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Synthesis of glycosyl-isoindigo derivatives

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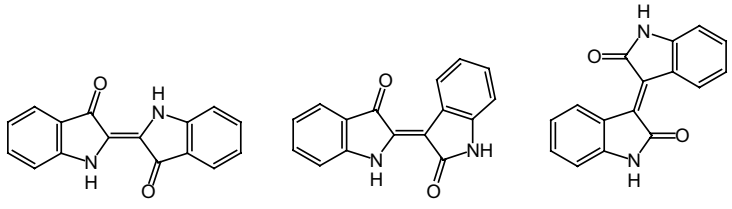
Abstract—The synthesis of 1-(β-D-glucopyranosyl)-isoindigo from commercially available indoline is described. The synthetic pathway used allowed the substitution of the aromatic moiety by either electron donor or acceptor substituents.

1. Introduction

As part of our ongoing studies concerning the preparation of potential biologically active compounds, we were interested in the synthesis of indigoïd derivatives. These heterocycles (indigo, indirubin, isoindigo) are derived from various natural sources and contain a bis-indole framework (Scheme 1).

Indirubin is an active ingredient of Danggui Longhi Wan, a traditional Chinese medicine recipe used in the treatment of leukemias. The antitumoral properties of indirubin and its analogues seem to be due to their inhibitory potencies toward several kinases such as GSK-3β and cyclin dependent kinases (CDKs).[1] The three-dimensional structure of CDK-2 in complex with indirubin has shown that indirubin interacts with the ATP-binding site of the kinase.[2] Moreover, 5-nitro and 5-bromoindirubin were tested as kinase inhibitors (GSK-3β, CDK-1, CDK-5) and have shown stronger activities than the parent indirubin.[1] In a previous paper, we have described the synthesis of indolin-2-one derivatives, which were tested as kinase inhibitors.[3] 3-Substituted indolin-2-one derivatives were usually known as ATP competitive receptor tyrosine kinase inhibitors such as VEGFR, FGFR, and PDGFR[4,5] (e.g., SU6668, SU11248). Recently, SU9516, possessing an indolin-2-one framework was described as an ATP competitive CDKs inhibitor[6] (Scheme 2).

In this letter, the synthesis of isoindigo derivatives (indirubin isomers possessing two indolin-2-one moieties) bearing a sugar residue attached to one of the aromatic nitrogens and diversely substituted on one of the aromatic rings is described. The presence of the glycosyl moiety and the substitution on the aromatic ring should improve the solubility of these heterocyclic compounds



Scheme 1.

Keywords: Indigoïds; Isoindigos; Kinases inhibitors.
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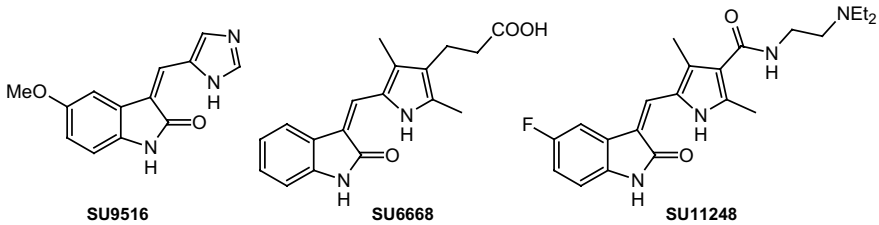
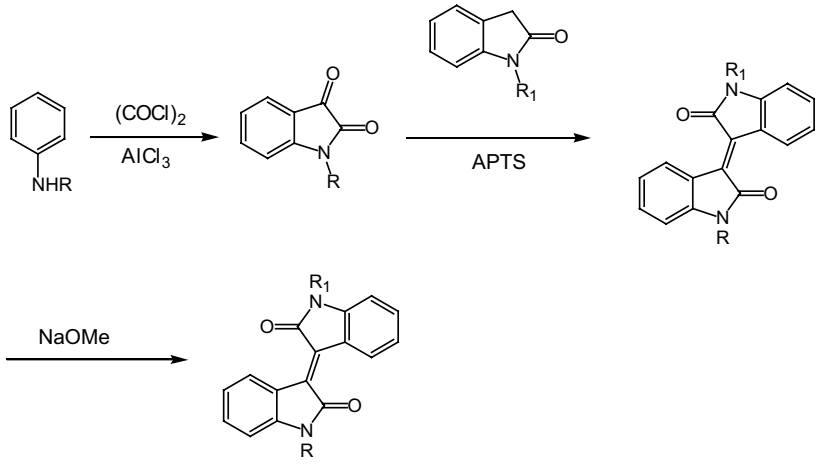


