ISSN PRINT 2319 1775 Online 2320 7876

Research paper Volume 10, Iss 10, 2021

Naphthalimide derivatives as DNA intercalators and anticancer agents: A Mini Review

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ABSTRACT

1,8-Naphthalimide moiety is well known to exhibit various biological activities as it can very well intercalate with DNA and exert their antitumor activities through Topoisomerase I/II inhibition, photoinduced DNA damage or related mechanism. In recent years, much of the attention has been given to the preparation of naphthalimide derivatives by substitution at different positions of the 1,8-naphthalimide ring for their exploration as anticancer agents. These derivatives possess different anticancer properties, which cover a broader range of cancer cell lines. Interestingly, some derivatives are more potent against the selective cancer cell lines than the reference compounds like cisplatin, amonafide, mitonafide. The main objective of this study is to know the effect of different modulations at various positions of the 1,8-naphthalimide ring with a polyamine, thiourea, benzothiazole, benzimidazole, and formation of metal complexes and bis-naphthalimides which affects the overall cytotoxic properties of the resulting 1,8-naphthalimides. Moreover, the structure–activity relationship of these variations for the resulting derivatives' anticancer properties has also been discussed.

Key Words: 1,8-Naphthalimides, DNA intercalators, Topoisomerase inhibitors, Anticancer agents, Amonafide.

Introduction

According to World Health Organization (WHO) data, cancer is the second leading cause of death worldwide, which has caused 9.6 million deaths in 2018[1]. International Agency for Research on Cancer (ICAR) has estimated over 21.7 new cases and 13 million deaths due to this deadly disease by 2030[2]. Therefore, the design and synthesis of the more potent anticancer agents with limited side effects, has attracted a lot of attraction over the several years. Anticancer agents with DNA intercalating properties have been well explored and are generally associated with planar chromophores like a tri or tetracyclic ring system substituted with flexible substituent groups. This planar structure of the chromophore results in strong binding with DNA leading to the death of the tumor cell. The intercalation of the molecules

ISSN PRINT 2319 1775 Online 2320 7876

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with DNA which involves electrostatic or hydrophobic interaction, is non-covalent and reversible[3, 4] and can lead to unwinding, lengthening, or stiffening of the DNA double helix, thereby affecting the interaction of DNA with enzymes[5]. Topoisomerases are the target DNA enzymes causing cleavage of DNA followed by rearrangement. Therefore, the molecules that can intercalate with DNA are also associated with the inhibition of Topo I and Topo II[6].

Naphthalimide (1*H*-benzo[*de*]isoquinoline-1,3-(2*H*)-diones), consisting of a flat, generally π–deficient aromatic or heteroaromatic amide, are a class of compounds known to exhibit wide-ranging biological activities[7], such as antitumor activity against both murine and human tumor cells, antitrypanosomal, antiviral, local anesthetics, analgesic, serotonin 5-HT3 and 5-HT4 receptor antagonist activity and as chemosensors, etc. Apart from this, naphthalimide derivatives have also been used in non-biological applications like optical brighteners, non-biological sensors, fluorescent probes and lucifer dyes etc.

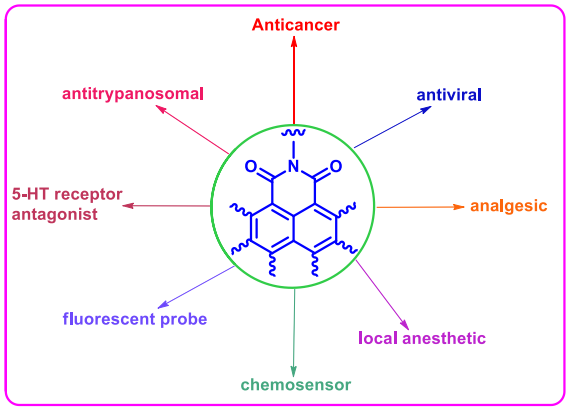

Figure 1: Therapeutic applications of naphthalimides.

Naphthalimides as anticancer agents

Two novel mono naphthalimide homospermidine derivatives (**1**, **2**) with three or four methylene unit as linkages were synthesized by Tian *et al*. and evaluated them for cytotoxicity against human leukemia K562, murine melanoma B16 and Chinese hamster ovary CHO cell lines (Fig. **2**).[8] The presence of homospermidine motif could greatly elevate the potency of 1,8-naphthalimide. Conjugate **2** with longer spacer exhibited higher in vitro cytotoxicity than **1**. The same research group reported anticancer activity of naphthalimide polyamine conjugates in which compounds **3** and **4** (Fig. **2**) exhibited best potency against all tested cells.[9] Moreover, a series of naphthalimide–polyamine conjugates were synthesized and evaluated them for cytotoxicity by Tian and co-workers. [10] It was found that lead compound **5** (Fig. **2**) obviously inhibited Akt phosphorylation.

