [h] TMS-N=C=O or CH_3-N=C=O

The synthetic route to the desired *N*-hydroxyureas is shown in the Scheme. For 7-aryloxy derivatives, the aryloxy phenols (**1**, **2**[7]) and thiophenol (**3**[8]) were first alkylated with ethyl 4-bromobutyrate and hydrolyzed. The carboxylic acids were subjected to cyclization with PPA[9] to yield the corresponding ketones (**4** - **6**) in good overall yields from **1** - **3**. Condensation of **4** - **6** with the oxonium salt derived from triethyl orthoformate and BF_3·OEt_2, followed by reduction of the resultant crude ketoacetal and subsequent hydrolysis, according to the procedure described by Dasgupta and Ghatak,[10] gave the unsaturated aldehydes (**7** - **9**) in one step. The aldehydes were converted to the corresponding oximes, and reduced by BH_3·pyridine in the presence of trifluoroacetic acid.[6] The hydroxylamine derivatives thus formed were condensed either with trimethylsilyl isocyanate to give *N'*-unsubstituted *N*-hydroxyureas (**10**, **11**, **13**) or methyl isocyanate to the *N'*-methyl derivative (**12**). The 8-phenoxy analog (**15**) was synthesized similarly from 3-phenoxyphenol. Cyclization of **14** with PPA takes place highly regiospecifically to yield 8-phenoxybenzoxepinone as the exclusive product.

Table. Inhibition of 5-LO by Benzoxepin and Benzothiepin Derivatives.

Compound[a]	*in vitro* IC_{50}, μM[b]		*ex vivo* (1.0 mg/kg iv)[c]		*ex vivo* (1.0 mg/kg po)[d]	
	5-HETE	LTB_4	Inhibition, %[e]	DA[f]	Inhibition, %[e]	DA[f]
10	0.089	0.091	80 (3.0 h)	19.4	94 (0.5 h)	9.1
11	0.091	0.098	>95 (0.25 - 0.5 h)	>24	>95 (1.0 h)	10
12	0.10	0.13	>95 (0.08 - 1.0 h)	13	>95 (0.25 - 6.0 h)	13
13	0.12	0.13	>95 (0.08 - 1.0 h)	2.8	N.D.[g]	--
15	0.18	0.21	>95 (0.08 h)	1.1	28 (1.0 h)	--
Zileuton	1.8	2.2	>90 (0.08 - 0.5 h)	8.5	>90 (0.5 - 1.0 h)	9.8
CGS 23885	0.037	0.040	>95 (0.08 - 6.0 h)	20	>95 (0.08 - 6.0 h)	15

[a] All the spectroscopic data including ^1H NMR, ^{13}C NMR, IR and MS of the compounds of the present study are fully consistent with the assigned structures. Elemental analyses were within ± 0.4% of the calculated values. [b] *In vitro* 5-LO inhibition in guinea pig PMN's was determined based on 5-HETE and LTB_4 production.[6,11] [c] *Ex vivo* production of LTB_4 was measured following iv administration of the test compound at a 1.0 mg/kg dose. The blood was drawn at certain intervals from the dog and treated with A23187 to stimulate LTB_4 formation.[6,11] [d] The test compounds were administered orally at 1.0 mg/kg as a suspension in fortified corn starch. [e] The numbers in the parenthesis refer to the period where maximum inhibition was achieved. [f] Duration of Action (DA) was defined to be the period of time where greater than 50% of the inhibition is maintained, and determined graphically from the plot of % inhibition vs. time. [g] N.D. = Not Determined.

The *N*-hydroxyureas were tested for 5-LO inhibitory activity in guinea pig polymorphonuclear leukocytes (PMN).[11] The IC_{50} values were determined by a radiometric TLC method based on production of 5-hydroxyeicosapentaenoic acid (5-HETE) and LTB_4. As shown in the Table 1, extremely potent 5-LO inhibitors were identified. It appears that conversion of the chromene ring system to the benzoxepin and benzothiepin results in only a slight loss in the *in vitro* potency (**10** vs. CGS 23885). The regioisomeric 8-phenoxy analog (**15**) was half as potent than **10** in this assay.

An *ex vivo* dog model[11] was employed to assess *in vivo* biochemical efficacy of the 5-LO inhibitors (**10 - 13, 15**). This model allows the measurement of LTB_4 production in whole blood following *ex vivo* stimulation with the calcium ionophore A23187 after oral (po) or intravenous (iv) administration of the test compound at a dose of 1.0 mg/kg. Blood samples were collected at certain intervals and LTB_4 levels were compared to control values, determined in blood samples taken prior to drug administration.

Compounds **10 - 12** were shown to be extremely potent and long acting 5-LO inhibitors *ex vivo* in the dog following iv administration. Good oral efficacy was also demonstrated by these compounds. The *ex vivo* data for **10 - 12** compares favorably with those of zileuton and CGS 23885. Comparison of iv and po data suggests good oral bioavailablity of **10 - 12**. Although the benzothiepin analog **13** is essentially equipotent

with its oxygen counterpart **10** in the *in vitro* assay, a considerably shorter DA was observed upon iv administration.

The 8-phenoxy regioisomer **15**, which was half as active as **10** *in vitro*, also had a considerably shorter DA than **10** in the iv experiment, and was practically inactive orally. The benzoxepin series gives a valuable insight to the importance of the position of the aryloxy substituent. In the chromene series, the regioisomer corresponding to **15** could not be explored due to synthetic difficulties.[6]

In conclusion, replacing the chromene system with a benzoxepin or benzothiepin ring system provides highly potent inhibitors of guinea pig PMN 5-LO. Moreover, compounds **10** (CGS 25100), **11** (CGS 25456), and **12** (CGS 25477) are among the best so far tested in the dog model in terms of oral activity. The oral DA's for these compounds in the dog model compare favorably with zileuton, which is currently in Phase III clinical trials.

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