SU9516 CDK-2/cyclin A inhibitor

SU6668 VEGFR-2, PDGFR- β, FGFR-1 inhibitor

SU11248 VEGFR-2 and PDGFR-β inhibitor

Scheme 2.



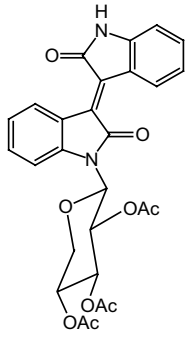
Scheme 3.

and/or enhance the interaction with the active site of the target enzyme(s).

Recently, two patents[7,8] described a method for the preparation of glycosyl-isoindigo derivatives from *N*-glycosylaniline (Scheme 3).

The isatine ring was first formed by cyclization of a *N*-glycosylaniline derivative in the presence of oxalyl chloride, this intermediate was coupled to an oxindole derivative in an acidic medium. None of the described compounds were substituted on the aromatic rings. The most potent as CDKs inhibitor was the isoindigo derivative called Natura (1-(β-D-*O*-triacetylxylopyranosyl)-isoindigo) shown in Scheme 4.

These publications prompted us to publish our synthetic pathway to prepare substituted glycosyl-isoindigos from commercially available indolines (Scheme 5, 6).



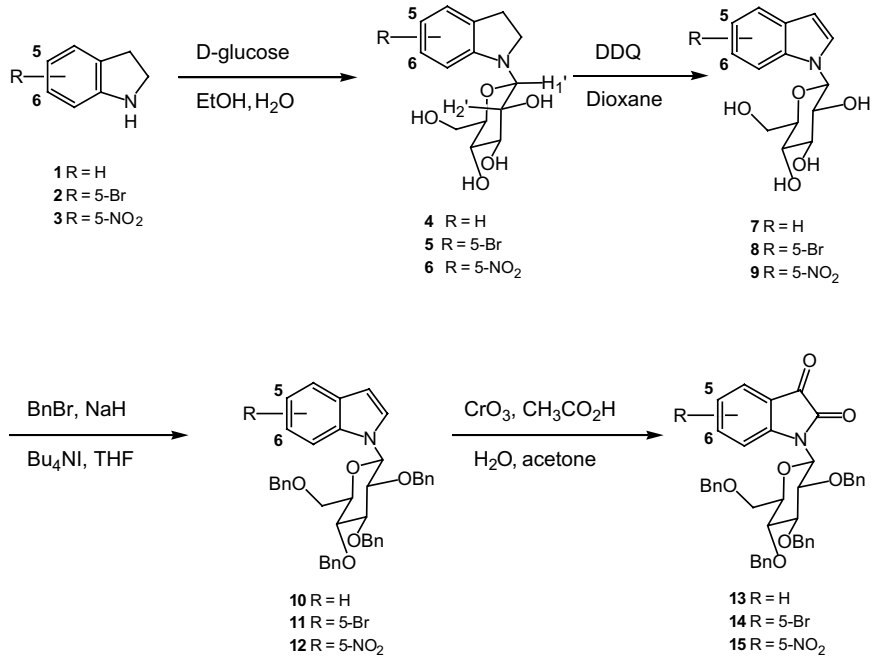
Natura 1-(β-D-*O*-triacetylxylopyranosyl)-isoindigo

Scheme 4.

