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SYNTHESIS AND BIOLOGICAL EVALUATION OF KETOROLAC ANALOGS

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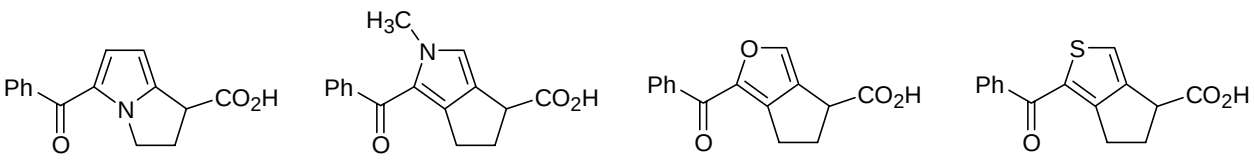
Abstract - Ketorolac analogs were synthesized and biologically evaluated. For the preparation of the *N*-methylpyrrole Ro114-1907, and the furan Ro113-8905, a hydroxyethyl-assisted regioselective benzoylation gave intermediates **(4)** and **(12)**, and subsequently a key copper-mediated ring closure 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.[1] When given intravenously, Ketorolac is as effective as morphine in the management of surgical and cancer related pain.[2] 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.[3]

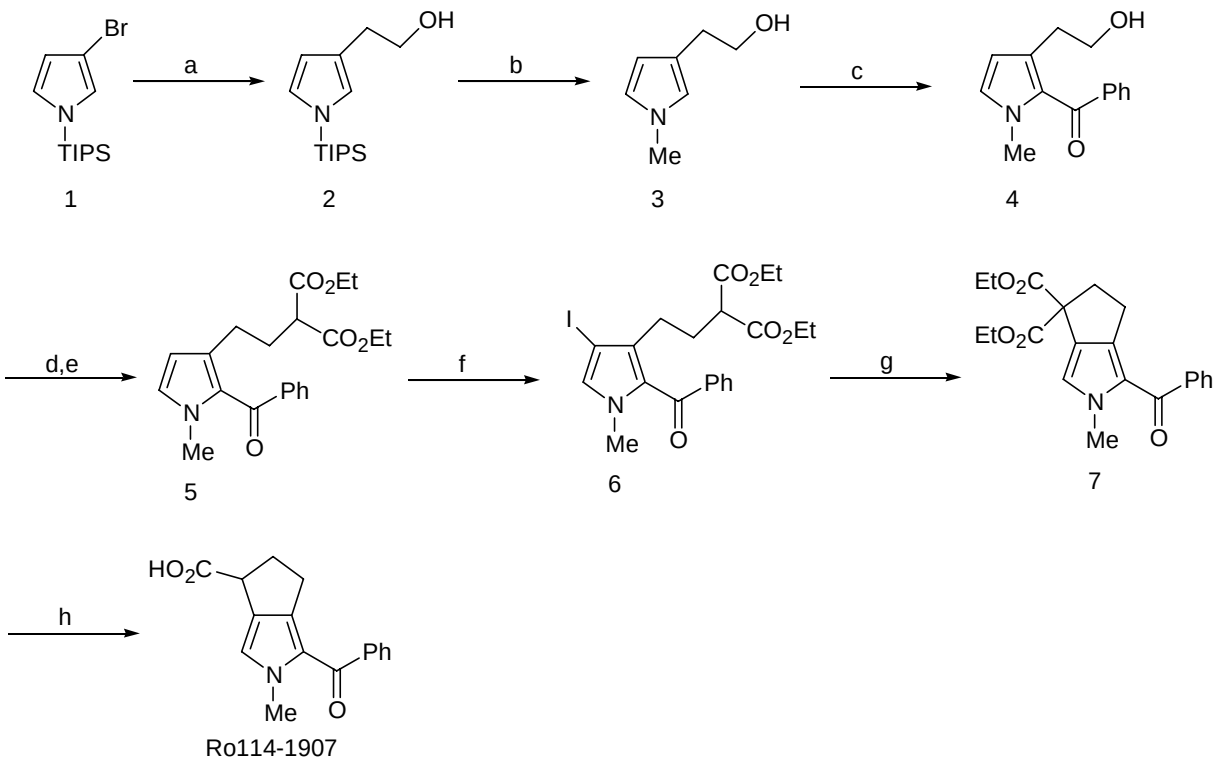
In this communication, we would like to present the synthesis as well as the results of the biological evaluation of the Ketorolac analogs Ro114-1907, Ro113-8905 and Ro101-8244 (Scheme 1).



