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Novel Approaches in the Synthesis of Batracylin and Its Analogs: Rebirth of an Old Player?

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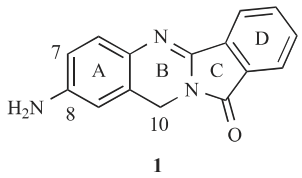
Abstract: Batracylin (8-aminoisoindol[1,2-b]-quinasolin-12(10H)-one, BAT), a heterocyclic amine, was isolated in 1978 (NCI, Bethesda, USA) in the course of search for the new anticancer drugs. It showed high *in vitro* and *in vivo* anticancer activities against murine leukemia P338 and colon adenocarcinoma 38. Mechanism of action of BAT is still not completely clear. It was reported, that BAT is a topoisomerase II inhibitor and induces unscheduled DNA synthesis (UDS) in non-proliferating cells. Low solubility of BAT in water, high toxicity and necessity of high drug dosing are major limitations of its use as a chemotherapeutic drug. As a result, new BAT analogs were synthesized to improve its pharmacological properties. The modifications of BAT chemical structure include various substituents introduced to isoindoloquinazoline moiety (Cl, Br, NO_2, CH_2, NH_2, Me, CO_2Me, OMe). It has been shown that the desamino derivative and the 8-aza analog of BAT retained the ability to inhibit topoisomerase II but did not induce unscheduled DNA synthesis. While less active than BAT, these analogs were cytotoxic toward CCRF-CEM leukemia cells. The isoindolo [2,1-a]benzimidazole derivatives were inactive as topoisomerase II inhibitors and, in general, failed to exhibit comparable antitumor activity or to induce unscheduled DNA synthesis. Batracylin was acylated with aminoacids, dipeptides, tripeptides to increase its solubility in water. Other modifications include introduction of nitrogen atom to ring A or D, extension of polycyclic ring 4, reduction of ring B from six- to five-membered one, and obtaining of benzimidazole, indole or derivatives containing a fucose ring. A series of novel BAT analogs bearing sugar residues and thiocarbonyl aminoacids, which provided better solubility in water and high cytostatic activity have been designed. Also, new azabatracylines, where aniline ring was replaced by pyridine or other substituted quinazolines, have been obtained. This paper reviews the most important approaches in batracylin synthesis and its analogs and presents structure-reactivity relationships for these compounds.

Keywords: Batracylin, BAT, batracylin analogs, synthesis, biological activity, cancer therapy.

INTRODUCTION

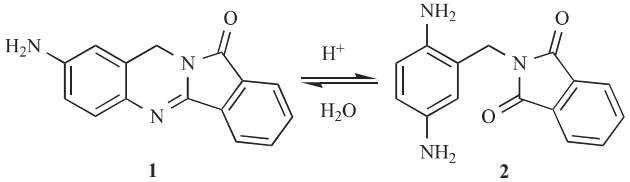
Batracylin (NSC 320846, 8-aminoisoindolo[1,2-b]quinazolin-12(10H)-one, BAT) (**1**) (Fig. (**1**)) was discovered by the Development Therapeutics Program of the National Cancer Institute (NCI) and is a heterocyclic arylamine that exists as a yellow solid. This compound is structurally related to many of the food mutagens including 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) [1, 2]. Previous studies have shown that this investigational drug not only exhibits potent antitumor activity *in vivo* against murine solid tumors including pancreatic ductal adenocarcinoma, colon adenocarcinoma #51, and hepatoma 129 but is also effective against murine leukemia P388 and colon adenocarcinoma 38 cell lines which are resistant to adriamycin, cisplatin and methotrexate. Interestingly, batracylin is inactive against other standard tumor models such as B16 melanoma, CD8F1 mammary carcinoma, L1210 leukemia, Lewis lung carcinoma, and human MX-1 mammary xenograft [3, 4]. Mechanistic studies revealed that batracylin inhibits the catalytic activity of DNA topoisomerases that leads to DNA lesions and induction of the unscheduled DNA synthesis [5, 6]. Batracylin is known to hydrolyze reversibly under acidic conditions to produce a ring-opened product (**2**) (Scheme **1**) [7]. While this ring-opened product was not detected in the plasma of mice, to which batracylin was administered, it does not exclude the possibility that it can still contribute to the antineoplastic activity observed for the parent drug. Batracylin has been tested in phase I clinical trial to evaluate the safety of its oral administration to subjects with solid tumors and lymphomas (see ClinicalTrials.gov). These studies were completed in 2011 and the obtained data are currently being analyzed.

Due to low water solubility of batracylin that limits its oral administration, numerous studies have sought analogs with more favorable pharmacological characteristics. The structural modifications applied to batracylin include the introduction of diverse substituents on the isoindoloquinazoline core (Cl, Br, NO_2, CH_2, NH_2, Me, CO_2Me, OMe) and will be presented in detail in this review. To increase batracylin solubility in water, batracylin was acylated with amino acids, dipeptide, tripeptide or coupled to sugar moieties; by the inclusion of a nitrogen atom in ring A or ring D (**3**, **4**); an increase in the size of the polycyclic system (**5**); and reduction of the chromophore size from six- to a five-membered moiety by removing the ring B to obtain benzimidazole (**6**) or indole (**7**) analogs (Fig. (**2**)) [8].



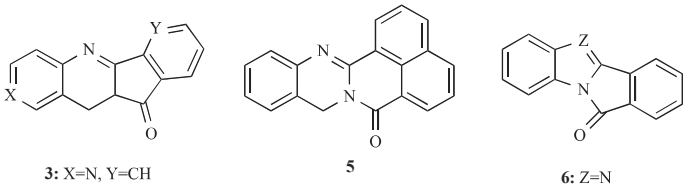
1

Fig. (1). Chemical structure of batracylin (**1**) [2].



1 **2**

Scheme 1. Acid-stimulated hydrolysis of batracylin (**1**) [7].



3: X=N, Y=CH
4: X=CH, Y=N

5

6: Z=N
7: Z=CH

Fig. (2). Analogs of batracylin [8].

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