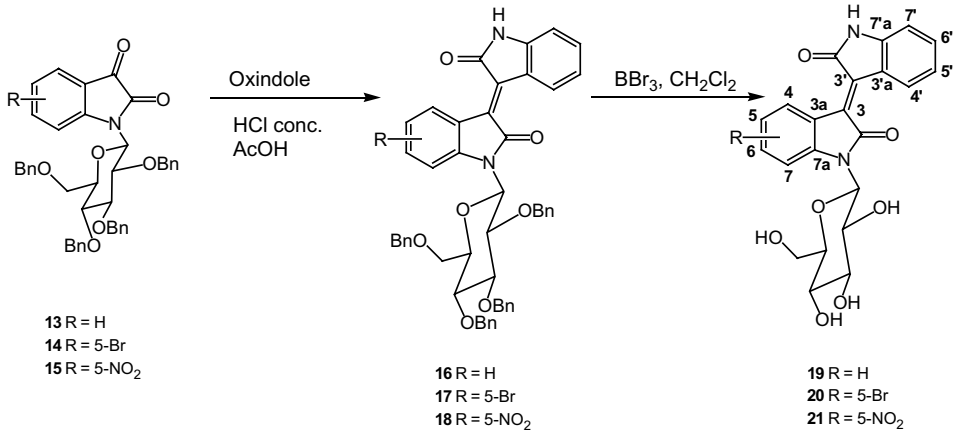
2. Chemistry

Recently, we described the synthesis of the glycosyl-isatine **13** in four steps from the corresponding commercially available indoline[3] (Scheme 5).

The glycosyl-indoline **4** was prepared by glycosylation of indoline **1**. The glycosylation step led to a single isomer with a β-*N*-glycosydic bond; this configuration was determined from ^{1}H NMR spectrum by the measurement of the coupling constant ($J = 8$ Hz) between $H_{1'}$ and $H_{2'}$. The corresponding indole **7** was obtained by oxidation with DDQ. To synthesize compound **13**, the hydroxy groups of the intermediate **7** were first protected before oxidation with chromium oxide. The



Scheme 5.



Scheme 6.

syntheses of glycosyl-isatin derivatives substituted on the aromatic ring either by electron donor or acceptor substituents **14**–**15** were achieved using the same approach (Scheme 5, Table 1).

The indoline **2** (starting material for the synthesis of **14**) was prepared in 81% yield from the corresponding *N*-acetyl analogue by basic hydrolysis. The first two steps were more difficult with electron acceptor susbtituents. Indeed, the glycosylation step was performed in 24 h with compounds **1**–**2** and 6 days for compound **3** bearing a nitro group in the 5 position. The aromatization step using DDQ was carried at room temperature during 12 h for **4**–**5** and at 50 °C during 72 h for **6**.

To obtain the corresponding glycosyl-isoindigo derivatives, compounds **13**–**15** were treated in an acidic medium[9,10] in the presence of oxindole. Deprotection of the hydroxy groups of the glycosyl moiety was performed by reaction of derivatives **16**–**18** with boron tribromide to give compounds **19**–**21** (Scheme 6, Table 1).[11–15]

Surprisingly, in contrast with derivatives **4**–**15**, the ^{1}H NMR signal of $H_{1'}$ for compounds with an isoindigo moiety **16**–**21** is not a doublet but appeared as a broad signal suggesting that the conformation of the sugar moiety could be different. Molecular modeling experiments are in progress to determine the conformation of the carbohydrate in our glycosyl-isoindigo derivatives.

In conclusion, we have described the preparation of diversely substituted 1-(β-D-glucopyranosyl)-isoindigos. The synthesis described here allows the substitution of the aromatic rings by either electron donor or acceptor

Table 1. Chemical yields for the synthesis of compounds **4**–**21**

Compounds	Yields (%)
4	95
5	66
6	80
7	74
8	88
9	65
10	78
11	82
12	64
13	62
14	49
15	66
16	40
17	40
18	25[a]
19	60
20	59
21	18[a]

[a] Chemical yield not optimized.

substituents what was not clearly established in the synthetic pathway described in the patents.[7,8] The biological properties of these compounds are currently under investigation.

