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SYNTHESIS OF REVERSED HYDROXAMIC ACIDS OF INDOMETHACIN: DUAL INHIBITORS OF CYCLOOXYGENASE AND 5-LIPOXYGENASE

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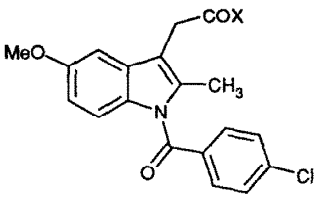
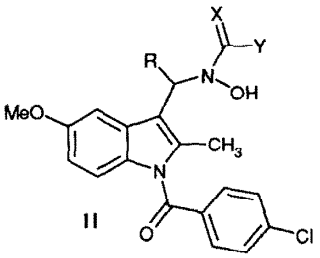
Abstract: Replacement of the carboxylic acid function of indomethacin with reversed hydroxamic acids converted this selective cyclooxygenase (CO) inhibitor into dual inhibitors of CO and 5-lipoxygenase (5-LO).

Prostaglandins and leukotrienes are potent mediators of inflammation[1,2] that are derived from arachidonic acid (AA) via the CO and 5-LO metabolic pathways respectively. Nonsteroidal antiinflammatory drugs (NSAIDs) inhibit the CO pathway.[1,3] The long-term use of NSAIDs often results in gastrointestinal ulcerations. Although the mechanism by which these side effects arise is not fully understood, decreased production of antisecretory and cytoprotective prostaglandins and increased production of pro-inflammatory leukotrienes have been implicated.[4] Dual inhibitors of CO and 5-LO are predicted to exhibit a profile featuring improved efficacy and reduced gastrointestinal side effects.[5] This paper describes the conversion of the NSAID indomethacin **Ia** into dual inhibitors of CO and 5-LO by incorporating 5-LO inhibiting pharmacophores into its structure.



