Synthesis of Indole Derivatives as Potential COX-2 Inhibitors from *N*-Substituted Indolyl Acetic Acids *via* Curtius Rearrangement

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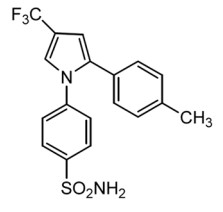
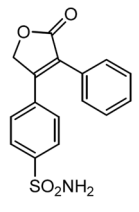
Due to the selective analgesic activity exhibited by cyclooxygenase-2 (COX-2) inhibitors, vast amount of research activities in these area were reported during last several years[1]. Among numerous COX-2 inhibitors, Celecoxib (**1**) and Rofecoxib (**2**) are the most popular commercial products on the present market. Recently, Kalguthar *et al.*[2] reported the ester and amide derivatives of nonsteroidal anti-inflammatory drug, indomethacin (**3**) as COX-2 selectivity-enhanced inhibitors. Their findings call our attentions by considering the structure of capsaicin (**4**), different class of analgesic which contains reversed amide functionality. So it was envisioned that compound **5** containing indole carbamates (R_1 = OR) or ureas (R_1 = NR), and yet different structure from the one reported by Kalguthar *et al.*, might exhibit an interesting pharmaco properties. Now we report a synthetic method to prepare target compounds **5** along with several unsuccessful attempts which are worthwhile to mention due to the peculiar properties of indole chemistry. The overall synthetic trials are outlined in Scheme 1.

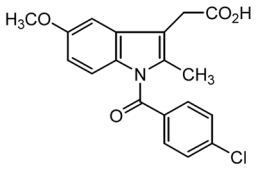
The first attempt was to synthesize indole **7** from hydrazine **6** followed by Curtius rearrangement to provide **8**, which would be acylated eventually to give the target compounds **5**. In this process the indole **7** was prepared with no incident,[3] but the subsequent Curtius rearrangement failed. It is noteworthy that the transformation of hydrazine **6** to indole **7** by treatment with levulinic acid instead of its ester did not occur.



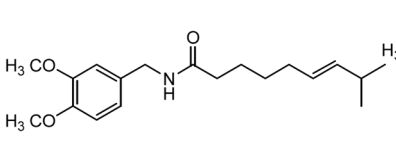
Celecoxib (1)



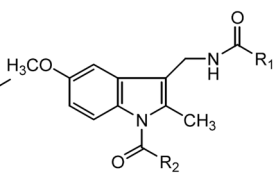
Rofecoxib (2)



Indomethacin (3)



Capsaicin (4)