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10. Typical procedure for preparation of **16**: A solution of glycosylisatine **13** (130 mg, 0.19 mmol) and oxindole (26 mg, 0.19 mmol) in a mixture of acetic acid (0.4 mL), and concentrated HCl (2.6 μL) was refluxed for 24 h. After cooling, EtOAc was added to the mixture, the organic phases were washed twice with H_2O, dried over $MgSO_4$, and concentrated under vacuum to give a residue, which was purified by flash chromatography (eluent cyclohexane/EtOAc 80:20). Compound **16** was obtained as red crystals (mp = 205 °C) with 40% yield.
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12. Typical procedure for preparation of **19**: BBr_3 (1.5 mL, 1.5 mmol) was added to a cooled (−80 °C) solution of **16** (80 mg, 0.102 mmol) in CH_2Cl_2 (9.5 mL). The mixture was stirred for 12 h before hydrolysis at −80 °C and warm up to room temperature. After decantation and extraction with EtOAc, the organic phases were dried over $MgSO_4$, and concentrated under vacuum to give a residue, which was purified by chromatography (eluent EtOAc/MeOH from 95:5 to 85:15). The glycosyl isoindigo **19** was obtained as a red solid (mp >300 °C) in 60% yield.
13. Spectral data of **19**: IR (KBr): $\nu_{NH,OH}$: 3377 cm^{-1}; $\nu_{C=O}$: 1696, 1680 cm^{-1}; $\nu_{C=C}$: 1604 cm^{-1}. HRMS (FAB+) calcd for $C_{22}H_{21}N_2O_7$ $[M+H]^+$: 425.1349. Found: 425.1357. ^1H (400 MHz, DMSO-d_6): 3.29–3.46 (m, 3H), 3.52–3.59 (m, 1H), 3.78–3.84 (m, 1H), 3.86–4.02 (br s, 1H); 4.68 (t, $J = 5.5$ Hz, 1H, OH), 5.18 (d, $J = 5.0$ Hz, 1H, OH); 5.22 (d, $J = 5.0$ Hz, 1H, OH), 5.40 (d, $J = 5.0$ Hz, 1H, OH), 5.36–5.44 (br s, 1H, $H_{1'}$), 6.92 (d, $J = 7.5$ Hz, 1H, $H_{7'}$), 7.04 (t, $J = 8.0$ Hz, 1H, $H_{5'}$), 7.13 (t, $J = 7.5$ Hz, 1H, H_5), 7.28 (d, $J = 8.0$ Hz, 1H, H_7), 7.42 (t, $J = 7.5$ Hz, 1H, $H_{6'}$), 7.48 (t, $J = 7.5$ Hz, 1H, H_6), 9.05 (d, $J = 8.0$ Hz, 1H, $H_{4'}$), 9.19 (d, $J = 7.5$ Hz, 1H, H_4), 11.0 (s, 1H, NH). ^{13}C (100 MHz, DMSO-d_6): 61.0 (CH_2), 68.4, 69.8, 77.3, 80.1, 81.9 (CH_{sugar}), 109.7 ($C_{7'}$), 111.5 (C_7), 121.2 ($C_{5'}$), 121.7 (C_5), 128.8 (C_4), 129.4 ($C_{4'}$), 132.3 (C_6), 132.9 ($C_{6'}$), 121.1 (C_{3a}), 121.6 ($C_{3'a}$), 132.1 (C_3), 134.0 ($C_{3'}$), 142.3 (C_{7a}), 144.3 ($C_{7'a}$), 167.0, 168.7 (C=O).
