European Journal of Medicinal Chemistry 115 (2016) 179–190

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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

Research paper

Synthesis and biological evaluation of indeno[1,5]naphthyridines as topoisomerase I (TopI) inhibitors with antiproliferative activity

Concepción Alonso [a], María Fuertes [a], María González [a], Gloria Rubiales [a], Cinzia Tesauro [b], Birgitta R. Knudsen [b], Francisco Palacios [a, *]

[a] Departamento de Química Orgánica I, Facultad de Farmacia and Centro de Investigación Lascaray (Lascaray Research Center), Universidad del País Vasco/Euskal Herriko Unibertsitatea (UPV/EHU), Paseo de la Universidad 7, 01006, Vitoria-Gasteiz, Spain
[b] Department of Molecular Biology and Genetics and Interdisciplinary Nanoscience Center (iNANO), Aarhus University, Aarhus, 8000, Denmark

ARTICLE INFO

Article history:
Received 3 February 2016
Received in revised form
11 March 2016
Accepted 12 March 2016
Available online 14 March 2016

Keywords:
[1,5]-Naphthyridines
Topoisomerase I
Enzyme inhibition
Antiproliferative effect

ABSTRACT

In an effort to establish new candidates with improved anticancer activity, we report here the synthesis of various series of *7H*-indeno[2,1-*c*][1,5]-naphthyridines and novel *7H*-indeno[2,1-*c*][1,5]-naphthyridine-7-ones and *7H*-indeno[2,1-*c*][1,5]-naphthyridine-7-ols. Most of the products which were synthesized were able to inhibit Topoisomerase I activity. Moreover, *in vitro* testing demonstrated that a subset of the products exhibited a cytotoxic effect on cell lines derived from human breast cancer (BT 20), human lung adenocarcinoma (A 549), or human ovarian carcinoma (SKOV3).

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1. Introduction

Cancer still continues to be one of the major causes of death worldwide although over the years great efforts have been made to discover and develop more effective cancer drugs [1]. The highly proliferative nature is one feature of cancer cells. Thus, an effective tool in cancer therapy could be the inhibition of their proliferation pathways. In this respect, topoisomerase I (TopI), whose activity is higher in cancer cells compared to healthy ones, is known as a good target [2,3]. The role of TopI is essential in the metabolic processes of DNA in cells, releasing the stress produced during the processes of replication, transcription and DNA repair.

Enzyme activity can be affected by TopI inhibitors which can be classified into two types, poisons or suppressors, depending on how they take up with the enzyme. Among the most representative TopI poison drugs are camptothecin (CPT, Fig. 1, left) and its derivatives (CPTs). These derivatives are currently used in systemic treatment of colon cancer, ovarian and non-small cell lung cancers [4–6]. As described in the action mechanism observed in classic poisons, the cytotoxic effect of CPTs is directly related to the level of intra-cell activity and relies on active replication [7].

Camptothecin derivatives present several fused heterocycles in their chemical structure among other features. Unfortunately, some physicochemical limitations of these CPT derivatives have been observed during their use in cancer therapy. The most important limitation would be the chemical instability of the lactone ring structure in the blood plasma, and another is the clinical resistance of cancer cells to CPTs [8]. Bearing this in mind, we think that other quasi-flat heterocycles such as naphthyridine derivatives (Fig. 1, right) could also behave as TopI inhibitors and overcome some of the inherent limitations that CPTs present.

A wide range of nitrogen-containing heterocycles are being extensively used in biochemistry, pharmacology and material science [9]. Additionally, multicomponent reactions (MCR) [10], strategies frequently applied in medicinal chemistry [11], present several advantages over the classic step-by-step strategies. The hetero-Diels-Alder reaction (HDAr) is an atom-economic method for carbon–carbon bond formation [12]. This represents an excellent tool for the generation of six-membered rings with a high molecular complexity [13] which may have industrial applications [14]. By means of the Povarov reaction [15,16], an example of HDAr,

Abbreviations: CCK8, cell counting kit; CPT, camptothecin; CPTs, camptothecin derivatives; DDQ, dichloro-5,6-dicyanobenzoquinone; HDAr, hetero-Diels-Alder reaction; MCR, multicomponent reactions; TopI, topoisomerase I; TLC, thin layer chromatography.4.

* Corresponding author.
E-mail address: francisco.palacios@ehu.es (F. Palacios).

http://dx.doi.org/10.1016/j.ejmech.2016.03.031
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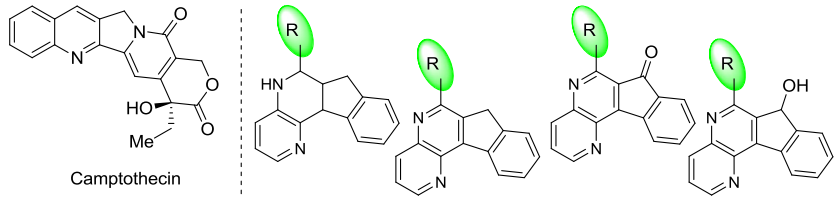


Fig. 1. Structure of camptothecin (left) and of several newly synthesized anticancer *7H*-indeno[2,1-c][1,5]-naphthyridines, and novel *7H*-indeno[2,1-c][1,5]-naphthyridine-7-ones and *7H*-indeno[2,1-c][1,5]-naphthyridine-7-ols (right).

