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Synthesis of Indomethacin Conjugates with D-Glucosamine

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Abstract: Two series of indomethacin conjugates with D-glucosamine were prepared with the objectives of reducing ulcerogenic potency, increasing the bioavailability of indomethacin and exerting the coordinative effects on osteoarthritis. The structures of the conjugates were identified by ^{1}H NMR and ^{13}C NMR. The ester conjugates inhibited edema as potent as indomethacin.

Keywords: Indomethacin, D-glucosamine, NSAIDs, glycoconjugates.

It is well known that the major limitation of non-steroidal anti-inflammatory drugs (NSAIDs) is their adverse effects on gastrointestinal mucosa[1]. Numerous NSAIDs ester derivatives have been synthesized for reduced gastrointestinal toxicity. For example, Uhrig[2] *et al.* have synthesized some glucoconjugates of ibuprofen, while Borowiecka[3] *et al.* have synthesized glycosyl esters of 2-bromosugar for NSAIDs including indometha- cin, aspirin and diclofenac. As known, glucoconjugates can be transported by cellular glucose transporters[2, 4], so the glucoconjugates of NSAIDs could be expected to increase the bioavailability of NSAIDs.

NSAIDs only can act as anti-inflammation and pain release agent in the treatment of osteoarthritis (OA), but it can not reform the underlying degenerative disorder. NSAIDs inhibit the synthesis of proteoglycans, which are the main component of cartilage, while glucosamine can partially reverse the inhibiting effects of NSAIDs on proteoglycans synthesis, normalize cartilage biochemistry, and in turn stimulate the healing process of osteoarthritis[5, 6].

These findings indicated that the glycoconjugates of NSAIDs might lead to reduce ulcerogenic potency, increase bioavailability and possess coordinative effects on osteoarthritis. We describe herein the synthesis of some new glycoconjugates of indomethacin. Considering the half-life in the blood[7], N-acetyl-D-glucosamine was chosen as the sugar residue. Two series of glycoconjugates containing amide or ester functional group were prepared.

Results and Discussion

Compound **3** and **5** are the derivatives of indomethacin, which bonded with glucosamine

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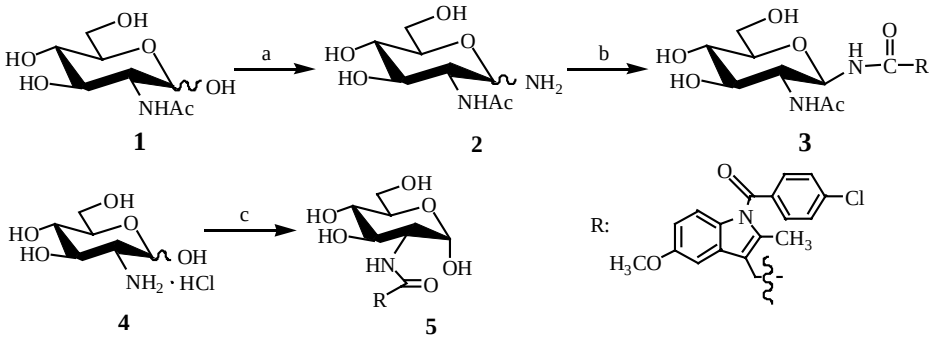
in 1, 2 position respectively. **3** was synthesized from **2**, which was prepared from **1**[8], and separated by filtration directly in 52.8% yield (**Scheme 1**). In ^{1}H NMR, the coupling constant of the anomeric proton $J_{1,2}$ was 9.1 Hz, it indicated **3** is β-anomer.

D-Glucosamine **4** was condensed with indomethacin chloride in methanol in the presence of Et_3N to give compound **5** in 65.1% yield (**Scheme 1**). The $J_{1,2}$=3.7 Hz of the anomeric proton in **5** clearly demonstrated the sole α-configuration**.**

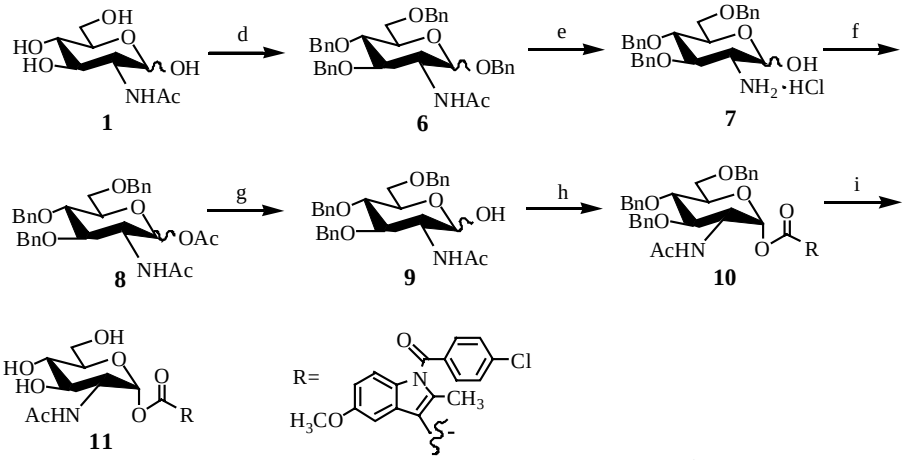
The esters **11** and **14** were obtained by esterifying indomethacin with corresponding glycosyl residue. Compound **11** was synthesized from the glycol donor **9**. Employing the similar procedure developed by H. G. Fletcher *et al.*[10, 11], N-acetylglucosamine **1** was converted into the key intermediate **9** in four steps. Major component of **9** was α-anomer. The condensation of **9** with indomethacin in the presence of DCC/DMAP gave **10** in 74.7% yield. Formation of the ester bond at the anomeric carbon resulted in

