Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 17 (2007) 2166–2170

Novel *N*-oxide of naphthalimides as prodrug leads against hypoxic solid tumor: Synthesis and biological evaluation

Hong Yin, Yufang Xu,* Xuhong Qian,* Yuanli Li and Jianwen Liu

Shanghai Key Lab of Chemical Biology, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, China

Received 15 October 2006; revised 24 December 2006; accepted 25 January 2007
Available online 9 February 2007

Abstract—Novel tertiary amine *N*-oxides of naphthalimides were designed and synthesized as potential anticancer agents against hypoxic solid tumors. Although their ctDNA-binding affinities and cytotoxic activities against usual tumor cell lines were lower than those of corresponding amines, the *N*-oxides **A1** and **A4** showed hypoxia preference activities against A375 cells in vitro and might be used as interesting candidates of prodrug leads in hypoxic tumor cells.
© 2007 Elsevier Ltd. All rights reserved.

The majority of clinically used anticancer drugs generally killed large numbers of tumor cells with constant proportion kinetics primarily by attacking their DNA at some level (synthesis, replication or processing).[1] However, these drugs were not truly selective for cancer cells. On one hand, normal cells such as those in the bone marrow and gut epithelia which divided rapidly were damaged;[2] on the other hand, in the treatment of solid tumors, where the majority of cells did not divide rapidly, their therapeutic efficacy was limited. It was, therefore, imperative that innovative approaches were employed to reduce the toxicity and improve the therapeutic index of the anticancer agents.

To fulfill this need, one strategy was the development of tumor-activated prodrugs (TAP), which were relatively non-toxic and can be selectively activated in tumor tissue.[3] We knew that, hypoxia was the common and unique property of cells in solid tumors,[4] which was an important potential mechanism for the tumor-specific activation of prodrugs, consequently hypoxia-dependent cytotoxicity arose such as Tirapazamine (TPZ), AQ4N, NLCQ-1, SN 23862,[5] and so on (see Fig. 1). Among them, TPZ discovered by Brown and Lee almost 20 years ago had been carried onto phase II clinical trials, and AQ4N also exhibited high selectivity against solid tumors, which encouraged us to develop novel prodrug leads for hypoxic tumor.

Naphthalimides with side chains as antitumor agents had been first discovered by Brana and co-workers.[6] Two famous compounds known as Amonafide and Mitonafide had been selected for phase II clinical trials, which inhibited the activity of topoisomerase through binding with DNA. Unfortunately, Mitonafide had inappropriate central nervous system (CNS) toxicity and Amonafide had myelosuppression, vomiting, and erythra side effects,[7] which hampered further studies. Therefore, in an attempt to find new agents with therapeutically advantageous profiles, we initiated a program to prepare novel tumor-activated prodrugs derived from naphthalimides such as Amonafide and Mitonafide (see Fig. 2).

The cationic tertiary amine side chains on these agents played an important role on electrostatic binding affinity with DNA, which also ensured good uptake into cells, then interfered with the topoisomerase function to inhibit the tumors.[8] In order to lower the toxicity and improve extravascular drug transport properties, the oxidized tertiary amine was introduced into the naphthalimide backbone to form a prodrug lead[9] instead of original amino side chain. When the compounds were induced into hypoxic cells, the tertiary amine *N*-oxides could be bioreduced to the corresponding tertiary amine and showed the high bioactivity of the amine. Of course, this process could be inhibited by oxygen.[10] Herein we designed, synthesized, and evaluated a series of novel

Keywords: *N*-Oxide of naphthalimides; Prodrug leads; Hypoxic solid tumor; Synthesis; Biological evaluation.
* Corresponding authors. Tel.: +86 21 64253589; fax:+86 21 64252603 (Y.X); e-mail addresses: yfxu@ecust.edu.cn; xhqian@ecust.edu.cn

0960-894X/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2007.02.015

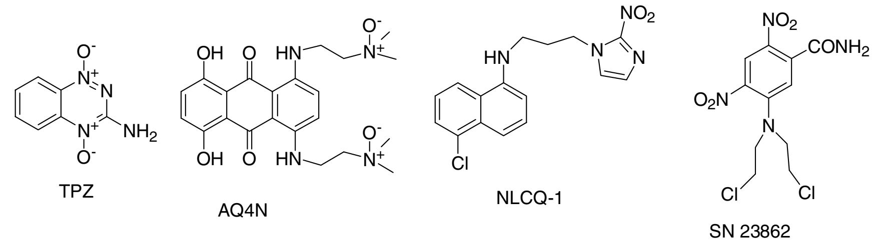

Figure 1. Structures of some reported hypoxia-selective prodrugs.

