Bioorganic & Medicinal Chemistry Letters 28 (2018) 1320–1323

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Synthesis and biological evaluation of novel carbazole-rhodanine conjugates as topoisomerase II inhibitors

Hong Jiang [a], Wen-Jin Zhang [a], Peng-Hui Li [a,*], Jian Wang [b], Chang-Zhi Dong [a,c], Kun Zhang [a,d], Hui-Xiong Chen [a,e], Zhi-Yun Du [a,*]

[a] Institute of Natural Medicine & Green Chemistry, School of Chemical Engineering and Light Industry, Guandong University of Technology, Guangzhou 510006, China
[b] School of Pharmaceutical Sciences, Tsinghua University, Beijing 100084, China
[c] Universite Paris Diderot, Sorbonne Paris Cite, ITODYS, UMR 7086 CNRS, 15 rue J-A de Baif, 75270 Cedex 13 Pairs, France
[d] Wuyi University, Jiangmen 529020, China
[e] CNRS, UMR8601, Laboratoire de Chimine et Biochimie Pharmacologiques et Toxicologiques, CBNIT, Universite Paris Descartes PRES Sorbonne Paris Cite, UFR Bio5medicale, 45 rue des Saints-Peres, 75270 Paris Cedex 06, France

ARTICLE INFO

Article history:
Received 23 January 2018
Revised 4 March 2018
Accepted 5 March 2018
Available online 6 March 2018

Keywords:
Carbazole
Rhodanine
Topoisomerase II
Cytotoxic
Hybrid molecule

ABSTRACT

In this study, a series of carbazole-rhodanine conjugates was synthesized and evaluated for their Topoisomerase II inhibition potency as well as cytotoxicity against a panel of four human cancer cell lines. Among these thirteen compounds, **3a**, **3b**, **3g**, and **3h** possessed Topoisomerase II inhibition potency at 20 μM. Mechanism study revealed that these compounds may function as Topo II catalytic inhibitors. It was found that the electron-withdrawing groups on the phenyl ring of compounds played an important role on enhancing both enzyme inhibition and cytotoxicity.

Human topoisomerase has been recognized as an important target in anticancer drugs discovery. Two types of topoisomerase exist in humans, namely, type I topoisomerase (Topo I) and type II topoisomerase (Topo II). Both isomers are nuclear enzymes essential to resolve topological problems that occur during DNA transcription, replication, and chromosome segregation.[1–3] Topo II is the target for several commonly prescribed anticancer drugs, including etoposide, doxorubicin, and mitoxantrone.[4] Since the identification of amsacrine as a Topo II-targeted anticancer drug in 1984, about 50% of current treatment protocols still employ at least one drug directed against topoisomerases.[5] However, drug resistance and the severe side effects of Topo II-targeted drugs are an issue.[6–8] Novel and safer Topo II inhibitors for better anticancer therapeutics are highly active research field.[9–14]

A hybrid molecule comprising two pharmacophoric groups is often used for the design of new drugs.[15] The hybrid may have increased potencies and/or modified selectivity profiles compared to the corresponding single molecule. Accordingly, several hybrid compounds have been designed, synthesized and identified as novel Topo II inhibitors (Compounds **1**, **2**, **3**, and **4**; Fig. 1).[16–19] Our previous studies demonstrated that these conjugates were generally more potent activity than the individual molecule alone (Compounds **5** and **6**; Fig. 1).[20,21] Continuing with our interest in searching novel anticancer agents that targeting Topo II with high potency, we designed and synthesized novel carbazole-rhodanine conjugates, which contain biologically active carbazole and rhodanine moiety, as shown in Fig. 2.

Carbazole are of great interest due to their broad spectrum of biochemical effects and pharmaceutical functions, including antimalarial, antibacterial and antitumor activity.[22] In particular, there have been intense research efforts in recent years in the design and development of carbazole derivatives as a new class of Topo II inhibitors.[21,23,24] For example, compounds **7**, **8**, and **9** (Fig. 2) are function as potential Topo II inhibitors and display high cytotoxicity against human cancer cell lines.[25–27]

Another pharmacophoric group in the target compounds is rhodanine moiety, which has been reported to present a variety of pharmacological activities, including antibacterial, antiparasitic, anti-microbial, and anticancer.[28] In recent years, a lot of efforts have focused on the anticancer activity of rhodanine compounds. For example (Fig. 2), GSK1059615 (compound **10**) is a reversible inhibitor of PI3Kα, which shows potential anticancer activity.[29]

* Corresponding authors.
E-mail addresses: liphsiming@163.com (P.-H. Li), zhiyundu@gdut.edu.cn (Z.-Y. Du).

https://doi.org/10.1016/j.bmcl.2018.03.017
0960-894X/

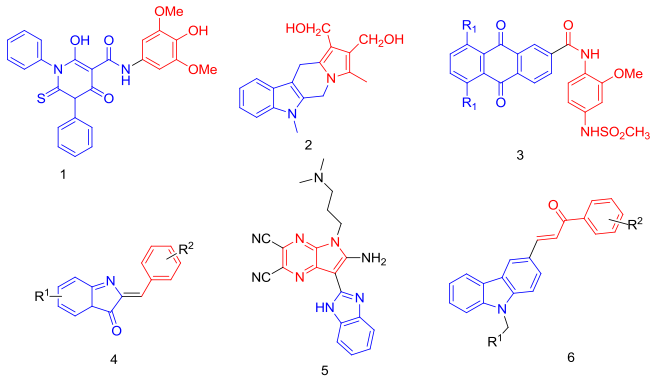


Fig. 1. Hybrid molecule as novel Topo II inhibitors.

