A Synthesis of New Pyrrolo[3,2-*c*]Quinolines

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A synthesis of pyrrolo[3,2-*c*]quinolines substituted in the 7- and 8- positions by methoxy groups and in the 3- position by an amido group is described. The structures were designed to have a crescent shape, a planar fused cyclic moiety with two *ortho* methoxy groups and ionisable amino or amidinic group at pH 7.

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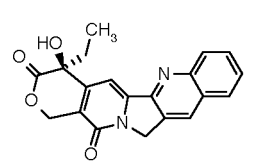
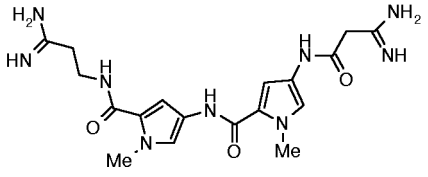
Topoisomerase inhibitors possess significant anticancer activity against many solid tumours including breast, ovarian, and lung carcinomas. Two major classes of inhibitors exist: topoisomerase poisons and catalytic inhibitors [1]. Our work has focused on the action mechanism of topoisomerase poisons which is primarily based on the ability to inhibit the religation of DNA cleavage induced by topoisomerase enzymes. Topoisomerase poisons like camptothecin [2] (Figure 1) chiefly bind to both the active site of the enzyme and DNA by hydrogen bonding, whereas netropsin [3] (Figure 1) essentially binds to the minor groove of DNA, thereby preventing the approach of topoisomerase.

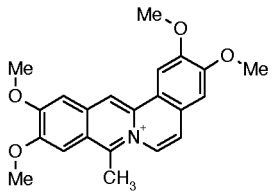
The synthesis of **11** proceeded according to Scheme 1. Ester **4** [4] was saponified with aqueous sodium hydroxide and the resulting β-ketoacid **5** was submitted to decarboxylation by heating at 200° in phenyl ether to give dihydroquinolinone **6** which was treated with phosphorous oxychloride. The crude chloride derivative **7** [5],[6] was immediately condensed with phenylhydrazine in ethanol to give **8**. A Michael addition of the more acidic phenylhydrazinic NH on ethyl propiolate gave **9** which was easily converted to **10** at reflux of DMF by a Fischer indole-type synthesis [7]. Finally, saponification of **10** gave **11** in a moderate yield.



