

## SYNTHESIS AND BIOLOGICAL EVALUATION OF KETOROLAC ANALOGS

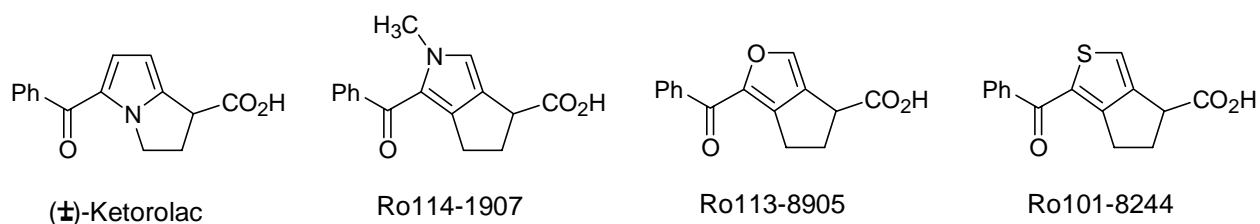
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**Abstract** - Ketorolac analogs were synthesized and biologically evaluated. For the preparation of the *N*-methylpyrrole Ro114-1907, and the furan Ro113-8905, a hydroxyethyl-assisted regioselective benzylation gave intermediates (**4**) and (**12**), and subsequently a key copper-mediated ring closure gave entry to the required bicyclic compounds (**7**) and (**15**). Ro113-8905 and the thiophene Ro101-8244 significantly inhibited both the writhing response and edema formation in rat, but were less potent than Ketorolac.

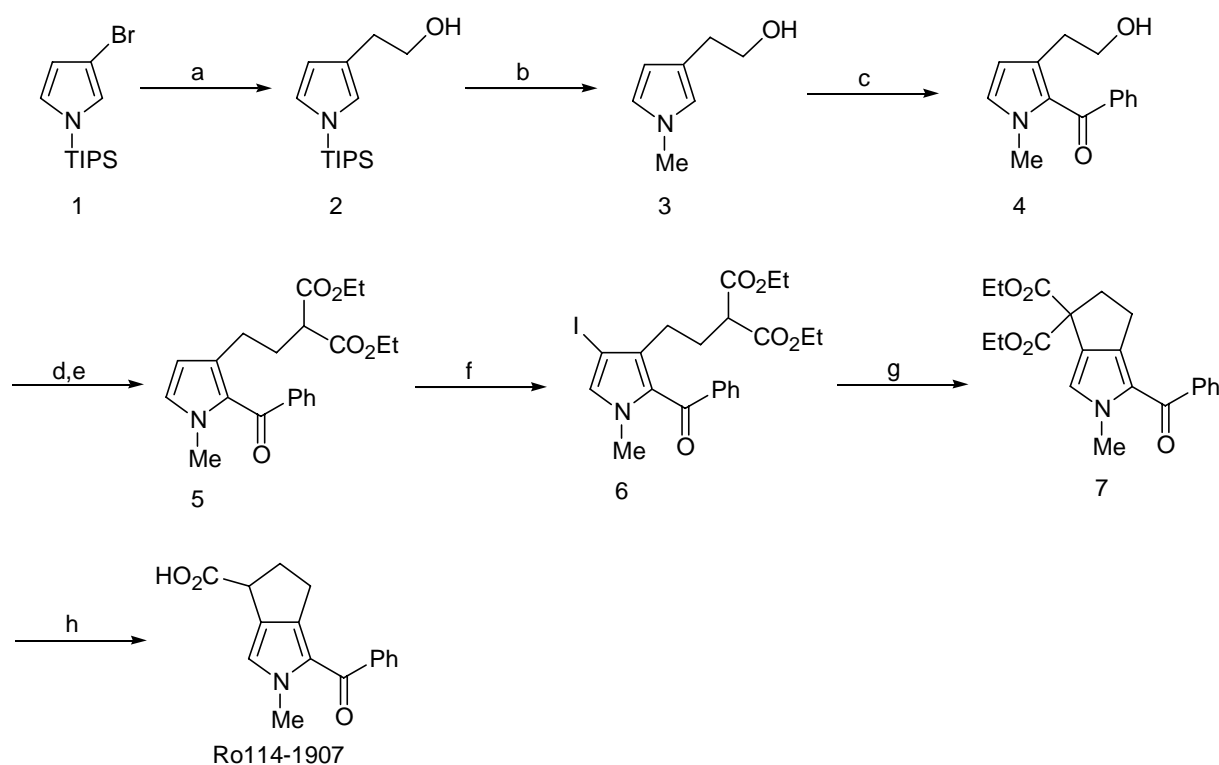
Ketorolac (Toradol) (Scheme 1) is a potent non-steroidal, anti-inflammatory drug (NSAID) that is effective as an analgesic for the treatment of post operative pain.<sup>1</sup> When given intravenously, Ketorolac is as effective as morphine in the management of surgical and cancer related pain.<sup>2</sup> Inhibition of cyclooxygenase (COX) contributes to the anti-inflammatory effect and analgesic action of Ketorolac. However, the long term use of Ketorolac is limited by side effects, such as GI ulceration and renal dysfunction.<sup>3</sup>