14. Spectral data of **20** obtained as a red solid (mp >300 °C): IR (KBr): $\nu_{NH,OH}$: 3540, 3500–3200 cm^{-1}; $\nu_{C=O}$: 1700, 1680 cm^{-1}; $\nu_{C=C}$: 1620, 1600 cm^{-1}. ^1H (400 MHz, DMSO-d_6): 3.27–3.45 (m, 3H), 3.49–3.58 (m, 1H), 3.78 (dd, $J_1 = 11.0$ Hz, $J_2 = 5.0$ Hz, 1H), 3.79–3.96 (m, 1H); 4.66 (t, $J = 5.5$ Hz, 1H, OH), 5.17 (d, $J = 5.0$ Hz, 1H, OH), 5.21 (d, $J = 4.0$ Hz, 1H, OH), 5.34–5.39 (m, 1H), 5.40 (d, $J = 5.0$ Hz, 1H, OH), 6.91 (d, $J = 8.0$ Hz, 1H), 7.03 (td, $J_1 = 8.0$ Hz, $J_2 = 1.0$ Hz, 1H), 7.23 (d, $J = 8.5$ Hz, 1H), 7.43 (td, $J_1 = 7.5$ Hz, $J_2 = 1.0$ Hz, 1H), 7.64 (dd, $J_1 = 8.5$ Hz, $J_2 = 2.0$ Hz, 1H), 9.04 (d, $J = 8.0$ Hz, 1H), 9.43 (d, $J = 2.0$ Hz, 1H); 11.04 (s, 1H, NH). ^{13}C (100 MHz, DMSO-d_6): 61.0 (CH_2), 68.4, 69.7, 77.2, 80.1, 82.0 (CH_{sugar}), 109.9, 113.3, 121.3, 129.8, 130.9, 133.6, 134.2 ($CH_{arom.}$), 113.7, 121.4, 122.9, 130.4, 135.6, 141.2, 144.7 ($C_{quat.\ arom.}$), 166.6, 168.7 (C=O).
15. Spectral data of **21** obtained as a red solid (mp >300 °C): IR (KBr): $\nu_{NH,OH}$: 3424 cm^{-1}; $\nu_{C=O}$: 1720, 1703 cm^{-1}; $\nu_{C=C}$: 1618 cm^{-1}. ^1H (400 MHz, DMSO-d_6): 3.30–3.45 (m, 3H), 3.47–3.58 (m, 1H), 3.80 (dd, 1H, $J_1 = 10.5$ Hz, $J_2 = 5.5$ Hz), 3.76–3.95 (m, 1H), 4,70 (t, $J = 5.5$ Hz, 1H, OH), 5.21 (d, $J = 5.0$ Hz, 1H, OH), 5.23 (d, $J = 4.5$ Hz, 1H, OH), 5.45 (d, $J = 4.5$ Hz, 1H, OH), 5.38–5.45 (br s, 1H, $H_{1'}$), 6.94 (d, $J = 7.7$ Hz, 1H), 7.09 (td, $J_1 = 8.0$ Hz, $J_2 = 1.0$ Hz, 1H), 7.47 (td, $J_1 = 7.5$ Hz, $J_2 = 1.0$ Hz, 1H), 7.51 (d, $J = 9.0$ Hz, 1H), 8.38 (dd, $J_1 = 9.0$ Hz, $J_2 = 2.5$ Hz, 1H), 9.05 (d, $J = 8.0$ Hz, 1H), 10.21 (d, $J = 2.5$ Hz, 1H), 11.10 (s, 1H, NH). ^{13}C (100 MHz, DMSO-d_6): 61.0 (CH_2), 68.7, 69.7, 77.0, 80.2, 82.2 (CH_{sugar}), 110.1, 111.7, 121.5, 124.2, 127.6, 130.0, 134.2 ($CH_{arom.}$), 121.1, 121.2, 129.2, 136.9, 142.1, 145.2, 147.0 ($C_{quat.\ arom.}$), 167.1, 168.7 (C=O).