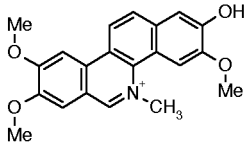
Camptohecin



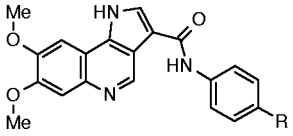
Netropsin



Coralyne



Fagaronine



1 R = C(=NH)NH$_2$
2 R = CH$_2$NH$_2$
2 R = CH

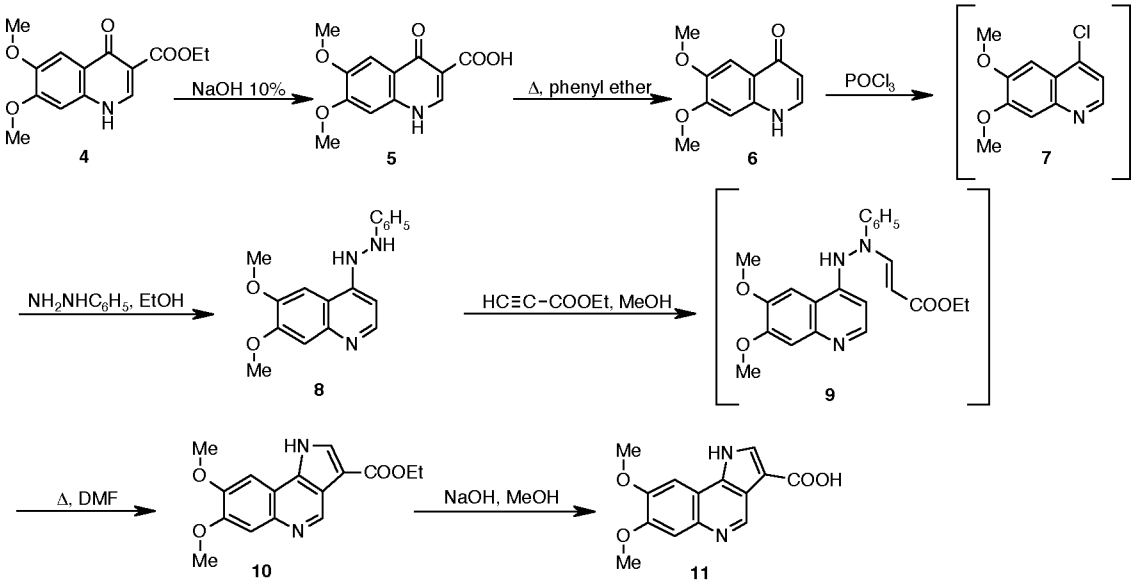
Figure 1

Molecules **1** and **2** were designed to combine these two inhibition mechanisms and to offer a different sequence selectivity toward DNA. They contain the pyrroloquinoline structure of camptothecin and the pyrrolocarboxamide moiety of netropsin. Moreover, they present the crescent shapes of both reference compounds as well as a roughly planar tricyclic moiety where the homocycle was substituted with two *ortho* methoxy groups, like some topoisomerase inhibitors such as Coralyne and Fagaronine (Figure 1). In addition, a cationic amino or amidino group, as in netropsin, was appended to the ring system in order to further enhance their DNA binding affinities. For the purpose of comparison, the synthesis of non cation-containing compound **3** was undertaken.

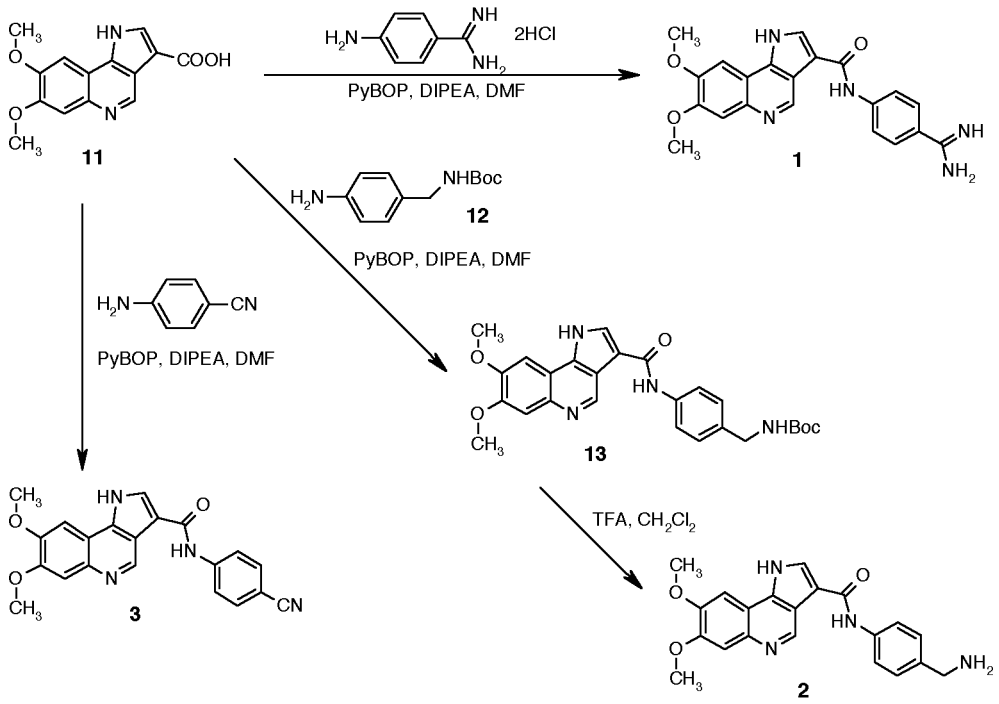
Compounds **1**, **2** and **3** were synthesized according to Scheme 2 and using the techniques of peptidic synthesis. Carboxylic acid **11** was coupled with 4-aminobenzamidine or 4-cyanoaniline in the presence of benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP) in dimethylformamide to give amides **1** and **3**. Similarly, the coupling of **11** with the aniline derivative **12** in the same conditions resulted in amide **13**. The carbamoyl group of **2** was classically removed by treatment of **13** with trifluoroacetic acid in methylene chloride.