In this communication, we would like to present the synthesis as well as the results of the biological evaluation of the Ketorolac analogs Ro114-1907, Ro113-8905 and Ro101-8244 (Scheme 1).



Scheme 1

Preparation of the *N*-methylpyrrole analog, Ro114-1907, is presented in Scheme 2. 3-Bromo-1-TIPS-pyrrole<sup>4</sup> was transformed to the 3-hydroxyethyl derivative (**2**) by treatment with *t*-BuLi/ethylene oxide in 72% yield. Removal of the TIPS group and *N*-methylation of (**2**) gave **3**, which was treated with *n*-BuLi/*N*-methoxy-*N*-methylbenzamide<sup>5</sup> to provide regioselectively (**4**)<sup>6</sup> in 66% yield. Transformation of alcohol (**4**) to the iodide, followed by malonate displacement gave the diester (**5**), which was transformed to the 4-iodo derivative (**6**) regioselectively<sup>7</sup> by treatment with iodine monochloride. The key ring closure to the bicycle (**7**) was achieved by treatment of the sodium salt of (**6**) with copper(I) bromide in DMPU<sup>8</sup> in 74% yield. Final decarboxylation of the corresponding diacid gave the desired pyrrole analog, Ro114-1907.

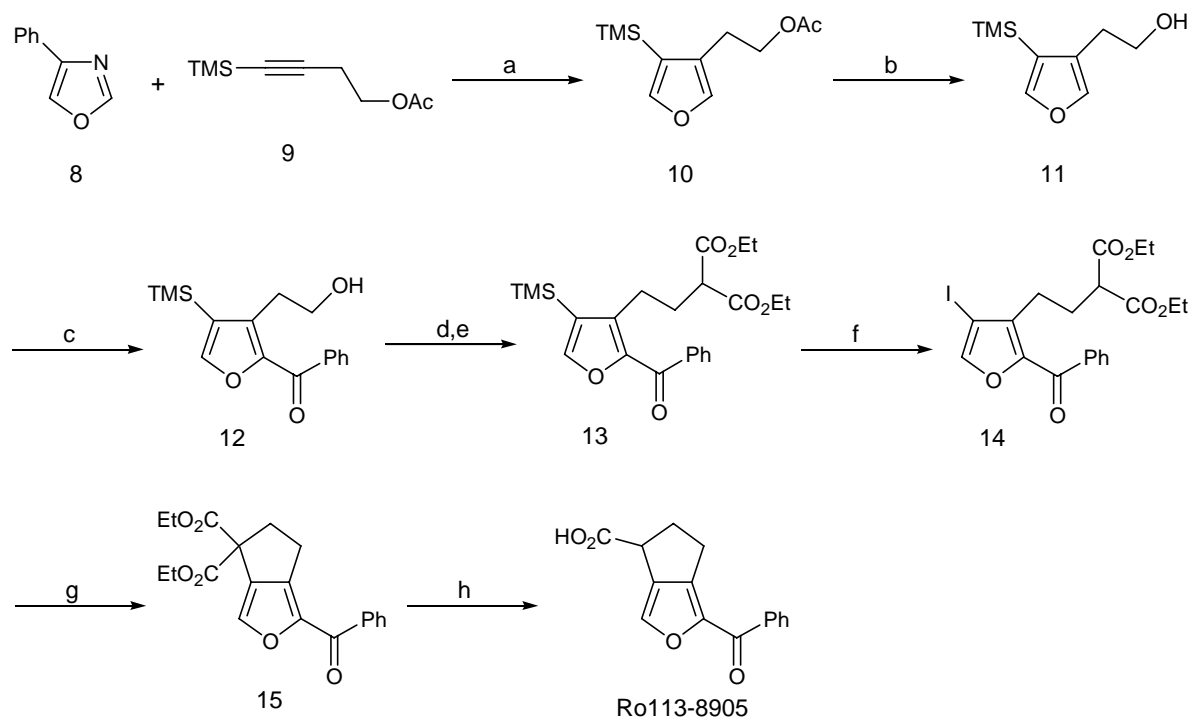