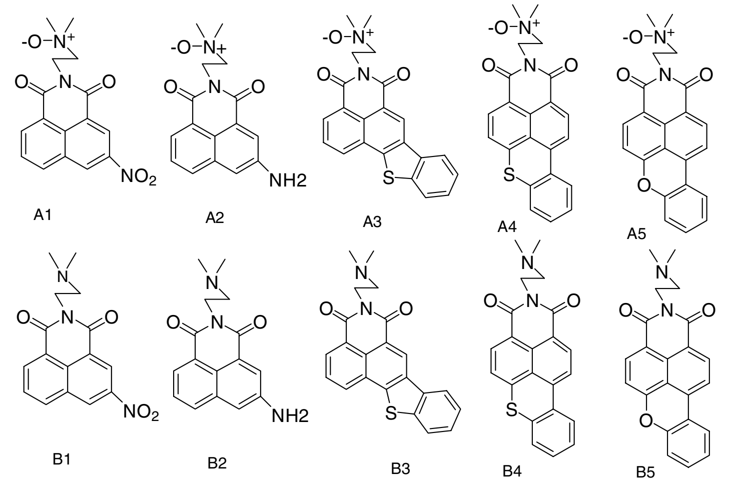

Figure 2. Novel compounds designed as potential hypoxia-selective antitumor agents (**A1**–**A5**) and some reported antitumor agents (**B1**–**B5**).

potential anticancer agents as prodrug leads against hypoxic solid tumor shown in Figure 2.

The compounds (**A1**–**A5**) were synthesized from 4-bromonaphthalic anhydride shown in Figure 3 (with compound **A5** as an example). 4-Bromonaphthalic anhydride and *o*-nitrophenol were dissolved in DMF and stirred for 1 h under reflux with NaOH and Cu as catalysts to give a yellow solid **1**. The solid **1** was treated with Fe powder in glacial acetic acid and refluxed for 1 h to afford khaki solid **2**. Then **2** was added into the hydrochloric acid and sodium nitrite at 0–5 °C for 1 h, followed by the addition of $CuSO_4$ solution, and refluxed for 0.5 h to give a yellow solid Benzo (*k*, *l*) xanthene-3,4-dicarboxylic anhydride **3**, which was mixed with *N*,*N*-dimethyl ethylenediamine in ethanol and refluxed for 3 h to give the intermediate product **4**. The important intermediates **B1**–**B4** were synthesized according to the reported methods.[11] Finally, the NO group was introduced by oxidation with H_2O_2 (30%) in CH_2Cl_2 or methanol under reflux for 1–3 h, and removal of the solvent gave the desired compounds **A1**–**A5** in high yields (Fig. 4). All of the structures were confirmed by IR, ^{1}H NMR, and HR-ESI.[12] A strong N–O stretching vibration appeared in the range of 2349–2338 cm^{-1} in their infrared spectra, which was characteristic of the *N*-oxides.

The UV–vis and fluorescence data of **A1**–**A5**, **B1**–**B5** were listed in Table 1. It was found that the quantum yields of the *N*-oxides were 0.13 and 0.123–0.99 (Φ), and the corresponding amines were 0.0046, 0.03–0.52 (Φ), which indicated that the fluorescence intensities have big changes between the *N*-oxides and their corresponding amines.

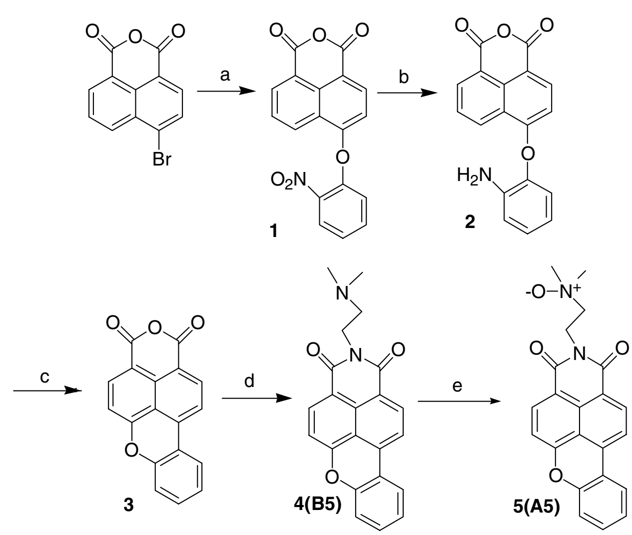

Figure 3. Reagents and conditions: (a) *o*-nitrophenol, NaOH, DMF, Cu, reflux 1 h; (b) Fe, acetic acid, reflux 1 h; (c) hydrochloric acid, acetic acid, $NaNO_2$, 0–5 °C, $CuSO_4$, HAc, H_2O; (d) *N*,*N*-dimethylethylenediamine, ethanol, reflux 3 h; (e) H_2O_2 30%, methanol, reflux, 3 h, 0.64 g (86%).

The binding properties between the compounds and ctDNA were evaluated (Fig. 5). The fluorescence data

Download English Version:

https://daneshyari.com/en/article/1366810

Download Persian Version:

https://daneshyari.com/article/1366810

Daneshyari.com