Biological experiments are currently in progress to test DNA affinity, anti-proliferation properties and topoisomerase inhibition of these compounds.

Scheme 1



Scheme 2



EXPERIMENTAL

Melting points were determined on a Büchi 535 apparatus using the capillary method and are uncorrected. Analytical tlc was performed on precoated Kieselgel 60F_{254} plates (Merck); the spots were located by uv light (254 and 366 nm). Column chromatography was performed on silicagel 60 230-400 Mesh purchased from Merck. ^{1}H nmr spectra were recorded on a Bruker AC 300 spectrometer; chemical shifts are reported in parts per million relative to the internal standard tetramethylsilane and the splitting patterns are designated as follows: s singlet, bs broad singlet, d doublet, t triplet, q quartet, m multiplet. The spectra confirmed the proposed structures. The mass spectra were recorded on a quadripolar Finnigan TSQ 700 instrument in electron impact mode. Elemental analyses for C, H, N were performed by the 'Service Central d'Analyses' at the CNRS, Vernaison, France.

1,4-Dihydro-6,7-dimethoxy-4-oxoquinoline-3-carboxylic Acid (**5**).

A mixture of **4** [4] (4 g, 14 mmol) and 10% aqueous sodium hydroxide (10 ml, 29 mmol) was stirred at reflux for 18 hours. The solvent was removed and the residue was extracted with ethyl acetate after addition of water. The aqueous phase was acidified with 3 *M* hydrochloric acid. After concentration, acid **5** precipitated and was purified through recrystallization from water (1.57 g, 45%). mp 274-276° (lit.[5] 276°). ^{1}H nmr (dimethylsulfoxide-d_6): δ 3.94 (s, 3H), 3.99 (s, 3H), 7.01 (s, 1H), 7.52 (s, 1H), 8.40 (s, 1H), 10.51 (bs, 1H, exchangeable in deuterium oxide).

Anal. Calcd. for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.62. Found: C, 57.88; H, 4.40; N, 5.61.

1,4-Dihydro-6,7-dimethoxy-4-oxoquinoline (**6**).

Acid **5** (1 g, 4.9 mmol) and phenyl ether (10 ml) were heated at reflux for 18 hours. Chromatography on silica gel with 5% methanol/methylene chloride was followed by recrystallization with ethyl acetate to afford **6** (0.55 g, 55%). mp 234-237° (lit.[5] 236-237°). ^{1}H nmr (dimethylsulfoxide-d_6): δ 3.82 (s, 3H), 3.83 (s, 3H), 7.23 (s, 1H), 7.54 (d, J = 7.0 Hz, 1H), 8.46 (d, J = 7.0 Hz, 1H), 8.50 (s, 1H), 10.00 (bs, 1H).

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.32; H, 5.46; N, 6.79.

6,7-Dimethoxy-4-[2-(1-phenylhydrazino)]quinoline (**8**).

A mixture of **6** (0.5 g, 2.4 mmol) and phosphorus oxychloride (1.13 ml, 12 mmol) was heated for a few minutes. The mixture was concentrated and the residue diluted with toluene. After evaporation of the solvent, the resulting oil was poured onto ice and made basic with aqueous 10% ammonium hydroxide. The mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over magnesium sulfate, evaporated to give crude **7** (0.41 g, 80%). A solution of crude **7** (1 g, 4.5 mmol) in ethanol (20 ml) was added to phenylhydrazine (2.2 ml, 22.5 mmol). The mixture was heated at reflux for 18 hours. The solvent was removed and the product purified by chromatography with 50% ethyl acetate/heptane, followed by recrystallization from ethanol to give **8** as a pale yellow solid (0.71 g, 54%). mp 240-243°. ^{1}H nmr (dimethylsulfoxide-d_6): δ 3.80 (s, 3H), 3.83 (s, 3H), 7.45 (s, 1H), 7.58 (d, J = 7.2 Hz, 1H), 7.65-7.95 (m, 5H), 8.51 (d, J = 7.2 Hz, 1H), 8.57 (s, 1H), 10.50 (bs, 2H). ms (electron impact) m/z 393, 394 (M+H).