(±)-Ketorolac Ro114-1907 Ro113-8905 Ro101-8244

Scheme 1

Preparation of the *N*-methylpyrrole analog, Ro114-1907, is presented in Scheme 2. 3-Bromo-1-TIPS-pyrrole[4] 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[5] to provide regioselectively **(4)**[6] 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[7] 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[8] in 74% yield. Final decarboxylation of the corresponding diacid gave the desired pyrrole analog, Ro114-1907.

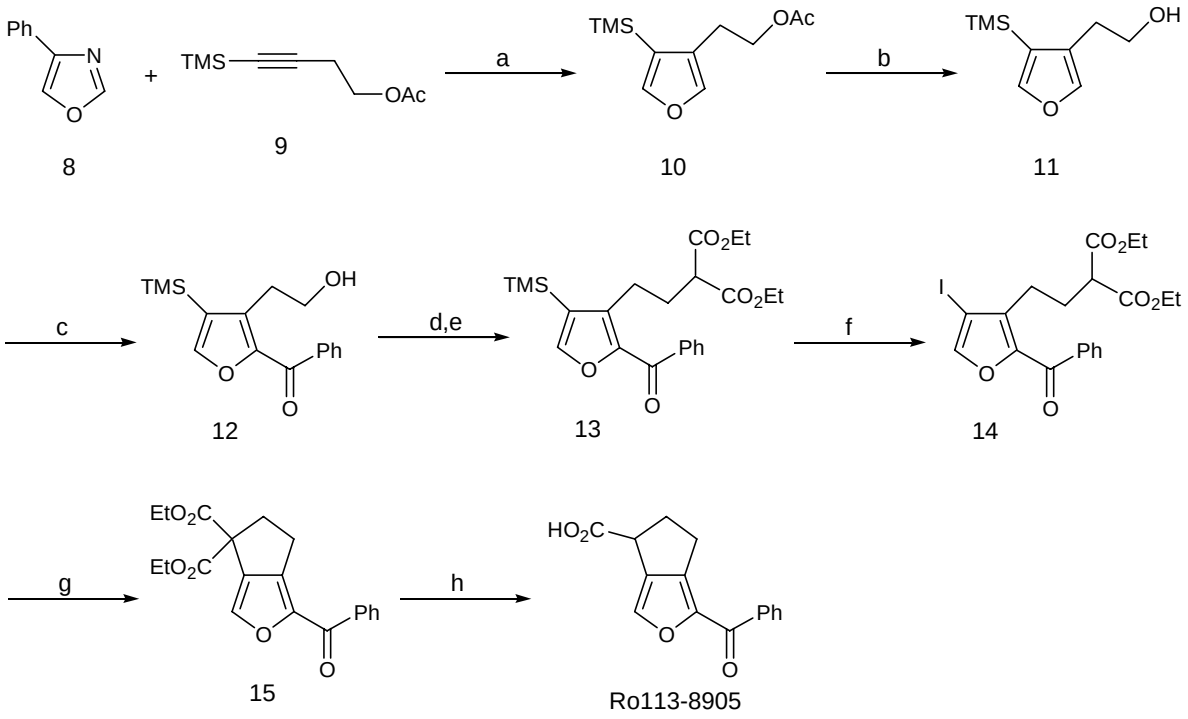


Conditions: (a) *t*-BuLi, THF, 2.8 M ethylene oxide in THF, -78 to 25°C, 72%; (b) *n*-Bu_4NF, THF, then KO*t*-Bu, MeI, DMSO, 45%; (c) *n*-BuLi, ether, *N*-methoxy-*N*-methylbenzamide, -78 to 25°C, 66%; (d) *p*-TsCl, DMAP, DCM, then NaI, MeCN, reflux, 85%; (e) $NaCH(CO_2Et)_2$, THF, reflux, 88%; (f) ICl, CCl_4, -78°C, 75%; (g) NaH, CuBr, DMPU, 120°C, 74%; (h) KOH, H_2O, MeOH, then HCl, toluene, reflux, 95%.