Compound **11** displays significant anti-proliferation activity against several cancer cell lines.[30]

In the previous study, we reported a series novel Topo II inhibitors via a pharmacophore hybridization strategy.[20,21,31,32] We found that carbazole derivatives containing chalcone analogs displayed strong Topo II inhibition potency and antiproliferation activity. The SAR study revealed that the benzyl group with different substituent linked to carbazole play an important role on the activity.[21] To pursue our mission to promote novel anticancer agents that target Topo II with high potency, we introduced carbazole and rhodanine moiety into a new hybrid scaffold and linked the benzyl groups with different substituent to carbazole (Fig. 2). We found that these newly synthesized compounds displayed potent Topo II inhibitory activity and cytotoxic activity against four human cancer cell lines.

The synthetic route of carbazole-rhodanine conjugates is shown in Scheme 1. *N*-alkylation of carbazole was carried out with appropriate benzyl bromides in the presence of KOH to form **1a**–**1m** in 53–84% yields. The *N*-subsititued-9*H*-3-carbaldehydes (**2a**–**2m**) were synthesized from **1a** to **1m** through Vilsmeier-Haack reaction in 63–87% yields. The target compounds **3a**–**3m** were synthesized from **2a** to **2 m** through the Hornor-Wadsworth-Emmons reaction of rhodanine moiety in 66–91% yield. The synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR, and HRMS (ESI), which was in full accordance with their depicted structures and the structure of these compounds are shown in Table 1.

The resulting synthetic **3a**–**3m** were evaluated for their cytotoxic activities against human lung adenocarcinoma A549, human cervical cancer Hela cells, human acute leukemia HL-60 cells, and human chronic myeloid leukemia K562 cells using MTT assay as described by Mosmann with modification.[33,34] Etoposide was taken as a positive control. As shown in Table 1, most of compounds exhibited significant cytotoxicities toward four cancer cell lines with low to moderate micromolar values of IC_{50}. Almost all the compounds showed a cytotoxic selectivity for the HL-60 and K562 cell lines, and several compounds such as **3b**, **3g**, and **3h** displayed a nanomolar level IC_{50} toward HL-60, which was consistent with etoposide. It was found that the substituent on the benzyl group had a significant effect on cytotoxic activity. Compounds **3b**, **3g**, and **3h** with a strong electron-withdrawing group (–NO_2, –CN, and –CF_3, respectively) on the benzyl ring exhibited the most potent cytotoxic activity against all the tested cancer cell lines with an IC_{50} ranging between 0.96 and 7.51 μM, 0.71–8.20 μM, and

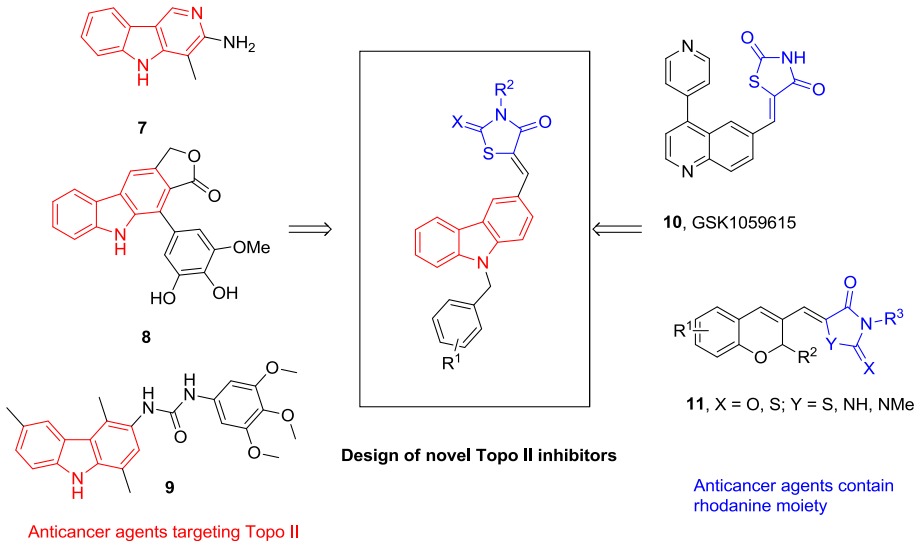
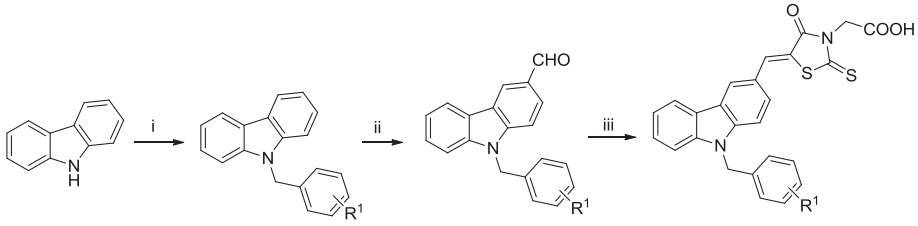


Fig. 2. Design of carbazole-rhodanine conjugates as novel Topo II inhibitors.



Scheme 1. Synthesis route of carbazole-rhodanine conjugates. Reagents and conditions: (i) DMF, appropriate benzyl bromide, K_2CO_3, rt, 24 h; (ii) $POCl_3$, DMF, DCM, 0–90 °C, 8 h; (iii) Rhodanine-3-acetic acid, NaOAc, acetic acid, 110 °C, 4 h.