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Expeditious Synthesis and Cytotoxic Activity of New Cyanoindolo[3,2-*c*]quinolines and Benzimidazo[1,2-*c*]quinazolines

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Abstract—Novel 6-cyanoindolo[3,2-*c*]quinoline and 6-cyanobenzimidazo[1,2-*c*]quinazoline derivatives have been synthesised by treatment of the appropriate aromatic amines with 4,5-dichloro-1,2,3-dithiazolium chloride **1** (Appel salt). The cytotoxicity and the effect of these compounds on cellular growth were measured.

Introduction

Cryptosanguinolentine, a member of a family of indolo[3,2-*c*]quinolines, is very rare in Nature and has been isolated in 1996 from a West African plant *Cryptolepsis sanguinolenta*.[1] In recent years, considerable interest has arisen for the synthesis of indoloquinoline derivatives, due to their potential pharmaceutical value (these compounds can interact with DNA and are studied for their antitumour activity).[2] As part of our work on the applicability of 4,5-dichloro-1,2,3-dithiazolium chloride **1** (Appel salt) to the synthesis of polyheterocyclic systems of potential pharmacological value,[3] we have discovered that condensation of 2-(2-aminophenyl)indole and Appel salt **1** leads to new 6-cyanoindolo[3,2-*c*]quinoline derivatives which are related to cryptosanguinolentine. In this paper we describe the rapid synthesis of these compounds and their cytotoxic evaluation. Preparation of a cyanobenzimidazoquinazoline analogue, obtained by treatment of 2-(2-aminophenyl)benzimidazole with the salt **1**, is also detailed.

Chemistry

It is now well known that reaction of 4,5-dichloro-1,2,3-dithiazolium chloride **1** (Appel salt) with primary aromatic amines allows access to *N*-arylimino-1,2,3-dithiazoles, usually in high yield.[4] These imines have proved to be very versatile synthetic intermediates in heterocyclic chemistry, undergoing a variety of reactions initiated by nucleophilic attack at different sites on the dithiazole ring (the driving force being the regeneration of the latent cyano group in the dithiazole ring, see Figure 1).

For example, they can be converted into 2-cyano derivatives of benzothiazoles,[5] benzoxazines,[6] imidazoles[7] and quinazolines.[8]

Exploring the chemistry of Appel salt, we planned to prepare the imino-1,2,3-dithiazole **2**, resulting from the reaction of **1** with 2-(2-aminophenyl)indole, and to study the cyclisation process of such compounds into new indole derivatives (**3** and/or **4**, Scheme 1) with angular fused annelated patterns in which the presence of a cyano group may increase the cytotoxic activity as we recently demonstrated with benzothiazoles.[9]

Following the usual methods,[3–8] treatment of 2-(2-aminophenyl)indole with 4,5-dichloro-1,2,3-dithiazolium chloride **1** in dichloromethane at room temperature in the presence of pyridine (2 equiv) gave a product in satisfactory yield (60%) which was identified as the cyclised indolo[3,2-*c*]quinoline **3**.[10] Formation of this tetracyclic compound could involve a rapid cyclisation of the supposed intermediate **2** in a mechanism related to the

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process previously described by Molina for the preparation of such rings by intramolecular reaction of iminophosphoranes with isocyanates.[11] Formation of the indolo[3,2-*c*]quinoline ring suggests nucleophilic attack by carbon 3 of the indole ring at the imino-carbon, with loss of both sulfur atoms from the dithiazole ring (Scheme 2). Whichever method was applied (tetrahydrofuran instead of dichloromethane, low temperatures) none of the alternative ring closed product, indolo[1,2-*c*]quinazoline **4**, was detected.

Alkylation of **3** in the presence of bases led to *N*-substituted products, **5** and **6**, in reasonable yields (57 and 60%, respectively). This result confirmed the indolo[3,2-*c*] quinoline structure of **3**. The new benzimidazo[1,2-*c*] quinazoline analogue **7** was also prepared in reasonable yield (50%) by treatment of 2-(2-aminophenyl)benzimidazole with Appel salt **1**, following the conditions described above. In order to evaluate the impact of the cyano group on the biological activity of the rings prepared, the parent benzimidazo[1,2-*c*]quinazoline **8**[12] was obtained by cyclocondensation of triethylorthoformate with 2-(2-aminophenyl)benzimidazole in *N,N*-dimethylacetamide.