Anal. Calcd. for $C_{17}H_{16}N_3O_2$: C, 69.37; H, 5.48; N, 14.28. Found: C, 69.24; H, 5.32; N, 14.37.

Ethyl 7,8-Dimethoxy-1*H*-pyrrolo[3,2-*c*]quinoline-3-carboxylate (**10**).

A solution of ethyl propiolate (0.16 ml, 1.63 mmol) and **8** (0.4 g, 1.36 mmol) in methanol (10 ml) was heated at reflux for 18 hours. The solvent was removed and the product was purified by chromatography, eluted by 50% ethyl acetate/cyclohexane to give **9** (0.3 g, 56%).

A solution of crude **9** (0.3 g, 1 mmol) in dimethylformamide (25 ml) was heated at reflux for 24 hours. The solvent was evaporated, the resulting residue was extracted with ethyl acetate and the extract was washed with water. The organic layer was dried over magnesium sulfate, evaporated, and the residue purified by chromatography on silica gel with 5% methanol/methylene chloride to give **10** as a pure tan solid (0.19 g, 30%). mp 199-203°. ^{1}H nmr (dimethylsulfoxide-d_6): δ 1.29 (t, J = 7.1 Hz, 3H), 3.96 (s, 3H), 3.97 (s, 3H), 4.59 (q, J = 7.1 Hz, 2H), 6.79 (s, 1H), 7.85 (s, 1H), 8.90 (s, 1H), 8.95 (s, 1H), 9.50 (bs, 1H). ms (electron impact) m/z 300, 301 (M+H).

Anal. Calcd. for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 64.15; H, 5.28; N, 9.28.

7,8-Dimethoxy-1*H*-pyrrolo[3,2-*c*]quinoline-3-carboxylic Acid (**11**).

A solution of **10** (0.5 g, 1.8 mmol) in methanol (10 ml) with 10% sodium hydroxide (1.4 ml, 3.6 mmol) was stirred at room temperature for 18 hours and evaporated *in vacuo*. The resulting residue was extracted with methylene chloride and washed with water. The aqueous layer was removed, acidified with 1 *M* hydrochloric acid and extracted with methylene chloride. After evaporation, the resulting residue was purified through recrystallization from water to give **11** as a white solid (0.26 g, 55%). mp > 260°. ^{1}H nmr (dimethylsulfoxide-d_6): δ 3.93 (s, 6H), 6.60 (s, 1H), 6.91 (s, 1H), 7.28 (s, 1H), 8.70 (bs, 1H), 10.02 (s, 1H). ms (electron impact) m/z 272, 273 (M+H).

Anal. Calcd. for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.42; H, 4.73; N, 10.31.

7,8-Dimethoxy-3-(4-amidinoanilinocarbonyl)-1*H*-pyrrolo-[3,2-*c*]quinoline (**1**).

A solution of **11** (0.2 g, 0.73 mmol), 4-aminobenzamidine dihydrochloride (0.18 g, 0.8 mmol), benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (0.45 g, 0.88 mmol) and *N*-ethyldiisopropylamine (0.5 ml, 2.9 mmol) in dimethylformamide (10 ml) was stirred at room temperature for 24 hours. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was removed and then treated with 1 *M* hydrochloric acid. Separation and neutralization of the aqueous layer with sodium bicarbonate, followed by extraction with ethyl acetate gave a clear solution of **1** which was evaporated *in vacuo* (0.1 g, 30%). mp > 260°. ^{1}H nmr (dimethylsulfoxide-d_6): δ 3.98 (s, 6H), 6.77 (s, 1H), 7.81 (s, 1H), 7.95 (d, J = 8.1 Hz, 2H), 8.10 (d, J = 8.1 Hz, 2H), 8.15 (s, 1H), 8.20 (bs, 3H), 8.69 (s, 1H), 10.50 (bs, 1H), 11.56 (bs, 1H). ms (electron impact) m/z 389, 390 (M+H).

Anal. Calcd. for $C_{21}H_{19}N_5O_3$: C, 64.77; H, 4.92; N, 17.98. Found: C, 64.81; H, 4.88; N, 17.72.

