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Synthesis and Antiproliferative Evaluation of 7-Aminosubstituted Pyrroloiminoquinone Derivatives

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Abstract—Coupling of five amines on the 7-methoxy-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline core was achieved and afforded, in particular, an opened analogue of the natural alkaloid wakayin. Evaluation of cytotoxic activity of compounds **2**, **10**–**13** on L1210 cells afforded IC_{50} in the range 0.25–5.3 μM. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

Since the discovery of discorhabdin C in 1986 until isolation and characterization of veuitamine in 1997, more than 40 pyrroloiminoquinone alkaloids have been isolated from sponges and ascidians.[1] For these marine organisms devoid of skeleton and immune system, fixed or not very mobile, secondary metabolites would have a basic role in communication, defense or attack towards other organisms.

Pyrroloiminoquinones have recently received increasing attention as a source of new and useful anticancer drugs. In particular wakayin **1**, isolated from Ascidian *Clavelina* species, shows biological activities such as inhibition of topoisomerase I.[2] Until now, only two approaches to structures analogous to wakayin were reported with no biological activity described.[3] As part of our work on heterocyclic compounds with potential pharmacological value,[4] we planned to synthesize pyrroloiminoquinone **2** which is structurally very close to the natural alkaloid, by the retrosynthetic pathway shown in Scheme 1, from tryptamine and 7-methoxy-3,4-dihydro-1*H*-pyrrolo[4,3,2-*de*]quinolin-8-one **3**.

Chemistry

The strategy used for building the tricyclic system **3** was inspired by the work of Joule and Alvarez.[5] 6,7-Dimethoxy-4-methylquinoline **4** was formed by reaction between 3,4-dimethoxyaniline and methylvinylketone in refluxing acetic acid with iron(III) chloride. Nitration of **4** (concentrated nitric acid, −50 °C) led to the 5-nitro compound **5** in a good yield (78%). According to Vismara's method, oxidation of the methyl group to aldehyde was achieved in DMSO with trifluoroacetic acid, iodine, *tert*-butyliodide and iron(II) chloride. The aldehyde function was then protected as a dimethylacetal to give **7** in 87% yield. The pyridine ring and the nitro group were simultaneously reduced by an excess of sodium borohydride in methanol with nickel chloride to afford diamine **8** in a very good yield (95%). Cyclization of the pyrrole ring occurred by heating compound **8** at 80 °C in aqueous HCl and THF in a 62% yield (Scheme 2).

Aminoindole **9** was treated by ceric ammonium nitrate (CAN) in aqueous acetonitrile to generate the quinone structure. Substitution of the C-7 methoxy group by the amine was achieved in situ, without isolating the very unstable intermediate **3**. The product of coupling was then transformed into its trifluoroacetate salt (Scheme 3). In this way, tryptamine was condensed on the pyrroloiminoquinone core to afford compound **2**. Because some studies[6] have proved the utility of DNA-intercalating heterocyclic

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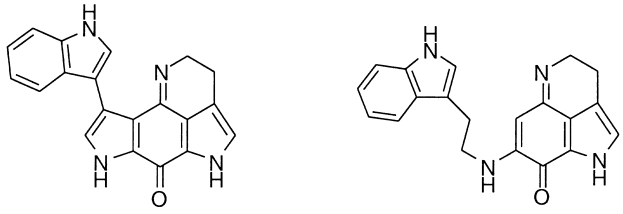


1 2

Figure 1.

compounds possessing a cationic side chain, products **10** and **11** were prepared by treatment of **3** with *N*,*N*-dimethylethylenediamine and 1-(2-amino-ethyl)pyrrolidine, respectively. Finally, makaluvamines D (**12**) and I (**13**) were obtained by reaction of **3** with tyramine and ammonium chloride, respectively.[7]