Scheme 2

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

(13). *Ipso*-substitution of the trimethylsilyl radical by the iodo group[12] was achieved by treatment of **(13)** with iodine monochloride at –78°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.

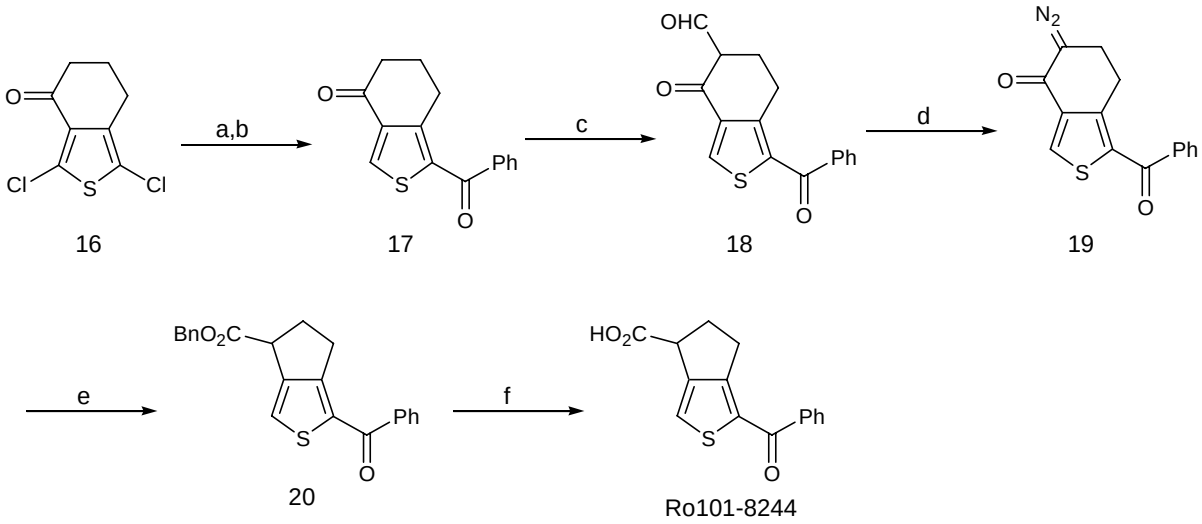


Conditions: (a) 220°C, 55%; (b) K_2CO_3, MeOH, 76%; (c) *n*-BuLi, ether, *N*-methoxy-*N*-methylbenzamide, -78 to 25°C, 92%; (d) *p*-TsCl, DMAP, DCM, then NaI, MeCN, reflux, 71%; (e) $NaCH(CO_2Et)_2$, THF, reflux, 58%; (f) ICl, CCl_4, -78°C, 77%; (g) NaH, CuBr, DMPU, 120°C, 58%; (h) LiCl, H_2O, DMSO, 160°C, then 2N NaOH, MeOH, 51%.

Scheme 3

Preparation of the thiophene analog, Ro101-8244 (Scheme 4), commenced with the known dichlorothiophenone **(16)**,[13] 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)[14]



Conditions: (a) HI, red P, H_2O, AcOH, 110°C, 67%; (b) PhCOCl, $AlCl_3$, CS_2, 76%; (c) MeONa, ethyl formate, THF; (d) *p*-TsN_3, Et_3N, 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_{50} mg/kg[1]	MPE %[2]	ID_{50} mg/kg[1]	MPEp %[3]
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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