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Facile syntheses of 7,9-dimethoxypyrrolo[3,2,1-*ij*]quinolin-6-ones

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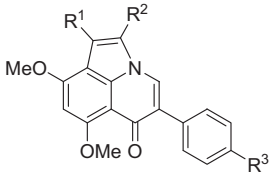
ABSTRACT

The activated dimethoxypyrrolo[3,2,1-*ij*]quinolin-6-one ring system was synthesized via two approaches, starting from an indole and quinolin-4-one, respectively. Subsequent demethylation led to both monohydroxy- and dihydroxypyrrolo[3,2,1-*ij*]quinolin-6-ones.

The pyrrolo[3,2,1-*ij*]quinoline system is an important heterocyclic scaffold that has been investigated for potential therapeutic use.[1] Pyrrolo[3,2,1-*ij*]quinolines possess a range of biological activities including analgesic, anti-pyretic, anti-inflammatory, and anti-convulsant. They also exist in a variety of oxidised forms which show a range of medicinal effects.[2] For example, 1,2,5,6-tetrahydropyrrolo[3,2,1-*ij*]quinolin-4-one (4-lilolidone),[3] 2-lilolidone,[4] and their derivatives show effective fungicidal activity against microbes causing rice blast disease.[5]

However, there have been no reports of the isolation or activity of any naturally occurring pyrroloquinolin-6-ones. Hence the chemistry and potential bioactivity of these compounds remains relatively unexplored. Moreover, pyrroloquinolin-6-ones are structurally related to the natural isoflavones, which are known to have a wide range of medicinal properties. In particular, the 5-phenylpyrrolo [3,2,1-*ij*]quinolin-6-one scaffold **1** was selected for this study on the basis of its structural similarity and related oxygenation pattern to the isoflavone genistein (**2**), which has anti-tumour activity.[6]



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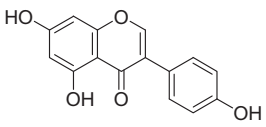

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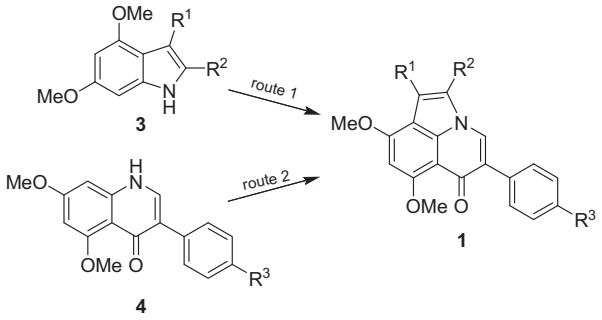
Herein we describe two alternate strategies for preparing the target system **1**. The first approach starts with an indole **3** and entails the construction of the six-membered pyridone ring between C7 and N1. The second route begins with quinolin-4-one **4** and involves formation of the corresponding pyrrole ring (Scheme 1).

Our group has previously investigated the reactivity of several 3-aryl and 2,3-disubstituted 4,6-dimethoxyindoles towards electrophilic substitution reactions and established routes for the synthesis of a variety of C7 and C2 substituted heterocyclic compounds.[2,7] It was therefore anticipated that the pyrroloquinolin-6-one nucleus **1** could be synthesized by C7 acylation of 4,6-dimethoxyindoles **3** followed by cyclisation of the resulting 7-indolyldeoxybenzoins **6** with a suitable one carbon reagent; a route used extensively for the preparation of isoflavones.[8,9]



Scheme 1. Synthetic strategies for 7,9-dimethoxypyrrolo[3,2,1-*ij*]quinolin-6-ones.

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Friedel–Crafts acylation of 4,6-dimethoxy-3-phenylindole (**3a**) with 4-methoxyphenylacetyl chloride and stannic chloride afforded only poor yields of 7-indolylideoxybenzoin **6b** and 2-indolylideoxybenzoin **7b**, with the undesired 2-isomer **7b** as the major product. Reaction optimisation was performed, however, it appeared that the indole nucleus complexed with tin salts, thus hindering the acylium ion from reacting at C7 as desired.