Scheme 1



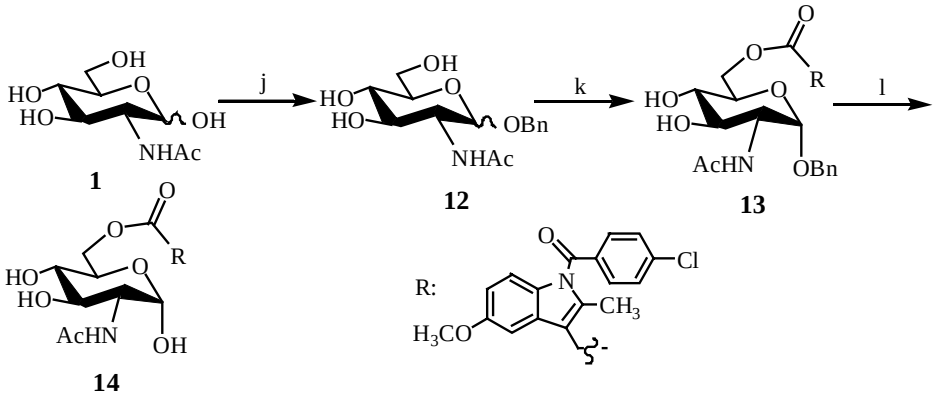
Reagents and conditions: (a) NH_4HCO_3/H_2O, 45°C, quant.; (b) RCOCl/MeOH, 52.8%; (c) RCOCl, $MeOH/CH_2Cl_2$, Et_3N, 0°C→r.t., 65.1%.

Scheme 2



Reagents and conditions: (d) BnBr, $Ba(OH)_2{\cdot}8H_2O$, BaO, DMF, $Bu_4N^+I^-$, 64.7%; (e) 3 mol/L HCl, THF, reflux, 30 h; (f) Ac_2O, Pyridine, r.t., 24 h; (g) MeONa/MeOH, three steps 62.3%; (h) R-COOH, DCC, DMAP, CH_2Cl_2/THF, 74.7%; (i) 5%Pd-C/H_2.

Scheme 3



Reagents and conditions: (j) BnOH, $BF_3 \cdot Et_2O$, 83.6%; (k) RCOOH, DCC/DMAP, 42.6%; (l) Pd-C / H_2, EtOAc/EtOH, 72.4%.

the shift of the H-1 from 5.21 ppm to 6.07 ppm. **10** was debenzylated with Pd/C to give the expected glycoside **11** (**Scheme 2**). The ^{1}H NMR data indicated that **11** was α-anomer.

The important intermediate **12**[12~14], for the synthesis of compound **14**, was obtained by selectively benzylation of 2-acetamido-2-deoxy-D-glucopyranoside **1** in boiling benzyl alcohol to give α-anomer as the major product. Compound **12** was reacted with indomethacin in THF and dioxane in the presence of DCC/DMAP to give selectively esterified compound in 6-position. **13** was purificated by silica gel column chromatography to give unique α-anomer ($J_{1,2}$=3.7 Hz). Upon deprotection of **13**, α-anomer of compound **14** was obtained (**Scheme 3**).

The structures of compound **3, 5**, **11** and **14** were identified by ^{1}H NMR and ^{13}C NMR.

The effects of compound **3**, **5**, **11** and **14** on croton oil-induced ear edema in mice were examined. **11** and **14** showed significant inhibition of ear edema ($P<0.05$) at dose 0.042 mmol/kg. While compound **3** and **5** were inactive at this dose. Their ulcerogenic potency is under testing.

In summary, two amides and two esters of NSAIDs indomethacin with glucosamine were synthesized with the aims to reduce ulcerogenic potency, increase bioavailability and improve effects on osteoarthritis. Ester derivatives compound **11** and **14** inhibited edema as potent as indomethacin at the same dose.

