Tetrahedron 72 (2016) 8230–8240

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of new pyrrolo-, and pyrido-anellated quinazolinones as potential antiproliferative agents

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ARTICLE INFO

Article history:
Received 22 July 2016
Received in revised form
4 October 2016
Accepted 20 October 2016
Available online 24 October 2016

Keywords:
Pyrroloquinazolinone
Pyridoquinazolinone
Antiproliferative activity
DNA intercalation
DNA topoisomerases

ABSTRACT

Some pyrrolo[3,2-*f*]quinazolinones (compounds **4**–**12**), two pyrido[3,2-*f*]- and two pyrido[2,3-*g*]quinazolinones (compounds **15**, **16** and **22**, **23**, respectively) were prepared via multistep syntheses. The tricyclic pyrroloquinazolinone nucleus was built starting from 5-aminoindole via a modified reported pathway to form the pyrimidine ring. To synthesize the tricyclic pyridoquinazolinones, new pathways were designed: the angular moiety was obtained starting from 6-aminoquinazolinone to form the pyridine ring and the linear one starting from the 6-aminoquinolinone to form the pyrimidine ring. An interesting antiproliferative activity was found for compound **23**, which was able to form a molecular intercalative complex with DNA and to interfere with the relaxation activity of both topoisomerase I and II. The activation of the apoptotic pathway was also demonstrated.

1. Introduction

The quinazoline skeleton is found in a number of biologically active molecules and in particular, 4(3*H*)-quinazolinone derivatives display a wide range of biological properties, well documented in the literature.[1] Quinazolinone derivatives have also been developed as antiproliferative agents acting as inhibitors of thymidylate synthase[2] or of tubulin polymerization.[3] Heterocycle-fused quinazolinones are less described and pyrimidoquinazolinones, due to their polycyclic planar structure bearing more or less complex side groups, were proposed as intercalators and topoisomerase II inhibitors.[4,5]

Although many papers describe various polyheterocycle alkylamino-substituted derivatives acting as intercalators and topoisomerase II inhibitors, those focusing on the synthesis and biological profiles of pyrrolo- and pyridoquinazolinones are very few.[6]

Considering the richness of the chemical, physicochemical and pharmacological properties of quinazoline derivatives, the preparation of new fused quinazoline structures remains a worthy area of research.

In the past few years we have focused our interest on the synthesis and biological evaluation of some pyrroloquinolines and pyridocarbazoles as analogues of ellipticine, a well-known intercalating anti-topoisomerase II agent.[7,8] The ability of ellipticine to intercalate into DNA and to alter topoisomerase II activity appears to play an important role in its antineoplastic activity.[9,10]

Recently, we have moved to the synthesis and characterization of some new poly-heterocycles containing the quinazolinone scaffold fused to a pyrrolo or pyridine ring to build both angular and linear tricycles. Fig. 1 shows the structures of clinically used prototypic topoisomerase inhibitors (top), inhibitors in clinical development (middle), our previous pyrroloquinoline derivatives,[7] and the new structures proposed in this paper (bottom). The structural similarity among all these compounds is evident: the presence of a planar platform linking side polar groups, two crucial elements for topoisomerase inhibition.[11–14]

2. Results and discussion

2.1. Chemistry

The synthesis of pyrrolo[3,2-*f*]quinazolinone derivatives **4**–**8** described in Scheme 1 was accomplished adopting a methodology previously reported to form the pyrimidine ring starting from an aromatic amine.[15] Thus, 5-aminoindoles **1**–**3** obtained by us as