Conditions: (a) *t*-BuLi, THF, 2.8 M ethylene oxide in THF, -78 to 25°C, 72%; (b) *n*-Bu<sub>4</sub>NF, THF, then KO*t*-Bu, MeI, DMSO, 45%; (c) *n*-BuLi, ether, *N*-methoxy-*N*-methylbenzamide, -78 to 25°C, 66%; (d) *p*-TsCl, DMAP, DCM, then NaI, MeCN, reflux, 85%; (e) NaCH(CO<sub>2</sub>Et)<sub>2</sub>, THF, reflux, 88%; (f) ICl, CCl<sub>4</sub>, -78°C, 75%; (g) NaH, CuBr, DMPU, 120°C, 74%; (h) KOH, H<sub>2</sub>O, MeOH, then HCl, toluene, reflux, 95%.

### Scheme 2

Preparation of the furan analog, Ro113-8905, is presented in Scheme 3. 4-Phenyloxazole<sup>9</sup> and 4-trimethylsilyl-3-butynyl acetate<sup>10</sup> were submitted to a Diels-Alder/retro Diels-Alder reaction<sup>11</sup> to form the acetoxyethylfuran (**10**). Hydrolysis and Weinreb benzylation furnished regioselectively (**12**)<sup>6</sup> in 70% overall. Transformation of alcohol (**12**) to the iodide, followed by malonate displacement gave diester

(13). *Ips*o-substitution of the trimethylsilyl radical by the iodo group<sup>12</sup> was achieved by treatment of (13) with iodine monochloride at  $-78^{\circ}\text{C}$  in 77% yield. The critical ring closure was performed under the same conditions as in the pyrrole route to obtain (15) in 58% yield. Hydrolysis and decarboxylation gave the desired furan analog, Ro113-8905.