References and Notes

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15. Spectral data of **3**: ^{1}H NMR (DMSO-d_6, 600 MHz, δ ppm): 8.03 (d, 1H, *J*=8.4 Hz, N-H_1), 7.80-6.70 (m, 8H, N-H_2, Ar-H), 5.00 (brs, 1H, -OH), 4.96 (brs, 1H, -OH), 4.72 (t, 1H, *J*=9.1 Hz, H-1), 4.53 (brs, 1H, -OH), 3.77 (s, 3H, -OCH_3), 3.64 (m, 1H, H-6), 3.58 (d, 1H, *J*=15.7 Hz, -CH_2-), 3.53 (q, 1H, *J*=9.5 Hz, H-2), 3.47 (d, 1H, *J*=15.7 Hz, -CH_2-), 3.44 (m, 1H, H-6), 3.26 (t, 1H, *J*=8.0 Hz, H-3), 3.09 (m, 2H, H-4, H-5), 2.24 (s, 3H, -CH_3), 1.48 (s, 3H, -CH_3). ^{13}C NMR (DMSO-d_6, 150 MHz, δ ppm): 170.3, 170.0, 168.0, 155.6, 137.6, 135.6, 134.3, 131.3 (2C), 130.8, 130.4, 129.0 (2C), 114.6, 113.4, 111.2, 101.8, 79.5, 78.7, 74.3, 70.4, 60.8, 55.5, 54.1, 31.2, 22.2, 13.3. **5**: ^{1}H NMR (DMSO-d_6, 600 MHz, δ ppm): 7.95 (d, 1H, *J*=8.1 Hz, N-H), 7.68-6.68 (m, 7H, Ar-H), 6.46 (dd, 1H, *J*=3.7 Hz, 1-OH), 4.94 (t, 1H, *J*=3.7 Hz, H-1), 4.91 (d, 1H, *J*=5.5 Hz, 3-OH), 4.62 (d, 1H, *J*=5.5 Hz, 4-OH), 4.42 (t, 1H, *J*=6.2 Hz, 6-OH), 3.76 (s, 3H, -OCH_3), 3.63-3.53 (m, 4H, H-2, H-4, H-5, H-6), 3.56 (s, 2H, -CH_2-), 3.48 (m, 1H, H-6), 3.13 (m, 1H, H-6), 3.13 (m, 1H, H-3), 2.23 (s, 3H, -CH_3). ^{13}C NMR (DMSO-d_6, 150 MHz, δ ppm): 169.5, 167.8, 155.5, 137.5, 134.9, 134.3, 131.1 (2C), 131.0, 130.1, 129.0 (2C), 114.8, 114.4, 111.5, 101.9, 90.6, 72.1, 71.2, 70.5, 61.1, 55.4, 54.5, 30.9, 13.4. **11**: ^{1}H NMR (CD_3OD, 600 MHz, δ ppm): 7.69-6.68 (m, 7H, Ar-H), 6.15 (d, 1H, *J*=3.7 Hz, H-1), 3.96 (dd, 1H, *J*=3.7, 11.0 Hz, H-2), 3.87 (d, 1H, *J*=15.8 Hz, -CH_2-), 3.80 (s, 3H, -OCH_3), 3.76 (d, 1H, *J*=16.1 Hz, -CH_2-), 3.61 (dd, 1H, *J*=8.8, 10.6 Hz, H-3), 3.53 (dd, 1H, *J*=4.4, 12.1 Hz, H-6), 3.49 (dd, 1H, *J*=2.2, 12.1 Hz, H-6), 3.42 (t, 1H, *J*=8.8 Hz, H-4), 3.27 (ddd, *J*=2.6, 4.4, 9.9 Hz, H-5), 2.34 (s, 3H, -CH_3), 1.90 (s, 3H, -CH_3). ^{13}C NMR (CD_3OD, 150 MHz, δ ppm): 173.8, 171.4, 169.9, 157.7, 140.2, 137.1, 135.5, 132.4 (2C), 132.2, 131.8, 130.3 (2C), 116.0, 113.7, 112.7, 102.5, 92.6, 76.2, 72.4, 71.3, 61.9, 56.2, 54.4, 30.9, 22.4, 13.4. **14**: ^{1}H NMR (CD_3OD, 600 MHz, δ ppm): 7.68-6.63 (m, 7H, Ar-H), 5.07 (d, 1H, *J*=3.3 Hz, H-1), 4.40 (dd, 1H, *J*=2.2, 11.7 Hz, H-6), 4.27 (dd, 1H, *J*=5.1, 12.1 Hz, H-6), 3.99 (ddd, *J*=2.2, 5.1, 10.3 Hz, H-5), 3.82 (m, 1H, H-2), 3.80 (s, 3H, -OCH_3), 3.76 (s, 2H, -CH_2-), 3.69 (m, 1H, H-3), 3.15 (m, 1H, H-4), 2.29 (s, 3H, -OCH_3), 1.98 (s, 3H, -OCH_3). ^{13}C NMR (CD_3OD, 150 MHz, δ ppm): 173.7, 173.0, 171.2, 157.3, 137.1, 133.9, 132.4, 132.0, 130.6 (2C), 130.2, 130.0 (2C), 115.9, 113.9, 112.6, 102.4, 92.6, 72.6, 72.5, 70.7, 65.4, 56.2, 55.8, 30.6, 22.6, 13.5.

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