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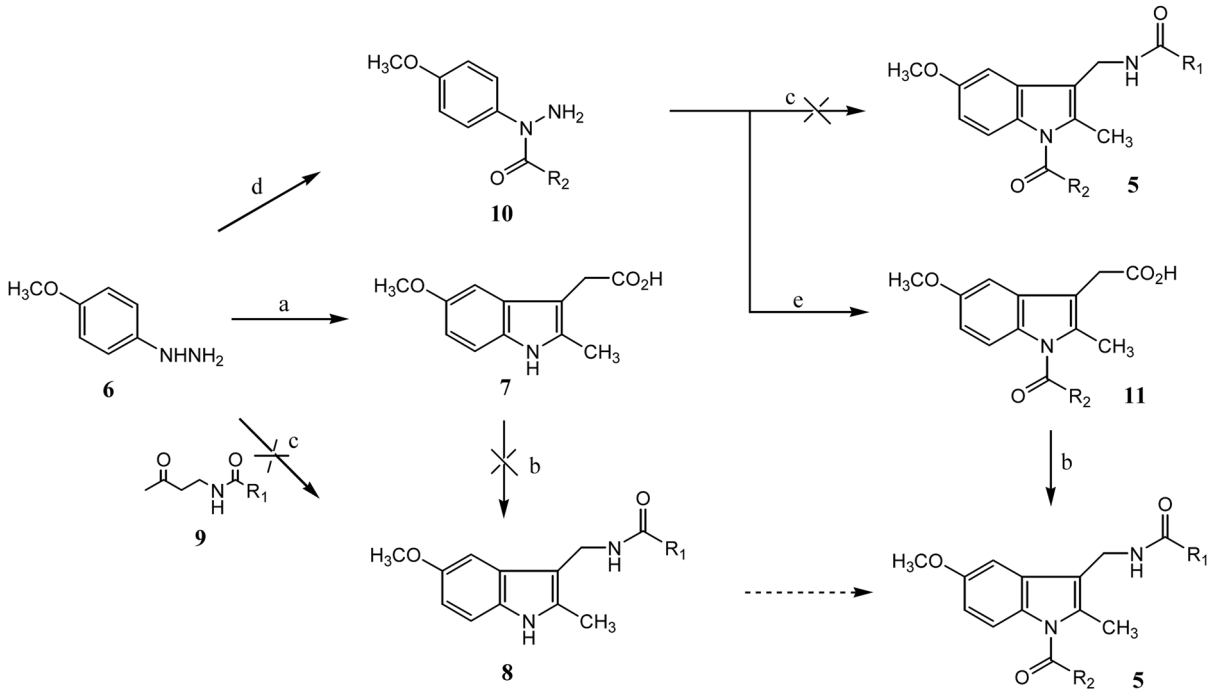
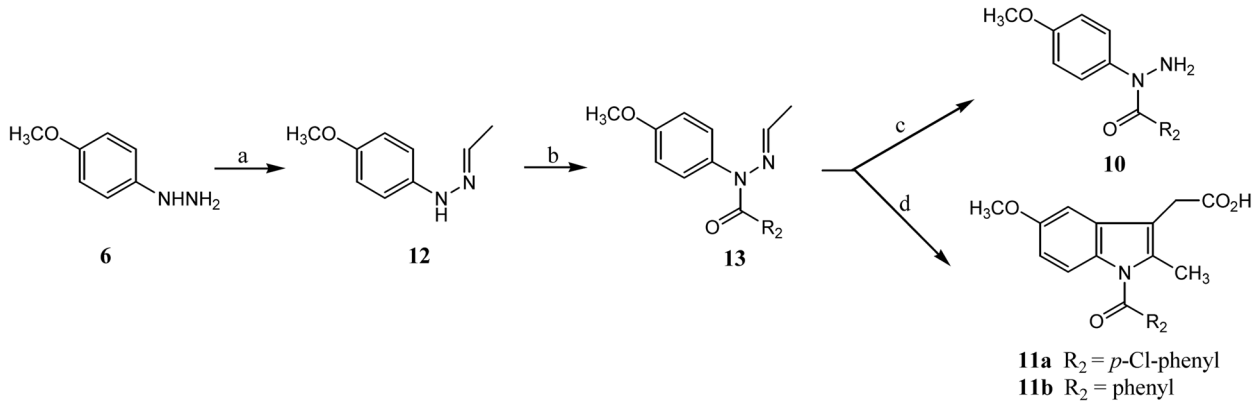
Inspired by the successful Fisher indole formation starting from hydrazine **6**, the hydrazine **6** was treated with *N*-(3-oxo-butyl)-carbamic acid methyl ester (**9**, R=OMe) to prepare **8** under the same reaction condition as for the preparation of indole **7**, but the reaction was not successful, either (bottom pathway c of scheme 1). The required reagent **9** was prepared by treating the toluene solution of levulinic acid with diphenylphosphoryl azide (DPPA)[4] and triethylamine followed by quenching with methanol. The yield generally exceeds 90%.

So we moved on a different pathway; thus, introduction of acyl group first and then formation of the required indole ring. The acylated compounds **10** were prepared by pathway d of Scheme 1, namely by treatment of hydrazine **6** with acetaldehyde (imine formation to block the primary amine function), acylation under normal conditions and then final deprotection of the imine protecting group (more details in Scheme 2). The next indole ring transformation of **10** by treating with compound **9** was tried, but was not successful again (upper pathway c of Scheme 1). Finally, the only successful method to prepare our target compound **5** as follows. The acylated compounds **10** were converted first to indoles **11** by treatment with levulinic acid. Practically, the imine protected compounds **13** instead of **10** can be directly used for the preparation of indoles **11**, thereby efficient synthesis of **11** is possible (Scheme 2). Now the indole compounds **11** (R_2 = aryl) were subjected to the Curtius rearrangement conditions by treating **11** with diphenylphosphoryl azide followed by quenching with various alcohols and amines to provide the target compounds **5**. The summarized physical properties of thus prepared compounds **5** are shown in Table 1. It is interesting to note that the *N*-substituted hydrazines **10** and **13** undergo the indole ring formation with levulinic acid itself instead of its methyl ester, which is quite contrast to the case of the unsubstituted indole **7** as mentioned earlier. Additionally for the *N*-acetyl substituted indole **11** (R_2 = CH_3 instead of aryl), the Curtius rearrangement did not occur under the same reaction conditions as for transforming **11** (R_2 = aryl) into the rearranged product **5** (R_2 = aryl).