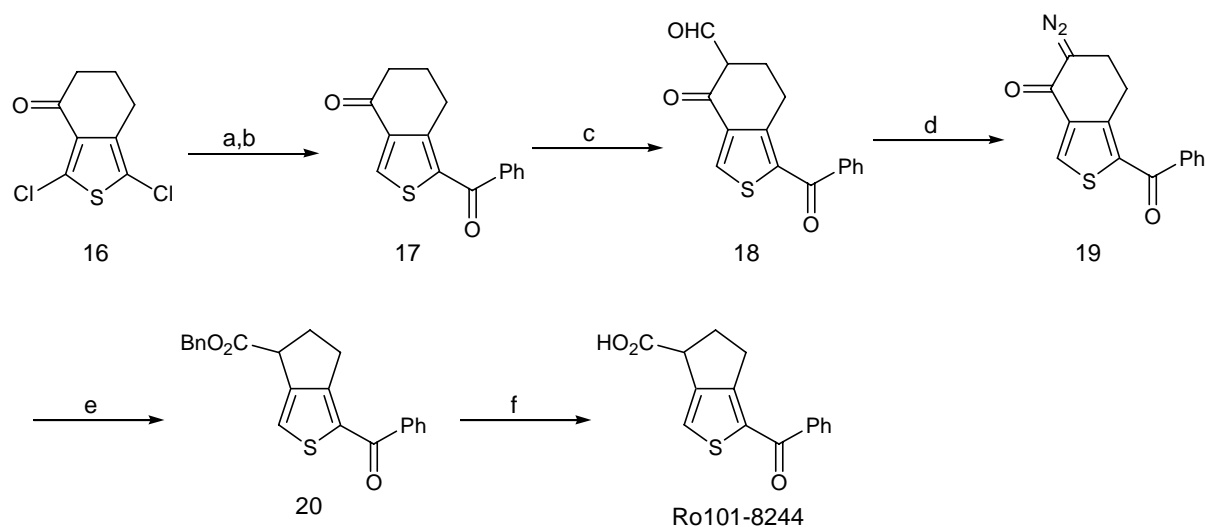


Conditions: (a)  $220^{\circ}\text{C}$ , 55%; (b)  $\text{K}_2\text{CO}_3$ , MeOH, 76%; (c) *n*-BuLi, ether, *N*-methoxy-*N*-methylbenzamide,  $-78$  to  $25^{\circ}\text{C}$ , 92%; (d) *p*-TsCl, DMAP, DCM, then NaI, MeCN, reflux, 71%; (e)  $\text{NaCH}(\text{CO}_2\text{Et})_2$ , THF, reflux, 58%; (f) ICl,  $\text{CCl}_4$ ,  $-78^{\circ}\text{C}$ , 77%; (g) NaH, CuBr, DMPU,  $120^{\circ}\text{C}$ , 58%; (h) LiCl,  $\text{H}_2\text{O}$ , DMSO,  $160^{\circ}\text{C}$ , then 2N NaOH, MeOH, 51%.

### Scheme 3

Preparation of the thiophene analog, Ro101-8244 (Scheme 4), commenced with the known dichlorothiophenone (16),<sup>13</sup> which was dechlorinated and then subjected to a Friedel-Crafts benzoylation to obtain (17). Contraction of the 6-membered ring was achieved through the diazoketone (19), which was subjected to a Wolff rearrangement to obtain (20). Final hydrolysis gave the desired thiophene analog, Ro101-8244.

The antinociceptive (suppression of pain) and anti-inflammatory actions of Ketorolac and analogs Ro114-1907, Ro113-8905 and Ro101-8244 were evaluated by subcutaneous administration in 2 rat models: acetic acid-induced writhing (antinociception) and the carrageenan-induced paw edema (anti-inflammatory)<sup>14</sup>



Conditions: (a) HI, red P, H<sub>2</sub>O, AcOH, 110°C, 67%; (b) PhCOCl, AlCl<sub>3</sub>, CS<sub>2</sub>, 76%; (c) MeONa, ethyl formate, THF; (d) *p*-TsN<sub>3</sub>, Et<sub>3</sub>N, DCM; (e) benzyl alcohol, collidine, 180°C, 52% for 3 steps; (f) 2N NaOH, MeOH, 75%.

#### Scheme 4

(Table 1). Ro113-8905 and Ro101-8244 significantly inhibited both the writhing response and edema formation, but were less potent than Ketorolac. Ro114-1907 is much less potent and efficacious than Ro113-8905 and Ro101-8244.

Table 1. Antinociceptive and anti-inflammatory action of Ketorolac and its analogs.

Compound	Acetic Acid Writhing		Carrageenan Paw Edema	
	ID <sub>50</sub> mg/kg <sup>1</sup>	MPE % <sup>2</sup>	ID <sub>50</sub> mg/kg <sup>1</sup>	MPEp % <sup>3</sup>
Ketorolac	0.24	100	0.08	100
Ro114-1907	2.42	57	5.62	63
Ro113-8905	0.40	100	0.62	100
Ro101-8244	0.67	100	0.44	88

1. Average of 2 determinations.
2. Maximum possible inhibition: (control-drug treated/control) x 100.
3. Maximum possible inhibition of prostanoid-dependent edema formation: MPE/MPE (indomethacin).

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