European Journal of Medicinal Chemistry 45 (2010) 5428–5437

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis and biological activities of new furo[3,4-*b*]carbazoles: Potential topoisomerase II inhibitors

Youssef Hajbi [a], Cléopatra Neagoie [a,b], Bérenger Biannic [a], Aurélie Chilloux [a], Emeline Vedrenne [a], Brigitte Baldeyrou [c], Christian Bailly [c], Jean-Yves Mérour [a], Sorin Rosca [b], Sylvain Routier [a,*], Amélie Lansiaux [c,**]

[a] *Institut de Chimie Organique et Analytique, Université d'Orléans, CNRS UMR 6005, B.P. 6759, 45067 Orléans Cedex 2, France*
[b] *Universitatea Politehnica, 313, Splaiul Independentei, 77206 Bucuresti, Romania*
[c] *INSERM U-837, Centre Oscar Lambret, Université Lille Nord de France, Faculté de Médecine de Lille, IRCL, 59045 Lille, France*

ARTICLE INFO

Article history:
Received 4 June 2010
Received in revised form
27 August 2010
Accepted 1 September 2010
Available online 15 September 2010

Keywords:
Carbazoles
Synthesis
Azatoxin
Microwave
Topoisomérase II
Inhibition cytotoxicity

ABSTRACT

New 1,5-Dihydro-4-(substituted phenyl)-3*H*-furo[3,4-*b*]carbazol-3-ones were synthesised via a key step Diels–Alder reaction under microwave irradiation. 3-Formylindole was successfully used in a 6-step synthesis to obtain those complex heterocycles. The Diels–Alder reaction generating the carbazole ring was optimised under thermal conditions or microwave irradiation. After cleavage of functional groups, DNA binding, topoisomerase inhibition and cytotoxic properties of the new-formed furocarbazoles were investigated. These carbazoles do not present a strong interaction with the DNA, and do not modify the relaxation of the DNA in the presence of topoisomerase I or II except for one promising compound. This compound is a potent topoisomerase II inhibitor, and its cellular activity is not moderated compared to etoposide. The synthesis of these molecules allowed the generalisation of the method using indole and 5-OBn indole and several benzaldehydes. The synthesis of these molecules produced chemical structures endowed with promising cytotoxic and topoisomerase II inhibition activities.

1. Introduction

Lignans are natural products which can be isolated from a wide range of plants. The synthesis of such scaffolds is important as they exhibit great antiviral activities [1]. Some of them proved to be promising tools for the fight against cancer: podophyllotoxin and its glycosylated analogues etoposide and teniposide, for instance, are pro-apoptotic drugs strongly inhibiting tubulin polymerisation and topoisomerase II [2–4].

This enzyme has raised considerable attention due to its crucial role in the cell cycle and DNA replication. A lot of well-known compounds, such as mitoxantrone, inhibit its activity, but drug resistance prompted chemists to design new inhibitors by exchanging the quinonic chromophore for another. In lignans chemical series, naphthalenic analogues such as **I**, where the non-aromatic central ring was suppressed, were developed; they exhibit a good activity against the topoisomerase II (Fig. 1) [7].

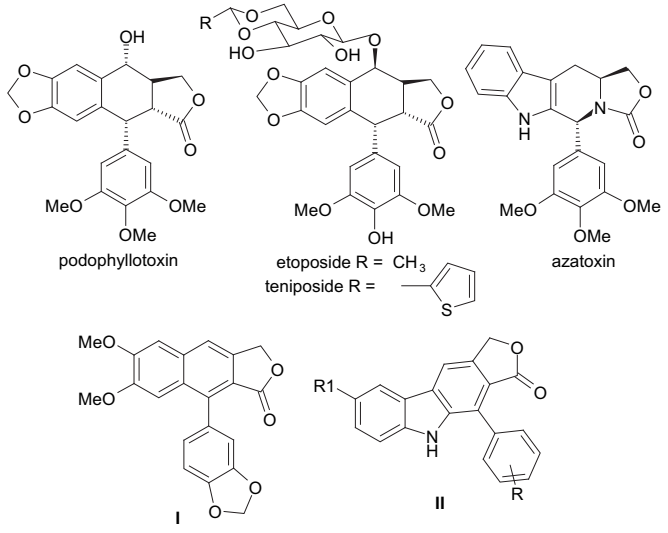


Fig. 1. The most representative lignans and derivatives.

* Corresponding author. Tel.: +33 238 49 48 53; fax: +33 238 41 72 81.
** Corresponding author. Tel.: +33 320 29 59 53; fax: +33 320 16 92 29.
E-mail addresses: sylvain.routier@univ-orleans.fr (S. Routier), a-lansiaux@o-lambret.fr (A. Lansiaux).

0223-5234/$ – see front matter © 2010 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2010.09.003

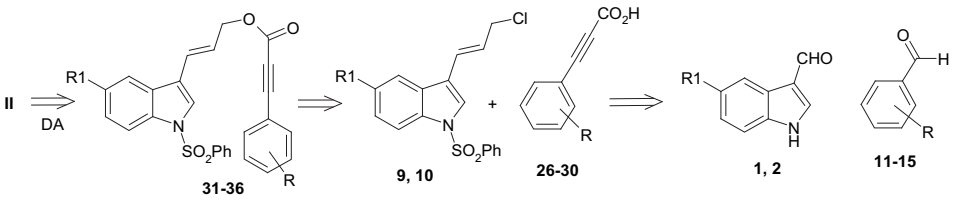


Fig. 2. Retrosynthetic scheme.