In summary, the hybrid type compounds **5** between capsaicin and indomethacin were prepared by utilizing the Curtius rearrangement as a crucial step, and their biological



Scheme 1. Several trials to prepare **5** together with unsuccessful attempts. (a) i) $CH_3C(O)CH_2CH_2CO_2CH_3$/EtOH/80 °C, ii) NaOH/EtOH/0 °C; (b) i) diphenylphosphoryl azide (DPPA)/Et_3N/benzene, ii) R_1OH or R_1NH_2; (c) $CH_3C(O)CH_2CH_2NHC(O)R_1$ (**9**)/EtOH/80 °C; (d) i) CH_3CHO/CH_2Cl_2, ii) $R_2C(O)Cl$/pyridine/0 °C, iii) HCl/EtOH/toluene; (e) $CH_3C(O)CH_2CH_2CO_2H$/EtOH/80 °C.



Scheme 2. Practical pathway for the synthesis of **11**. CH_3CHO/CH_2Cl_2; (b) $R_2C(O)Cl$/pyridine/0 °C, (c) HCl/EtOH/toluene; (d) $CH_3C(O)CH_2CH_2CO_2H$/AcOH/80 °C.

activities are awaiting. During these work, it was noticed that not only reaction sequences but the reaction conditions are critical in this subtle indole chemistry to come up with the desired compounds.

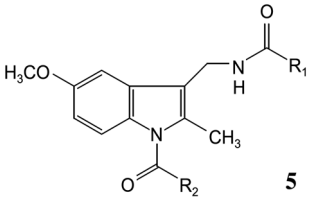
Experimental Section

Melting points were recorded on Electrothermal melting point apparatus and are uncorrected. Mass and NMR spectra were recorded on a JEOL JMS-DX 303 mass spectrometer (3 KV) and Jeol 400 MHz spectrometer, respectively.

Preparation of methyl 5-methoxy-2-methyl-3-indole acetate; methyl ester of compound 7. *p*-Methoxy phenyl hydrazine hydrochloride (**6**, 0.23 g, 1.32 mmol) and methyl levulinate (0.15 g, 1.1 mmol) were dissolved in acetic acid (10 mL). The resulting solution was heated at 80 °C with stirring for 3 h, cooled, diluted with water (200 mL) and then extracted with EtOAc (25 mL × 2) and brine (20 mL), dried over $MgSO_4$, concentrated *in vacuo* and the resulting residue was chromatographed with EtOAc/hexane = 3/7 as eluent to give pale yellow liquid (0.24 g). 94% yield; ^{1}H-NMR ($CDCl_3$): δ 2.31 (s, 3H), 3.65 (s, 2H), 3.65 (s, 3H), 3.84 (s, 3H), 6.74 (dd, 1H, J = 2.4, 8.8 Hz), 6.97 (d, 1H, J = 2.4 Hz), 7.05 (d, 1H, J = 8.8 Hz), 7.83 (br s, -NH); ^{13}C-NMR δ 11.821, 30.308, 51.905, 55.914, 100.330, 104.223, 110.831, 110.897, 128.782, 130.019, 133.426, 153.984, 172.397. Compounds **7** were prepared quantitatively by treating its methyl ester with ethanolic NaOH solution, and they are directly used for the next experiment.

Preparaion of [1-(4-chloro-benzoyl)-5-methoxy-2-

Table 1. Physical properties of [1-acyl-5-methoxy-2-methyl-1H-indol-3-ylmethyl]-carbamic acid derivatives (**5**)