7,8-Dimethoxy-3-(4-(*tert*-butoxycarbonylaminomethyl)anilinocarbonyl)-1*H*-pyrrolo[3,2-*c*]quinoline (**13**).

A solution of **11** (0.2 g, 0.73 mmol), amine **12** [8] (0.18 g, 0.8 mmol), benzotriazol-1-yloxytris(pyrrolidino)phosphonium-hexafluorophosphate (0.45 g, 0.88 mmol), *N*-ethyldiisopropylamine (0.5 ml, 2.9 mmol) in dimethylformamide (5 ml) was stirred for 24 hours. Water (10 ml) was added and the mixture extracted with methylene chloride. The product was purified by chromatography with 20% methanol/methylene chloride to give **13** as a tan product (0.1 g, 28%). mp > 260°. ^{1}H nmr (dimethylsulfoxide-d_6): δ 1.40 (s, 9H), 3.93 (s, 3H), 3.96 (s, 3H), 5.00 (s, 2H), 6.89 (s, 1H), 7.18 (d, J = 7.2 Hz, 2H), 7.64 (d, J = 7.2 Hz, 2H), 7.68 (bs, 1H), 7.75 (s, 1H), 7.80 (bs, 1H), 8.10 (s, 1H), 8.71 (s, 1H), 10.50 (bs, 1H), 11.90 (s, 1H). ms (electron impact) m/z 476, 477 (M+H).

Anal. Calcd. for $C_{26}H_{28}N_4O_5$: C, 65.53; H, 5.92; N, 11.76. Found: C, 65.42; H, 5.73; N, 11.51.

7,8-Dimethoxy-3-(4-(aminomethyl)anilinocarbonyl)-1*H*-pyrrolo[3,2-*c*]quinoline (**2**).

A solution of **13** (0.3 g, 0.6 mmol) in methylene chloride (5 ml) was cooled at 0° and acidified with a few drops of trifluoroacetic acid. The mixture was stirred for 2 hours at room temperature and evaporated. The resulting product was dissolved in a minimum of water. Following neutralization with sodium bicarbonate, the resulting precipitate was collected by filtration to give **2** as a tan product (0.12 g, 50%). mp > 260°. ^{1}H nmr (dimethylsulfoxide-d_6): δ 3.95 (s, 6H), 4.03 (s, 2H), 6.78 (d, J = 8.0 Hz, 3H), 7.64 (d, J = 8.0 Hz, 2H), 7.80 (s, 1H), 8.00 (bs, 2H), 8.05 (s, 1H), 8.66 (s, 1H), 8.90 (s, 1H), 10.50 (bs, 1H), 11.00 (bs, 1H). ms (electron impact) m/z 376, 377 (M+H).

Anal. Calcd. for $C_{21}H_{20}N_4O_3$: C, 67.01; H, 5.36; N, 14.88. Found: C, 66.75; H, 5.06; N, 15.03.

7,8-Dimethoxy-3-(4-cyanoanilinocarbonyl)-1*H*-pyrrolo[3,2-*c*]-quinoline (**3**).

Benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (0.45 g, 0.88 mmol), 4-cyanoaniline (0.1 g, 0.8 mmol) and *N*-ethyldiisopropylamine (0.5 ml, 2.9 mmol) were added to **11** (0.2 g, 0.7 mmol) in dimethylformamide (10 ml). The reaction was stirred for 24 hours at room temperature after which it was diluted with 20 ml of water and extracted with methylene chloride. The organic layer was dried over magnesium sulfate, evaporated and the resulting residue purified by chromatography (20% methanol/methylene chloride) to give **3** (0.1 g, 25%). mp > 260°. ^{1}H nmr (dimethylsulfoxide-d_6): δ 3.96 (s, 6H), 6.85 (s, 1H), 7.82 (s, 1H), 7.85 (d, J = 7.2 Hz, 2H), 7.95 (d, J = 7.2 Hz, 2H), 8.00 (s, 1H), 8.90 (s, 1H), 10.50 (bs, 2H). ms (electron impact): 372, 373 (M+H).

Anal. Calcd. for $C_{21}H_{16}N_4O_3$: C, 67.71; H, 4.34; N, 15.06. Found: C, 67.35; H, 4.28; N, 15.11.

REFERENCES AND NOTES

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