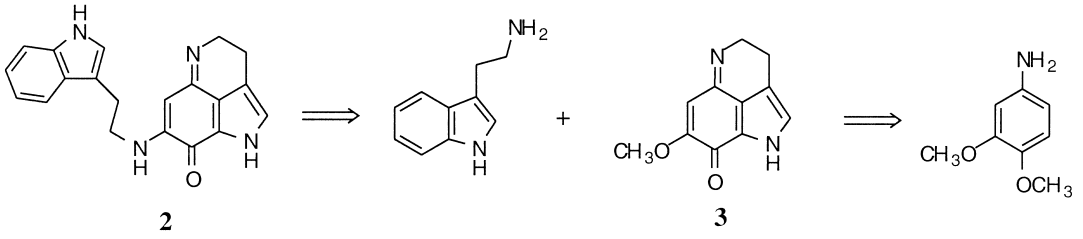
Pharmacology

Compounds **2** and **10**–**13** were evaluated in vitro for their antiproliferative activity using the murine L1210 leukemia cell line.[8] The results expressed as IC_{50} (concentration reducing the cell proliferation by 50%) are reported in Table 1. Because all the IC_{50}s were less than 20 μM, cell cycle perturbations were also investigated.

Results and Discussion

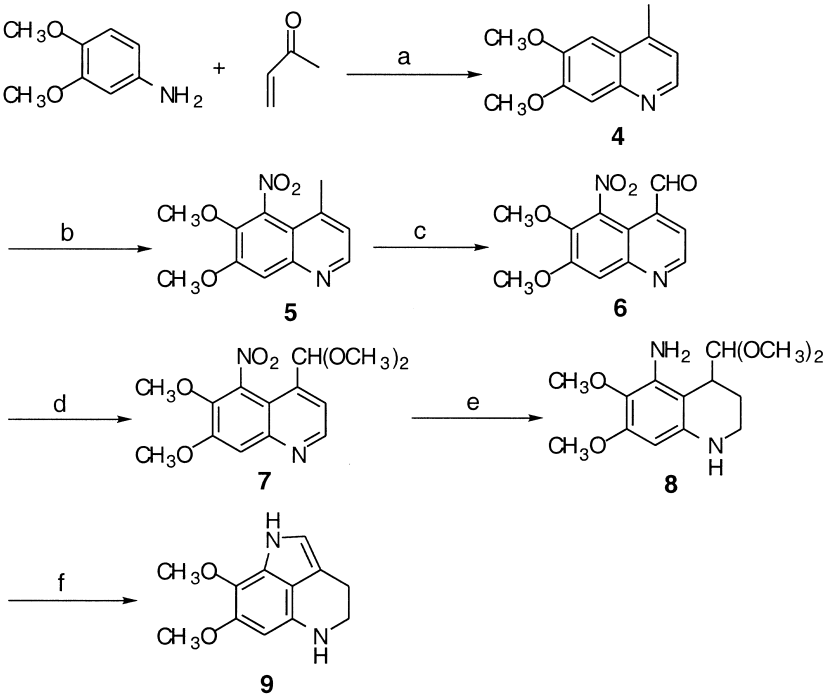
Compound **2**, a strict analogue of wakayin, is the least active of the tested molecules on the L1210 cell line. Compared to the natural alkaloid, the enhanced flexibility of the substituent at C-7 may not be favorable for interaction with biological targets. The most cytotoxic compounds (**10**, **11** and **13**) inhibit the growth of L1210 cells at concentrations less than 0.5 μM. These water soluble products are substituted by a primary amino or an aminoalkyl group. Makaluvamine D (**12**), bearing a hydrophobic side chain, showed a moderate antiproliferative activity in accordance with those reported for different cell lines (IC_{50}(HCT116) = 23.4 μM, IC_{50}(xrs-6) = 19.1 μM).[9]

Despite interesting antiproliferative properties, none of the pyrroloiminoquinone derivatives **2** and **10**–**13** induce significant modification of the L1210 cells cycle. This may

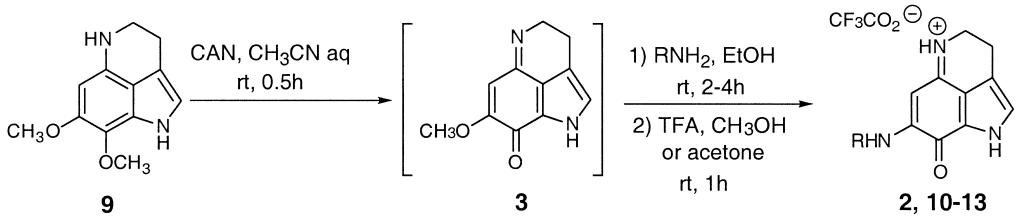


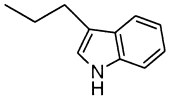
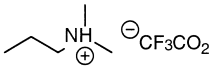
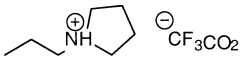
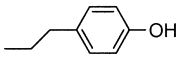
2 3

Scheme 1.