Xie *et al*. recently reported that NPC-16 (**6**) (Fig. **2**) triggered both apoptosis and autophagy in HepG2 cells, further autophagy facilitated cellular apoptosis. [11] Li *et al.*

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synthesized novel series of 4-(4-phenyl-[1,2,3]-triazol-1-yl)-1,8-naphthalimide derivatives easily by employing "click reaction". For anti-tumor activity in vitro, all the compounds were found to be more toxic against MCF-7 than Hela and 7721 cells. Among them **7** (Fig. **2**) showed potent cytotoxic activity against MCF-7 cells with an $IC_{50}$of 0.323 µM than amonafide. The UV-vis spectra and circular dichroism titration indicated that the compounds with photosensitive phenyltriazolyl side chain behaved as effective DNA-intercalating agents.[12]

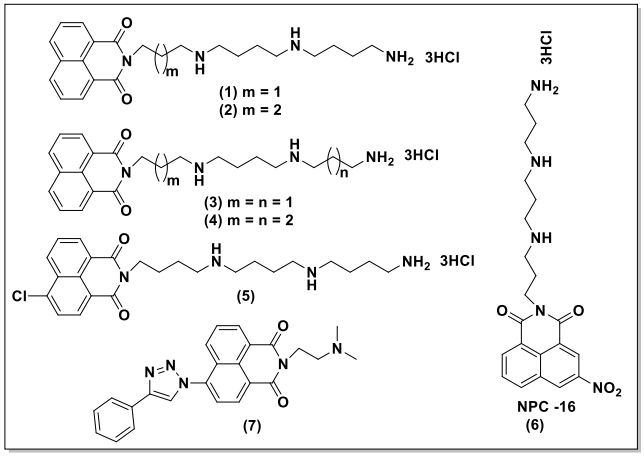

Figure 2:

Chen *et al*. developed some new naphthalimides by functionalizing at the imide N- and the 4-position of the naphthalene ring with polyamines and long alkyl chains to avoid the *in vivo* acetylation of amonafide.[13] All these conjugates show higher anticancer activity compared to amonafide against a variety of human cancer cell lines. These derivatives exhibit moderately high affinity for ct-DN and inhibit topoisomerase II activity. Linear and flexible polyamine conjugates **8**, **9**, and **10** (Fig. **3**) showed higher inhibitory activity.

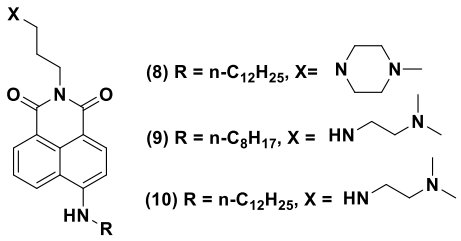

Figure 3: Chemical structure of DNA intercalative Naphthalimides.

Rao et al.[14] have reported in vitro cytotoxic activity of naphthalimide-benzothiazole/cinnamide derivatives (Fig. 4) against HT-29, A549, and MCF-7 human cancer cell lines using amonafide as standard. Derivatives containing electron-donating groups on benzene moiety of benzothiazole exhibited better activity against HT-29 and A549 (IC_{50} = 4.22–4.76 µM and 4.98–6.20 µM for **11a** and **11b**, respectively) than amonafide (IC50 = 5.46–7.76 µM). Overall, these results demonstrated that the hybrids **12a**, **12b** that have an amide

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bond at 6-position showed better activity compared to the analogs with an amide bond at 2-position of the benzothiazole moiety. All the synthesized hybrids were selectively more potent in HT-29 and A549 cell lines compared to MCF-7.

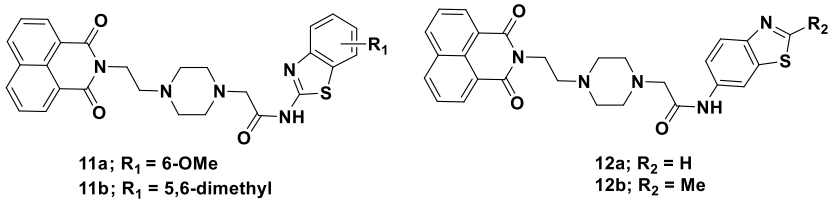

Figure 4: Chemical structure of naphthalimide–Benzothiazole hybrids

Structural requirements of naphthalimides

On comparing the biological activities of the several mono-naphthalimides the structure–activity relationship studies have pointed out some important parameters, which influence the cytotoxic property of naphthalimides related to mitonafide and amonafide.[15] A summary of the structural requirements for optimal activity found for the naphthalimides studied is shown in (Fig. **5**).

- The presence of a basic terminal group in the side chain is crucial for cytotoxic activity.
- Any decrease in the basicity of this terminal nitrogen leads to less active products. Quaternization of the terminal amino group produces a new compound with loss of cytostatic activity.
- The activity also decreases with the number of substituents on the terminal nitrogen atom. Presence of amine ($–NH_2$) and methylamine group ($–NHCH_3$) in the terminal position of nitrogen instead of dimethylamine ($–N(CH_3)_2$) displayed significant loss of anticancer activity.
- Growth inhibition is maximal when the nitrogen atom of the basic side chain is separated from the naphthalene ring nitrogen by two or three methylene units.

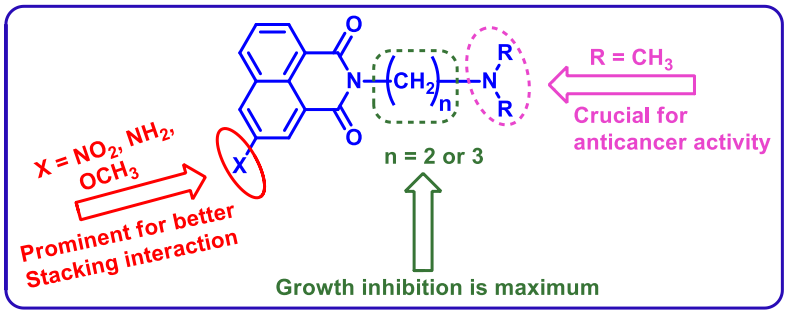

Figure 5: The best substituted mono-naphthalimides based on SAR studies.

ISSN PRINT 2319 1775 Online 2320 7876

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