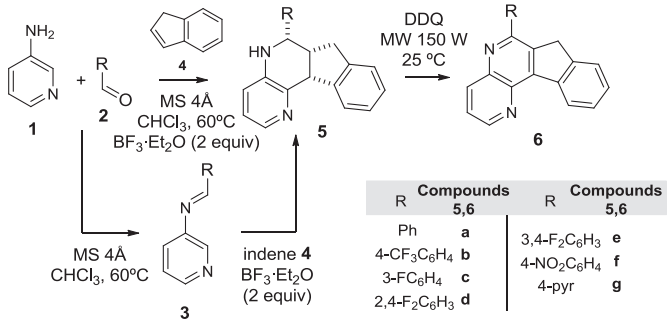
nitrogen-containing heterocyclic compounds can be prepared in an excellent way. In this case, aldimines derived from aromatic amines and aldehydes react with electron-rich alkenes in the presence of a Lewis acid catalyst. The Povarov reaction has been applied to total synthesis, for example in the synthesis of (±) −martinelline, (±) -martinellic acid, luotonin A, and camptothecin [17]. If pyridyl amines are used instead of anilines polynitrogenated derivatives, such as those of 1,5-naphthyridine derivatives [18], can be prepared by this strategy. Some methods for the synthesis of polycyclic 1,5-naphthyridines can be found in the literature [19], and some compounds with this skeleton present a wide range of biological activity [20]. Some 4-phenyl-1,5-naphthyridines show various biological activities including antibacterial activity [21] or FMS kinase inhibitory activity [22], and physicochemical applications [23]. Furthermore, we hypothesize that 7H-indeno[2,1-c][1,5] naphthyridine derivatives may be attractive candidates as new enzyme inhibitors with interesting pharmacological activity. For these reasons, their synthesis and biological evaluation represent an interesting challenge.

Herein, we report the synthesis of these new families of functionalized polycyclic 1,5-naphthyridine derivatives. Moreover we demonstrate the ability of the products to inhibit TopI activity *in vitro* and we observe a cytotoxic effect of the products on a selection of cancer cell lines.

2. Results

2.1. Chemistry

The preparation of substituted 1,5-naphthyridine derivatives (*vide supra*, Fig. 1) was explored by means of a Povarov type [4+2]-cycloaddition reaction [20], by both step-by-step and by multicomponent strategies (MCRs) [13–16]. First, the hetero-Diels–Alder reactions between indene **4** and *N*-(3-pyridyl) aldimines **3**, prepared *in situ* by reaction of 3-pyridylamine **1** and aldehydes **2**, in the presence of 2 equivalents of $BF_3{\cdot}Et_2O$ in refluxing chloroform were performed, and corresponding tetracyclic *endo*-1,2,3,4-tetrahydro-1,5-naphthyridines **5** were selectively obtained with good yields (41–93%, Scheme 1, Table 1) in a regio- and stereospecific way.



Scheme 1. Syntheses of Naphthyridine Derivatives (**5**a–g, **6**a–g).

Alternatively, three-component synthetic protocol was carried out by reacting commercially available 3-pyridylamine **1**, aromatic aldehydes **2** and indene **4** in the presence of 2 equivalents of $BF_3{\cdot}Et_2O$ in refluxing chloroform to afford also the corresponding *endo*-1,2,3,4-tetrahydronaphthyridines **5** with good yields (52–91%, Scheme 1, Table 1).

We studied the dehydrogenation of 1,2,3,4-tetrahydroindenonaphthyridine **5a** in the presence of 2 equivalents of DDQ in four different solvents (chloroform, dioxane, acetonitrile and toluene) and at two different temperatures (25 °C and 80 °C) under microwave irradiation for 15 min. The results indicated that toluene at 25 °C is able to produce 7*H*-indeno[2,1-c][1,5]naphthyridine derivatives **5a** in higher yields. The formation of compound **6a** was determined by ^{1}H NMR spectroscopy where signals corresponding to the protons of tetrahydronaphthyridine ring of starting compound **5a** disappeared while the appearance of only one signal as a singlet at 4.00 ppm corresponding to the methylene group present in the dehydrogenated derivative **6a** was observed. Then, the process was studied under microwave irradiation with 1 equivalent of DDQ and at longer reaction time. The analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed an increasing proportion of dehydrogenated compound **6a** with respect to the starting material **5a** from 15 min to 120 min when total conversion of starting material was observed. The reaction was extended to the other tetrahydroindenonaphthyridines **5b-g** and then the corresponding dehydrogenated derivatives **6b-g** were obtained by using these optimized conditions (Scheme 1, Chart 1).

The scope of this strategy is very wide, given that compounds **5** and **6** substituted not only with a pyridine group (R = 4-pyr), but also with a wide range of *ortho*, *meta* and *para* aromatic substrates containing electron-releasing and -withdrawing groups, including fluorine substituents [24], can be prepared.

Methylene oxidation of C-H bonds is a difficult task [25]. However, increasing the diversity of these polycyclic heterocycles for the preparation of planar carbonyl derivatives [3] is a very interesting goal. Methylene carbonylation of 7*H*-indeno[2,1-*c*][1,5] naphthyridines **6** was subjected to investigation using a mild oxidant such as manganese(III) acetate and acetic acid as an appropriate solvent under ambient atmosphere (Scheme 2).

In order to minimize energy consumption the reaction was performed using a microwave-assisted organic synthesis methodology. In this sense, reaction between 2-phenyl-7*H*-indeno[1,5] naphthyridine **6a** with 3 equivalents of $Mn(OAc)_3$ in a microwave reactor in acetic acid generated indeno[1,5]naphthyridin-7-one **7a** in moderate yield (41%) within 30 min. Similar results were observed when the other 7*H*-indeno[1,5]naphthyridines **6b-e** were treated under the same reaction conditions and corresponding indeno[1,5]naphthyridin-7-ones **7b-e** were obtained (Chart 2). The results demonstrated that a wide range of substituents with electron-donating and -withdrawing groups participated in this

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