Azatoxin, an indolic heterolignan, has also proved to be a good topoisomerase II inhibitor [5,6]. Based on our interests in designing indolocarbazole analogues as topoisomerase I inhibitors, we aimed to develop new DNA topoisomerase II inhibitors [8]. We thought that the frameworks of azatoxin and compound of type **I** could be combined to generate tetrahydrofuro[3,4-*b*] carbazole such as **II**, in which the indole ring is fused to the aromatic central ring.

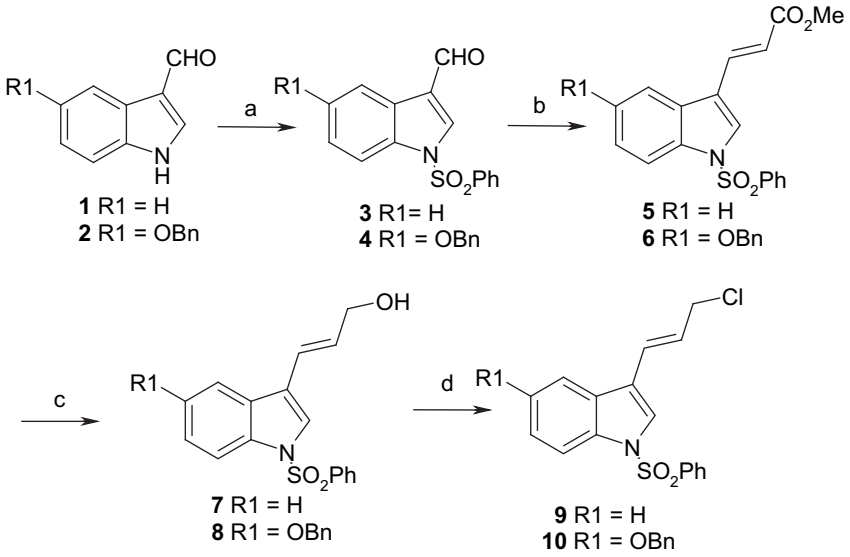
We hoped that this structure could result from an intramolecular Diels–Alder reaction (DA, Fig. 2) [9]. Precursors **31**–**36** could be obtained from indolic chloro derivatives (R = Cl) and alkynes **26**–**30**. Therefore, indoles **1**–**2** and benzaldehydes **11**–**15** constituted the starting materials. The first issue was the choice of an appropriate indolic protecting group. As the target **II** exhibits a base-sensitive lactone, synthesis involving a Boc group or even better, no protecting group was first envisaged.

Unfortunately, the synthesis of indoles **IV** without any protecting group failed in our work, and the Boc group was prematurely released during the synthetic pathway. These results prompted us to use the robust benzenesulphonyl group. The first studies were realised with 3-formylindole and 2,4,5-trimethoxybenzaldehyde. Herein, we present the results of our method applied to indole reacting with a wide range of benzaldehydes. Results obtained with 5-OBn indole **2** are also discussed.

2. Chemistry

2.1. Preparation of the indolic skeletons type *IV*

3-Formylindole **1** and 3-formyl-5-benzyloxyindole **2** [10] were first protected with a benzenesulphonyl group using benzenesulphonyl chloride (1.2 eq.) in the presence of $BnEt_3N^+Cl^-$ and NaOH. The protection of **1** was carried out at room temperature, whereas reflux conditions were necessary for indole **2**: compounds **3** [11] and **4** were both obtained in good yield (Scheme 1).



Scheme 1. (a) $BnEt_3N^+$, Cl^- (cat.), NaOH (3.0 eq.), $PhSO_2Cl$ (1.2 eq.), CH_2Cl_2, r.t., 2 h, from **1**: 0 °C to r.t., **3** 84%, from **2**: 0 °C to reflux, **4** 81%; (b) $PPh_3 = CHCOOCH_3$ (3 eq.), toluene, reflux, 12 h, from **3**: 5 98%, from **4**: 6 93%; (c) DibalH (2.5 eq.), toluene, 0 °C to r.t., from **5**: 2 h, **7** quant., from **6**: 2 h 30, **8** quant.; (d) $SOCl_2$ (1.9 eq.), benzotriazole (1.9 eq.), CH_2Cl_2, r.t., 15 min., from **7**: **9** quant, from **8**: **10** quant.

A Wittig reaction was next performed in toluene under reflux conditions using a slight excess of (carbethoxymethylene) triphenylphosphorane (3.0 eq.) to give compounds **5** [12] and **6** in 98 and 93% yields respectively. The ester moieties were then reduced with DibalH, affording alcohols **7** and **8** in quantitative yields [13]. Chlorination was then realised using thionyl chloride in the presence of benzotriazole, quantitatively affording compounds **9** and **10** [14].

2.2. Preparation of the propynoic acids type *V*

We then focused our efforts on the Corey–Fuchs alkyne methodology [15]. Benzaldehydes **10**–**15** were treated with PPh_3 and CBr_4 to afford geminated dibromo alkenes **16**–**20** in very good