Vilsmeier–Haack conditions were subsequently examined in order to overcome this lack of regiochemical control, with 3-aryl-4,6-dimethoxyindoles **3a** and **3b** being reacted with *N*,*N*-dimethylarylacetamides **5** in phosphoryl chloride, initially at 0 °C and then with heating at 70 °C for 1 h. 7-Indolylideoxybenzoins **6** and 2-indolylideoxybenzoins **7** were obtained in only low yields, which was attributed to decomposition of the acid sensitive 3-aryl-4,6-dimethoxyindoles under these concentrated conditions. However, the use of halogenated solvents such as dichloromethane or chloroform was found to facilitate the reactions and generally improved the yields, though the ratio of 7-indolylideoxybenzoins **6** to 2-indolylideoxybenzoins **7** varied (Scheme 2, Table 1, entries 1–4). In contrast, the 2,3-disubstituted indole system **3c** reacted exclusively at the 7-position, producing an 85% and 65% yield of 7-indolylideoxybenzoins **6e** and **6f**, respectively, in the presence of a chlorinated solvent (Table 1, entries 5 and 6).

The synthesis of isoflavones from deoxybenzoins has been efficiently achieved upon treatment with boron trifluoride diethyl etherate and methanesulfonyl chloride in DMF.[9] However, the analogous cyclisation of 7-indolylideoxybenzoins **6** to pyrrolo[3,2,1-*ij*]quinolin-6-ones **1** using these reagents gave poor results, possibly due to a competing formylation reaction at the indole C2 position. Efficient cyclisation was instead achieved through treatment of 7-indolylideoxybenzoins **6** with *N*,*N*-dimethylformamide-dimethyl acetal (DMF-DMA) at 160 °C for 24 h in toluene or tetrahydrofuran in a pressure tube. The resulting pyrrolo[3,2,1-*ij*]quinolin-6-ones **1** were afforded in good yields and purity (Scheme 3, Table 2).[10]

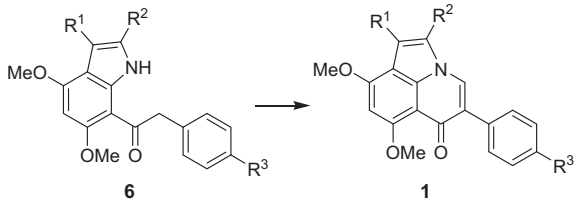
The structures of pyrroloquinolin-6-ones **1** were elucidated through a combination of analytical techniques. The ^{1}H NMR spectra of compounds **1a–e** displayed characteristic singlets at δ 6.5 and δ 7.9 which corresponded to H8 and H4, respectively. The 3-substituted analogues **1a–c** also displayed a characteristic H2 singlet at δ 7.2. The carbonyl carbon was observed between δ 175 and 179 ppm in the ^{13}C NMR spectra, which is consistent with other pyrroloquinolin-6-one examples. Formation of the pyrrolo[3,2,1-*ij*]quinolin-6-one nucleus was also confirmed by the X-ray crystal structure of compound **1d** (Fig. 1).

Overall, this strategy led to the successful preparation of the target pyrrolo[3,2,1-*ij*]quinolin-6-ones **1**, however, the poor yields and selectivity observed in the first step led to subsequent examination of an alternative approach.

It was anticipated that 5,7-dimethoxy-3-aryl-quinolin-4-ones **4** could undergo N-acylation with suitable α-bromoacetophenones to give quinolinoketones that could then undergo acid-catalysed cyclisation to generate pyrrolo[3,2,1-*ij*]quinolin-6-ones **1**.