Cytotoxicity Activity and Cell Cycle Effects

The antiproliferative activity of compounds **3**, **5**, **6**, **7** and **8** were assessed using the murine L1210 leukemia cell line.[13] The results, expressed as IC_{50} (concentration reducing 50% of the cell proliferation), are reported in Table 1. For the most active compounds (IC_{50} $< 10\,\mu M$), cytotoxicity was evaluated on the HT29 cell line as well as the perturbations induced on the L1210 cell cycle. Both compounds **5** and **7** were found able to block significantly the L1210 cells in the $G_2 + M$ phase of the cell cycle. Introduction of the *N,N*-dimethylaminoethyl chain on the indoloquinoline skeleton led to the significantly more active cyano compound **5** which exhibits a sub-micromolar activity on the HT-29 cell

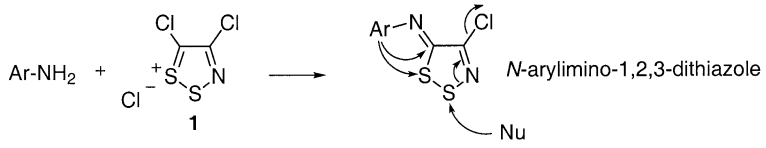
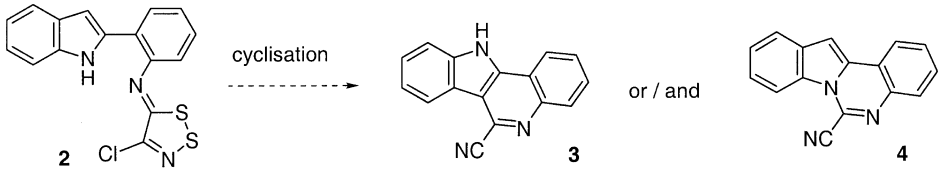
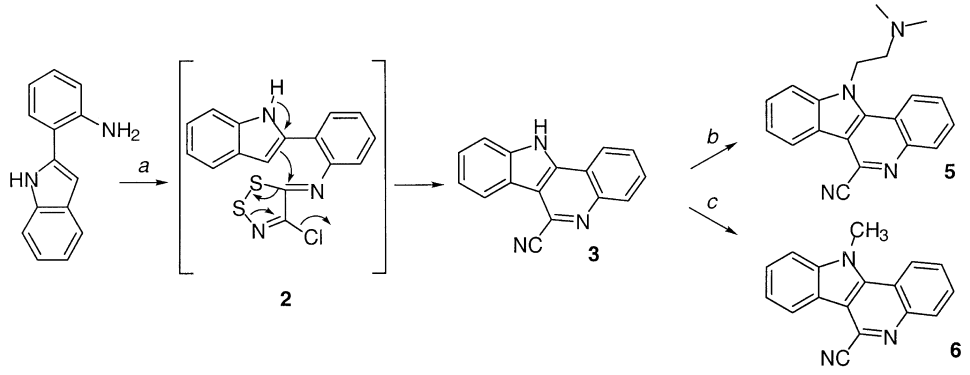


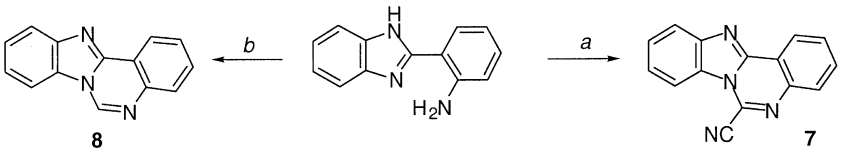
Figure 1.



Scheme 1.



Scheme 2. Reactions and conditions: (a) **1**, pyridine, CH_2Cl_2, rt, 2 h, 60%; (b) Cl-$(CH_2)_2$-N$(CH_3)_2$·HCl, NaH, THF/DMF, reflux, 3.5 h, 57%; (c) CH_3I, K_2CO_3, CH_3CN, reflux, 3 h, 60%.



Scheme 3. Reactions and conditions: (a) pyridine, CH_2Cl_2, rt, 2 h, 50%; (b) $HC(OEt)_3$, dimethylacetamide, reflux, 1.5 h, 85%.