Ia: X = OH = indomethacin
Ib: X = NHOH = hydroxamic acid

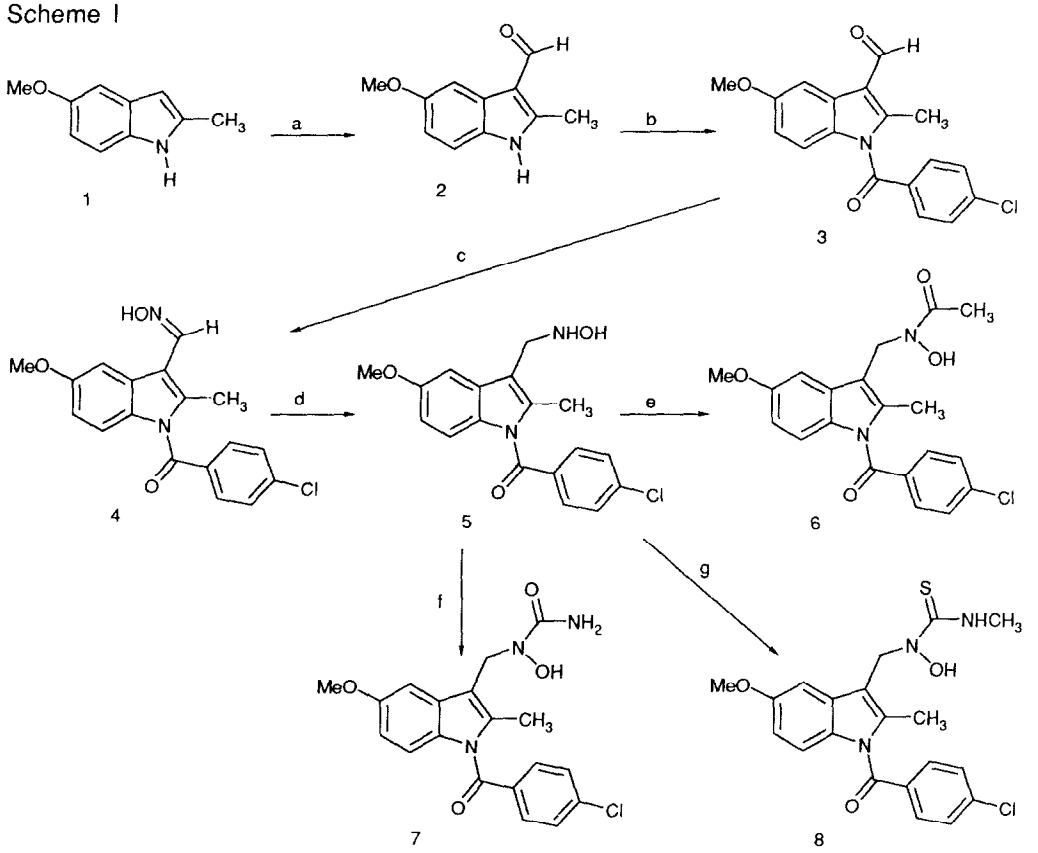


II

R = H, CH_3
X = O, S
Y = CH_3, NH_2, $NHCH_3$

Stimulated by Corey's[6] initial account that the hydroxamic acid analog of AA is a potent selective 5-LO inhibitor, our laboratories converted various NSAIDs to their corresponding hydroxamic acids.[7] This work revealed that via this transformation, indomethacin **Ia** could be converted to a dual inhibitor. However, it was clearly demonstrated that hydroxamic acids of this structural type are readily and completely metabolized to the parent carboxylic acid[8].