Table 1
Synthesis of 7- and 2-indolylideoxybenzoins

Entry	R^1	R^2	R^3	**6**	Yield (%)	**7**	Yield (%)
1	Ph	H	H	**6a**	40	**7a**	2
2	Ph	H	MeO	**6b**	15	**7b**	trace
3	4-BrC_6H_4	H	H	**6c**	39	**7c**	47
4	4-BrC_6H_4	H	MeO	**6d**	24	**7d**	16
5	Ph	Ph	H	**6e**	85	—	—
6	Ph	Ph	MeO	**6f**	65	—	—



Scheme 3. Reaction conditions: DMF-DMA, anhyd THF, 160 °C, 24 h, pressure tube.[10]

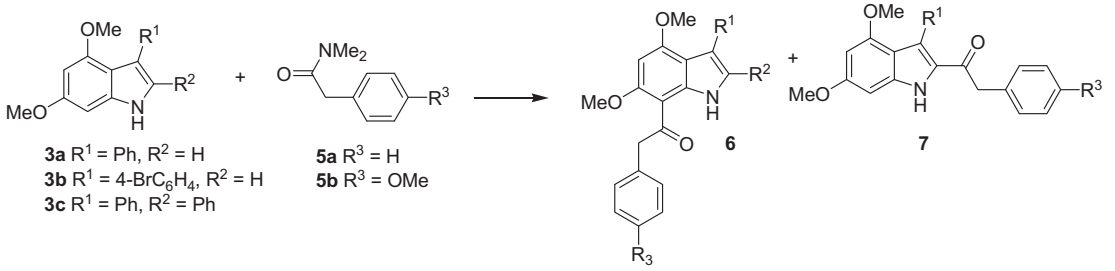
Table 2
Cyclisation of 7-indolylideoxybenzoins **6**

Entry	R^1	R^2	R^3	Product	Yield (%)
1	Ph	H	H	**1a**	51
2	4-BrC_6H_4	H	H	**1b**	92
3	4-BrC_6H_4	H	MeO	**1c**	62
4	Ph	Ph	H	**1d**	91
5	Ph	Ph	MeO	**1e**	97

Treatment of 5,7-dimethoxy-3-aryl-quinolin-4-ones **4a,b** for 4 h at room temperature with substituted α-bromoacetophenones **8** in DMF and in the presence of potassium carbonate afforded the desired quinolinoketones **9** in good yields of 60–68% (Scheme 4, Table 3). Interestingly, reaction of the less activated quinolinone **4b** afforded a much lower yield of 34%. The ensuing cyclisation reaction was performed at reflux for 1 h using polyphosphoric acid (PPA) and generated the pyrroloquinoline analogues **1** in good yields.

In comparison to the first investigated approach, this second synthetic route beginning from a quinolin-4-one proved to be a more versatile and efficient method of preparing pyrrolo[3,2,1-*ij*]quinolin-6-ones, though less activated analogues gave poorer yields across both steps.

In general, the phenolic isoflavones have far greater biological efficacy compared to their methylated analogues[12] and therefore the demethylation of these pyrroloquinolin-6-one systems was also of interest. Selective demethylation of the C7-methoxy group was performed by stirring pyrrolo[3,2,1-*ij*]quinolin-6-ones **1** at room temperature for 18 h with 4 equiv of boron tribromide, affording monohydroxy compounds **10a–c** in low 18–23% yields



Scheme 2. Reaction conditions: $POCl_3$, halogenated solvent, Δ, 1–2 h.