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	R_1	R_2	Yield (%)	Mp (°C)	FW.	Formula equation
a	OCH_3	*p*-Cl-C_6H_5	42	133-134	386.83	$C_{20}H_{19}ClN_2O_4$
b	OCH_2CH_3	*p*-Cl-C_6H_5	60	136	400.86	$C_{21}H_{21}ClN_2O_4$
c	$OCH(CH_3)_2$	*p*-Cl-C_6H_5	77	129-133	414.88	$C_{22}H_{23}ClN_2O_4$
d	$NHCH_2CH_2CH_3$	*p*-Cl-C_6H_5	51	172	413.90	$C_{22}H_{24}ClN_3O_3$
e	$NH(CH_2)_3CH_3$	*p*-Cl-C_6H_5	52	179	427.92	$C_{23}H_{26}ClN_3O_3$
f	$NHCH_2C_6H_5$	*p*-Cl-C_6H_5	54	194	461.94	$C_{26}H_{24}ClN_3O_3$
g	OCH_3	C_6H_5	37	119	352.38	$C_{20}H_{20}N_2O_4$
h	OCH_2CH_3	C_6H_5	42	122	366.41	$C_{21}H_{22}N_2O_4$
i	$NHCH_2CH_2CH_3$	C_6H_5	78	155	379.45	$C_{22}H_{25}N_3O_3$
j	$NHCH_2C_6H_5$	C_6H_5	82	182-184	427.50	$C_{26}H_{25}N_3O_3$

methyl-1H-indol-3-yl]-acetic acid (11a, R_2 = *p*-chlorophenyl): Typical procedure for the preparation of compound 11. 4-Chloro-benzoic acid-*N'*-ethylidene-*N*-(4-methoxy-phenyl)-hydrazine hydrochloride (**13**, 0.32 g, 1.0 mmol)[5] and levulinic acid (0.14 g, 1.2 mmol) were dissolved in acetic acid (10 mL). The resulting solution was heated at 80 °C with stirring for 1 h, cooled, diluted with water (200 mL) and then extracted with EtOAc (25 mL × 4). The organic extracts were washed with Sat. $NaHCO_3$ solution (25 mL × 2) and brine (20 mL), dried over $MgSO_4$ and then concentrated *in vacuo* to give faint yellow solid. The faint yellow solid was rinsed with hexane to provide white sand shape solid (0.323 g, 92%) which is identical with authentic indomethacin (**3**).

(1-Benzoyl-5-methoxy-2-methyl-1H-indol-3-yl)-acetic acid (11b, R_2 = phenyl). 37% yield; mp 167-168 °C; ^{1}H-NMR ($CDCl_3$) δ 2.37 (s, 3H, 3.69 (s, 2H), 3.82 (s, 3H), 6.63 (d, 1H, J = 8.8 Hz), 6.84 (d, 1H, J = 8.8 Hz), 6.94 (s, 1H), 7.46 (t, 2H, J = 7.6 Hz), 7.60 (t, 1H, J = 7.6 Hz), 7.69 (t, 2H, J = 7.6 Hz); ^{13}C-NMR δ 13.298, 29.974, 55.699, 101.037, 111.533, 111.608, 115.126, 128.742, 130.380, 130.946, 132.817, 136.335, 155.939, 169.480, 176.416; EIMS *m/z* 323.12 (M^+).

Preparation of [1-(4-chloro-benzoyl)-5-methoxy-1H-indol-3-yl-methyl]-carbamic acid methyl ester (5a); Typical procedure for the preparation of compound 5. To an oven dried flask was added compound **11a** (0.28 g, 0.78 mmol), diphenylphosphoryl azide (0.85 g, 3.12 mmol), Et_3N (0.78 g, 7.8 mmol) and benzene (20 mL). The whole reaction mixture was heated under reflux for 0.5 h. After adding methanol (10 mL), the reaction solution was further heated for 2 h and then cooled, concentrated *in vacuo* to leave brown liquid. The syrupy liquid was dissolved in EtOAc and then filtered through short path of celite. The filtrate was concentrated to give faint yellow solid as a crude product which was recrystallized from EtOAc to provide pure product as a white solid (0.125 g). 42% yield; Mp 133-134 °C; ^{1}H-NMR ($CDCl_3$) δ 2.33 (s, 3H), 3.62 (s, 2H), 3.75 (s, 3H), 4.38 (d, 2H), 4.77 (br s, -NH), 6.58 (d, 1H, J = 8.8 Hz), 6.74 (d, 1H, J = 8.8 Hz), 6.95 (s, 1H), 7.38 (d, 2H, J = 8.0 Hz), 7.56 (d, 2H, J = 8.0 Hz); ^{13}C-NMR δ 13.040, 35.006, 52.248, 55.675, 101.070, 111.883, 114.960, 116.008, 119.942, 125.357, 129.781, 129.906, 130.829, 131.154, 133.641, 136.144, 139.413, 156.039, 156.987, 168.349; EIMS *m/z* 386.10 (M^+).

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