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http://dx.doi.org/10.1016/j.tet.2016.10.055
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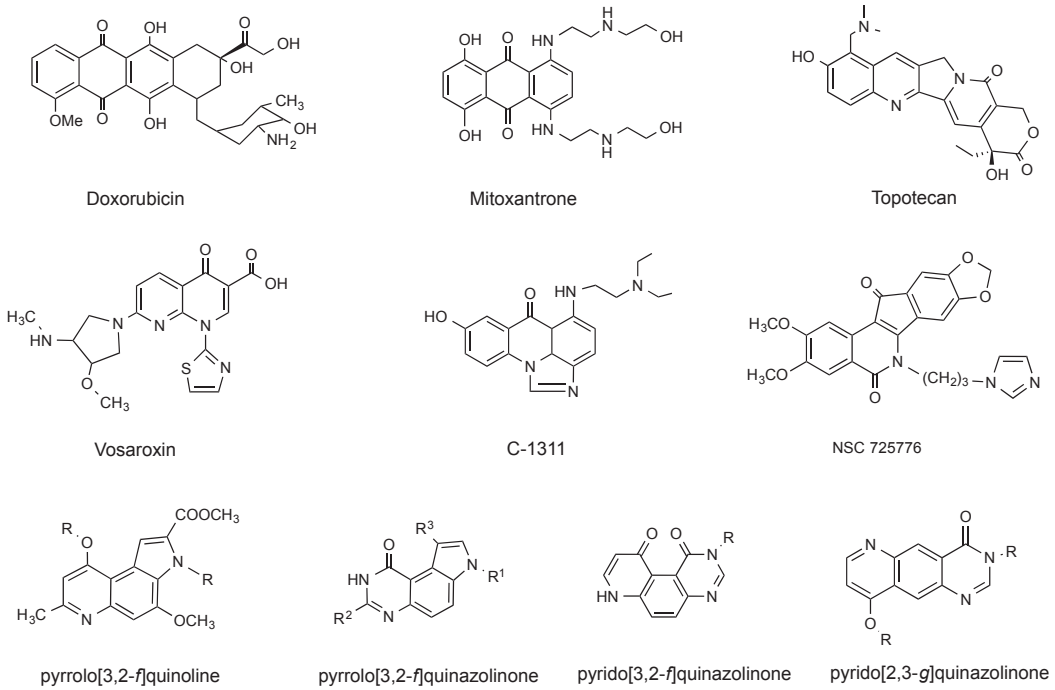
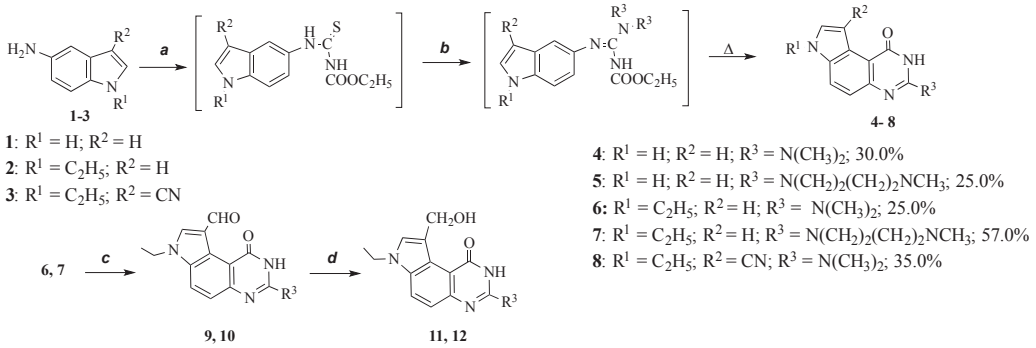


Fig. 1. Structures of clinically used prototypic topoisomerase inhibitors (top), inhibitors in clinical development (middle), previous pyrroloquinolines,[7] new pyrrolo- and pyrido-quinazolinone structures proposed in this paper (bottom).

previously reported[16] were submitted to a one pot reaction by successive addition of the reagents: ethoxycarbonylisothiocyanate, diethylamine or methylpiperazine, and $HgCl_2$ to the reaction mixture with the indicated stoichiometry. Finally, when the reaction mixture was subjected to thermal cyclization, the 2-alkyl amino-substituted pyrrolo[3,2-*f*]quinazolinones **4**–**8** were formed by means of a regio-selective reaction.[17] Indeed, it is worthy to note that the products obtained possess exclusively angular structures, and any product with linear geometry was not observed by proton NMR spectroscopy. The ^{1}H NMR spectra of compounds **4**–**8** showed two doublets at about δ 7.64 and 7.92 for an *ortho* coupling (J = 8.7 Hz) assigned to H-5 and H-6, respectively, and not two singlets as would be expected for a linear structure. In Scheme 1, the other four pyrroloquinazolinone derivatives described are obtained by modifying compounds **6** and **7** at position 8. Firstly, aldehydic compounds **9** and **10** were prepared by reacting **6** and **7**



Scheme 1. Synthesis of pyrrolo[3,2-*f*]quinazolinone derivatives **4**–**12**.