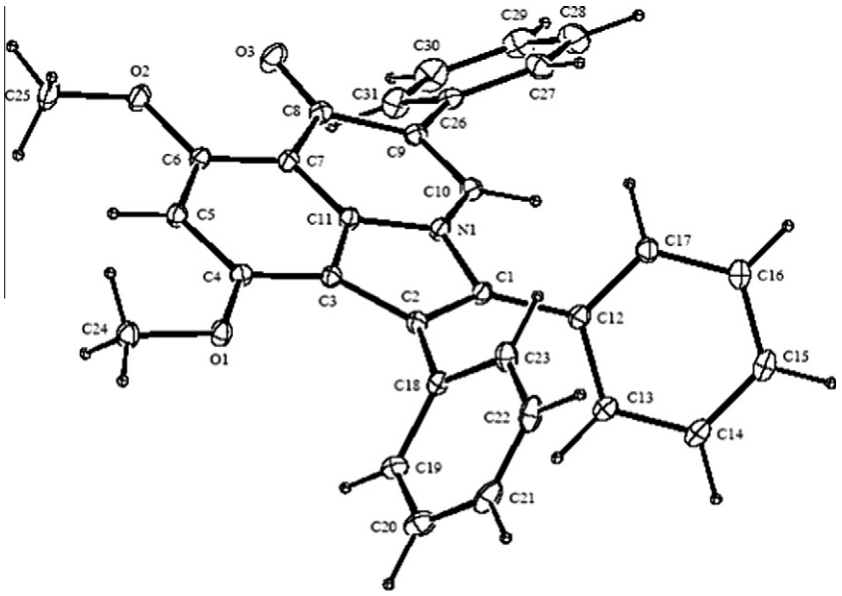
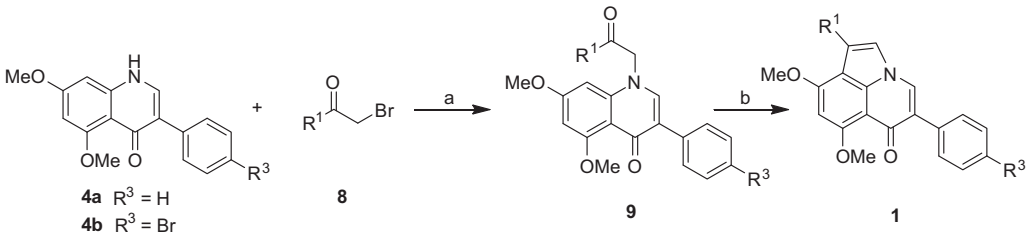


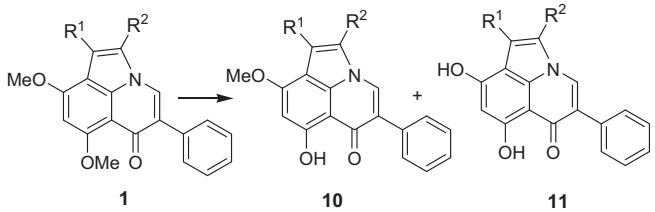
Figure 1. ORTEP diagram of compound **1d**.[11]



Scheme 4. Reaction conditions: (a) K_2CO_3, DMF, rt, 4 h; (b) PPA, reflux, 1 h.

Table 3
Synthesis of pyrrolo[3,2,1-*ij*]quinolin-6-ones 1

Entry	R^1	R^3	9	Yield (%)	1	Yield (%)
1	Ph	H	**9a**	68	**1a**	58
2	4-BrC_6H_4	H	**9b**	66	**1b**	56
3	4-FC_6H_4	H	**9c**	64	**1f**	56
4	4-ClC_6H_4	H	**9d**	60	**1g**	54
5	4-FC_6H_4	Br	**9e**	34	**1h**	30



Scheme 5. Reaction conditions: (a) BBr_3, CH_2Cl_2, rt, 18 h; (b) $CeCl_3.7H_2O$, NaI, MeCN, reflux, 8 h; (c) $AlCl_3$, chlorobenzene, reflux; (d) 48% HBr, AcOH, reflux, 72 h.

(Scheme 5, Table 4, entries 1–3). Alternatively, heating pyrroloquinolin-6-ones **1** at reflux with cerium trichloride and sodium iodide in acetonitrile for 8 h resulted in the monohydroxy compounds **10b** and **10c** being produced in higher yields of 40% and 48%, respectively (Table 4, entries 4 and 5). The ^1H NMR spectrum of compound **10b** showed the single methoxy resonance at δ 4.01 and the new hydroxy resonance at δ 12.55. The high chemical shift of the hydroxy group, coupled with the IR stretching frequency at

Table 4
Demethylation of pyrrolo[3,2,1-*ij*]quinolin-6-ones **1**

Entry	R^1	R^2	10	Yield (%)	11	Yield (%)
1	Ph	H	**10a**	18	**11a**	—
2	4-BrC_6H_4	H	**10b**	21	**11b**	—
3	4-FC_6H_4	H	**10c**	23	**11c**	—
4	4-BrC_6H_4	H	**10b**	40	**11b**	—
5	4-FC_6H_4	H	**10c**	48	**11c**	—
6	4-BrC_6H_4	H	**10b**	20	**11b**	—
7	4-BrC_6H_4	H	**10b**	10	**11b**	5
8	4-BrC_6H_4	H	**10b**	—	**11b**	10
9	Ph	Ph	**10d**	40	**11d**	53

2918 cm^{-1}, was indicative of hydrogen bonding to the adjacent carbonyl moiety.