Table 1. Cytotoxicity and antiproliferative activity results for compounds **3** and **5–8**

Compound	Formula	Cytotoxicity		Percent of L1210 cells in the cell cycle phases[a]	
		IC_{50} L1210 (μM)	IC_{50} HT29 (μM)	G_2+M (μM)	$>G_2+M$ (8N) (μM)
3	$C_{16}H_9N_3$	>100	ne[b]	ne	ne
5	$C_{20}H_{18}N_4$	3.1	0.68	50% (10)	21% (10)
6	$C_{17}H_{11}N_3$	58.8	ne	ne	ne
7	$C_{15}H_8N_4$	5.4	5.2	61% (10)	in[c]
8[12]	$C_{19}H_9N_3$	>100	ne	ne	ne

[a]Percent of untreated control cells in the phases of the cell cycle: 41% (G_1); 28% (S); 24% (G_2+M); 1% (8N).
[b]ne = Not evaluated (for IC_{50} >10 (μM).
[c]in = Inactive.

line (IC_{50} = 0.68 μM). The cyanobenzimidazoquinazoline **7** was also found more active than its parent compound **8** and the indoloquinoline analogue **3**.

In conclusion we have described the synthesis of new 6-cyanoindoloquinoline and benzimidazoquinazoline derivatives which exhibit interesting and significant in vitro cytotoxic activity. As we observed for various 2-cyanobenzothiazoles, the presence of the cyano group on the indolo[3,2-*c*]quinoline or benzimidazo[1,2-*c*]quinazoline rings led to enhanced cytotoxicity but did not apparently involve any specific effect on the cell cycle.

Acknowledgements

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10. Spectral data for compounds **5**, **6** and **8** are consistent with assigned structures. Selected data for **3** and **7**: 11*H*-indolo[3,2-*c*]quinoline-6-carbonitrile **3**: Brown powder, mp >260 °C (from acetonitrile) (Found: C, 78.7; H, 3.6; N, 17.2. $C_{16}H_9N_3$ requires C, 79.0; H, 3.7; N, 17.3); ν_{max} (KBr)/cm^{-1} 3312 (NH), 2294, 2238 (CN), 1562, 1504, 1462, and 735; δ_H (400 MHz, DMSO-d_6 + D_2O) 7.43 (1H, t, *J* 7.6 Hz, H_{Ar}), 7.59 (1H, t, *J* 7.6 Hz, H_{Ar}), 7.74 (1H, d, *J* 8.2 Hz, H_{Ar}), 7.78–7.87 (2H, m, H_{Ar}), 8.15 (1H, d, *J* 8.2 Hz, H_{Ar}), 8.31 (1H, d, *J* 8.1 Hz, H_{Ar}), 8.44 (1H, d, *J* 8.2 Hz, H_{Ar}); δ_C (100 MHz, DMSO-d_6) 112.5, 114.5, 117.3, 117.4, 119.3, 199.7, 121.6, 122.3, 126.0, 127.1, 128.4, 129.6, 129.7, 139.2, 141.0, 144.7; *m*/*z* 243 (M^+, 100%), 215 (7), 189 (4), 164 (2). Benzo[4,5]imidazo[1,2-*c*]quinazoline-6-carbonitrile **7**: Pale yellow powder, mp 252–254 °C (from ethanol) (Found: C, 73.9; H, 3.3; N, 22.8. $C_{15}H_8N_4$ requires C, 73.8; H, 3.3; N, 22.9); ν_{max} (KBr)/cm^{-1} 3048, 2242 (CN), 1950, 1588, 1525, 1449, 1383, 1328, 1203 and 746; δ_H (400 MHz, $CDCl_3$) 7.59 (1H, ddd, *J* 7.7, 7.2 and 1.2 Hz, H_{Ar}), 7.67 (1H, ddd, *J* 7.7, 7.2 and 1.2 Hz, H_{Ar}), 7.81–7.91 (2H, m, H_{Ar}), 8.04–8.09 (2H, m, H_{Ar}), 8.58 (1H, d, *J* 8.3 Hz, H_{Ar}), 8.71–8.75 (1H, m, H_{Ar}); δ_C (100 MHz, DMSO-d_6), 112.1, 112.3, 119.9, 120.5, 122.1, 124.3, 124.4, 127.1, 127.4, 129.2, 131.3, 132.3, 141.1, 144.0, 145.9; *m*/*z* 244 (M^+, 100%), 217 (1), 191 (3), 164 (3).
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