Scheme I

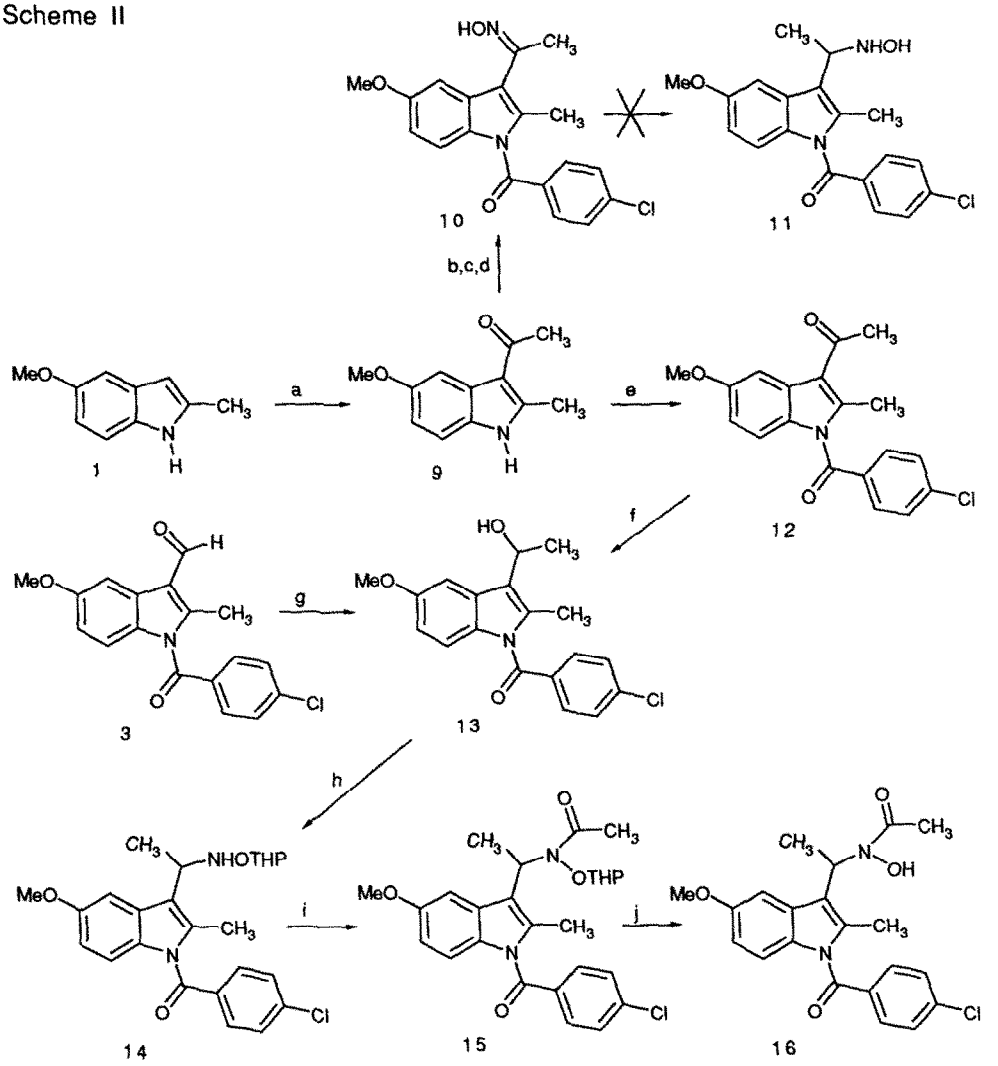


a) DMF, $POCl_3$, 95% b) (1) NaH, DMF (2) 4-chlorobenzoyl chloride, 82% c) H_2NOH-HCl, NaOAc, THF, 68%
d) 4 eq $NaCNBH_3$, AcOH e) AcCl, NaOAc, dioxane/H_2O, 47% f) NaOCN, 1N HCl, dioxane/H_2O, 53%
g) CH_3NCS, dioxane/H_2O, 54% from **4**

The reversal of the hydroxamic acid moiety in various selective 5-LO inhibitors was shown to greatly reduce the metabolic degradation while maintaining potent 5-LO inhibitory activity.[9] Metabolic stability was further enhanced by the substitution of a methyl group on the carbon adjacent to the hydroxamic acid nitrogen.[10] In light of these observation, it was our goal to prepare a variety of metabolically stable reversed hydroxamates of indomethacin (structure **II**) and determine their potencies as dual inhibitors.

The route used to prepare reversed hydroxamates **6**, **7**, and **8** is shown in Scheme I. 5-Methoxy-2-methylindole **1** was formylated under Vilsmeier-Haack[11] conditions. Benzoylation[12] of the indole nitrogen of **2** afforded compound **3**. The base-labile benzoyl group tolerated the mild oximation conditions to give **4**. Reduction of the aldoxime with sodium cyanoborohydride in acetic acid[13] provided the key intermediate hydroxylamine **5**. Acylation of **5** with acetyl chloride, sodium cyanate, and methyl isothiocyanate gave the desired reversed hydroxamates **6**, **7**, and **8**.