Synthesis of the corresponding dihydroxypyrroloquinolin-6-ones **11** proved to be more problematic. Heating pyrroloquinolin-6-one **10b** with 3 equiv of aluminium trichloride in chlorobenzene for 1 h returned only the monohydroxy compound **10b** in 20% yield (Table 4, entry 6). Extending the reaction time to 3 h led to a mixture of the monohydroxy and dihydroxy compounds **10b** and **11b** being produced (Table 4, entry 7), while heating at reflux for 8 h led to exclusive formation of the dihydroxy compound **11b**, though only a low yield of 10% was obtained (Table 4, entry 8). Both the methoxy resonances were absent from the ^1H NMR spectrum of compound **11b**, and the presence of a broad IR peak at 3297 cm^{-1} confirmed the presence of free hydroxy groups.

Demethylation of the 1,2-disubstituted analogue **1d** was found to be more robust than the corresponding 1-substituted compounds, with a 40% yield of the monohydroxypyrroloquinolin-6-

one **10d** and 53% yield of the dihydroxypyrroloquinolin-6-one **11d** being obtained upon treatment with 48% hydrobromic acid in glacial acetic acid (Table 4, entry 9). In general, the dihydroxypyrroloquinolin-6-ones **11** were found to be difficult to isolate and purify due to their low stability and susceptibility to degradation.

In conclusion, 7,9-dimethoxypyrrolo[3,2,1-*ij*]quinolin-6-ones **5** were prepared in two steps from both indole and quinolin-4-one starting materials. Demethylation of these 7,9-dimethoxypyrrolo[3,2,1-*ij*]quinolin-6-ones **1** was performed, with selective C7-demethylation being achieved in the presence of cerium trichloride and the dihydroxy analogues being obtained upon treatment with aluminium trichloride.

Acknowledgments

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9. Bass, R. J. *J. Chem. Soc., Chem. Commun.* **1976**, *2*, 78–79.
10. Representative procedure for the synthesis of pyrrolo[3,2,1-*ij*]quinolin-6-ones **1**: A mixture of 7-indolyldeoxybenzoin **6e** (0.400 g, 0.88 mmol) and *N*,*N*-dimethylformamide-dimethyl acetal (2 mL) in THF (2 mL) was heated in a pressure tube at 160 °C for 24 h. The resulting solid was filtered and washed with H_2O to afford **1b** as a yellow solid (0.347 g, 92%). Mp 306–307 °C (from $CHCl_3$/MeOH). Found: C, 65.04; H, 4.05; N, 2.96%. $C_{25}H_{18}BrNO_3$ requires: C, 65.23; H, 3.94; N, 3.04%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.96 (s, 3H, OMe), 4.08 (s, 3H, OMe), 6.50 (s, 1H, H8), 7.23 (s, 1H, H2), 7.35–7.42 (m, 3H, ArH), 7.54 (s, 4H, ArH), 7.60 (d, J = 8.7 Hz, 2H, ArH), 7.95 (s, 1H, H4). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.6, 56.6, 91.5, 107.5, 107.9, 120.2, 121.3, 124.2, 127.5, 127.9, 129.0, 129.2, 130.5, 131.1, 132.4, 134.9, 136.8, 159.2, 162.1, 175.6. IR (Nujol): ν_{max} 1643, 1622, 1595, 1537, 1460, 1434, 1377, 1354, 1322, 1309, 1295, 1213, 1178, 1138, 1093, 1051, 1005, 807, 767 cm^{-1}. UV (MeOH): λ_{max} 206 nm (ε 61121 cm^{-1} M^{-1}), 259 (53618), 345 (20508), 368 (19641). MS (ESI): m/z 482, [M+Na]$^+$ (35%).
11. Crystallographic data for the structure of **1d** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication No. CCDC 823849. X-ray crystal structures were obtained by Don Craig, Crystallography Laboratory, UNSW Analytical Centre, Sydney, Australia.
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