Scheme 2. Reaction conditions and yields: (a) AcOH, $FeCl_3$, reflux, 2 h, 37%; (b) concd HNO_3, −50 °C, 1.5 h, 78%; (c) I_2, *t*BuI, $FeCl_2$, DMSO, TFA, 100 °C, 4 h, 83%; (d) HCl in Et_2O, CH_3OH, reflux, 48 h, 87%; (e) $NaBH_4$, $NiCl_2$, CH_3OH, rt, 1 h, 95%: (f) HCl 1 N, THF, 80 °C, 1 h, 62%.



Product	Substituent (R)	Yield (%) (two steps)
2		20
10		29
11		22
12		16
13	H	27

Scheme 3.

Table 1. Antiproliferative activity of compounds **2** and **10–13** on L1210 cells

Compound	Formula	IC_{50} (μM)	Effect on cellular cycle
2	$C_{22}H_{19}N_4O_3F_3$	5.3	Nonspecific
10	$C_{18}H_{20}N_4O_5F_6$	0.3	Nonspecific
11	$C_{20}H_{22}N_4O_5F_6$	0.38	Nonspecific
12	$C_{20}H_{18}N_3O_4F_3$	2.1	Nonspecific
13	$C_{12}H_{10}N_3O_3F_3$	0.25	Nonspecific

prove that the pyrroloiminoquinone skeleton on its own is not able to exert a specific cytotoxic action.

Conclusion

In conclusion, we achieved the synthesis of an opened analogue of wakayin whose structure is the closest to the natural compound yet published. Two products with basic side chains were also formed as well as the marine alkaloids makaluvamines D and I. These products, especially water soluble compounds **10**, **11** and **13**, proved to be quite good cytotoxic agents despite their lack of interaction with the L1210 cellular cycle.

We are now focusing our efforts on the introduction of a C–C bond at C-6 in order to mimic veiutamine, the most active pyrroliminoquinone alkaloid recently isolated from the Fijian sponge *Zyzzya fuliginosa*.

Acknowledgements

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7. Selected data for compound **2**: IR (KBr) ν 3121, 1680, 1555, 1403, 1338, 1206 cm^{-1}. ^1H NMR (DMSO-d_6) 2.87 (t, 2H, *J* 7.5 Hz), 3.03 (t, 2H, *J* 7.5 Hz), 3.59 (m, 2H), 3.79 (dt, 2H, *J* 7.5 Hz and *J* 3 Hz), 5.49 (s, 1H), 6.99 (t, 1H, *J* 7.3 Hz), 7.07 (t, 1H, *J* 7.3 Hz), 7.22 (d, 1H, *J* 2.4 Hz), 7.34 (d, 1H, *J* 7.3 Hz),

7.34 (s, 1H), 7.56 (d, 1H, *J* 7.3 Hz), 9.11 (t, 1H, *J* 6.2 Hz), 10.43 (s, 1H), 10.92 (s, 1H), 13.10 (s, 1H). ^{13}C NMR (DMSO-d_6) 18.15; 23.30; 42.43; 44.15; 83.96; 110.62; 110.63; 111.49; 118.18; 118.42; 118.70; 121.10; 122.64; 123.12; 123.81; 126.97; 136.24; 153.12; 157.07; 167.48. MS (FAB) *m*/*z* 331 (M + H, 100%), 201 (M−C_9H_8N, 21), 188 (10). Anal. calcd for $C_{22}H_{19}N_4O_3F_3$: C, 59.46; H, 4.31; N, 12.61; found: C, 59.51; H, 4.35; N, 12.76. All compounds were fully characterized by spectroscopic and elemental analysis. Structural data for compounds **13** and **14** are consistent with those previously reported.

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