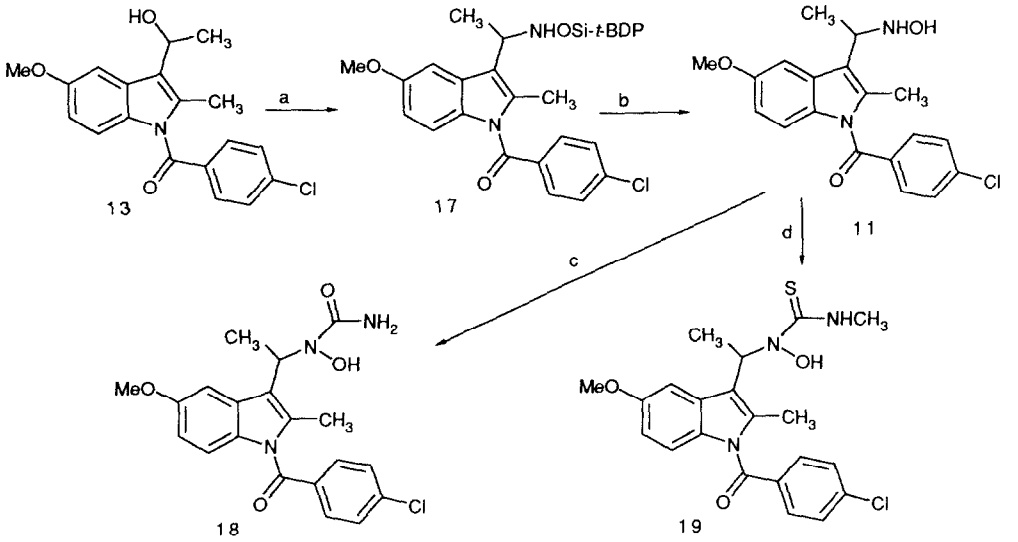
Scheme II



a) dimethylacetamide, $POCl_3$, 65% b) H2NOTHP, pyr-HCl, pyridine, 92% c) (1) NaH, DMF (2) 4-chlorobenzoyl chloride, 79% d) conc. HCl, MeOH, 70% e) (1) NaH, DMF (2) 4-chlorobenzoyl chloride, 85% f) BH_3/THF, 85% g) $CH_3Ti(OiPr)_3$, THF, 90% h) (1) 0.33 eq PBr_3, CH_2Cl_2 (2) excess $THPONH_2$, 78% i) AcCl, pyridine, CH_2Cl_2 j) conc. HCl, EtOH, 58% from **14**

Initial attempts to synthesize the α-methyl analogs **16**, **18**, and **19** were problematic. As shown in Scheme II, **1** was acylated under Vilsmeier-Haack[14] conditions to provide **9**. While the ketoxime **10** was readily prepared from **9**, reduction of **10** did not proceed to our satisfaction. Therefore, a new route was designed utilizing **13** as the key intermediate. Compound **13** was prepared by either of two methods. Methylation of **3** using $CH_3Ti(OiPr)_3$[15] gave **13** in 90% yield. Alternatively, **9** was benzoylated[12] to give **12**. The ketone **12** was reduced to **13** using BH_3/THF.

Scheme III

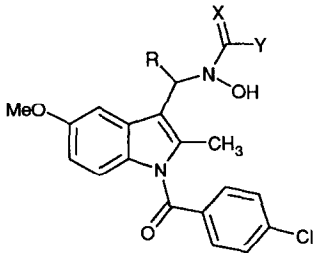


a) (1) TMSBr, CH_2Cl_2 (2) *t*-BDPSiONH$_2$, b) aq 48% HF, CH_3CN, 77% from **13** c) NaOCN, 1N HCl, THF/H_2O, 44% d) CH_3NCS, THF, 82%

A cold solution of **13** was converted to the unstable bromide using PBr_3, and a large excess of tetrahydropyranyl hydroxylamine[16] was added to provide **14**. Acylation of **14** with acetyl chloride and deprotection afforded **16**.

In analogy to the sequence depicted in Scheme I, acylation of **14** with sodium cyanate gave the desired product. It was not possible to cleanly remove the tetrahydropyranyl (THP) group from this acylated derivative. We also could not obtain **11** via deprotection of **14**. To circumvent this obstacle we replaced the THP group with the *t*-butyldiphenylsilyl (*t*-BDPSi) protecting group. As shown in Scheme III, **13** was treated sequentially with bromotrimethylsilane followed by O-*t*-butyldiphenylsilyl hydroxylamine[17] (2 equiv.). The crude mixture was treated with aqueous 48% HF to provide **11**. The hydroxylamine was acylated with sodium cyanate and methyl isothiocyanate converting **11** to **18** and **19** respectively.

The reversed hydroxamates were evaluated for inhibition of CO (ARBC) and 5-LO (ARBL) in calcium-stimulated rat basophilic leukemia cells (RBL-1).[7] The results shown in Table I indicate that the carboxylic acid group of indomethacin can be replaced by reversed hydroxamates to give potent dual inhibitors of CO and 5-LO.



II

Table I

Compound No.	R	X	Y	ARBL*	ARBC*
Ia				>100	0.50
Ib				7.5	1.1
6	H	O	CH_3	1.4	15
7	H	O	NH_2	0.34	>20
8	H	S	$NHCH_3$	0.40	7.1
16	CH_3	O	CH_3	0.83	2.4
18	CH_3	O	NH_2	1.4	0.89
19	CH_3	S	$NHCH_3$	0.57	7.0

*IC_{50} (μM) from regression analysis of percent inhibition vs. inhibitor concentration

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