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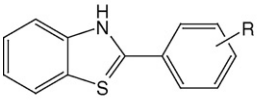
MOLECULES

Combinatorial chemistry improves molecular options over pre-existing leads

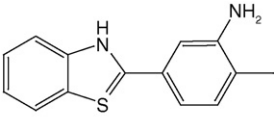
Combinatorial synthesis of benzothiazoles and evaluation of topoisomerase II inhibitory activity

2-(4-Aminophenyl)benzothiazoles display potent and selective antitumour activity against breast, ovarian, colon and renal cancer cell lines, but their mechanism of action has yet to be elucidated [1]. Of interest is the fact that compounds are active only against certain human cancer cell lines, such as breast MCF-7, MDA 468, renal TK 10, and ovarian IGROV1 [1]. The activities were considered to be related to their metabolism, given that the sensitive cell lines efficiently retained and metabolized 2-(4-aminophenyl)benzothiazoles to acetylated and 6-hydroxylated derivatives [2]. DNA topoisomerases are ubiquitous enzymes that control and modify the topological states of DNA. They are considered to have important roles in areas such as replication, recombination and transcription by catalyzing the passage of individual DNA strands (topoisomerase I) or double helices (topoisomerase II) through one another. Topoisomerase activities are activated in cancer cell growths and, thus, are good targets for antineoplastic drugs.

A recent study [3] has sought to investigate one possible mechanism of action of the cytotoxic activity of benzothiazoles through the synthesis of 2-(substituted-phenyl) benzothiazoles and subsequent evaluation of their cytotoxicity and ability to inhibit topoisomerase II activities. The synthesis of a small library of 2-(substituted-phenyl) benzothiazoles [general structure **(i)**] was undertaken on solid-phase 4-methoxytrityl resin. The *in vitro* cytotoxic activities of compounds were evaluated using the human solid tumour cell lines A549 (lung cancer), Col2 (colon cancer), SNU-638 (stomach cancer), HT1080 (fibrosarcoma cancer) and HL-60 (myeloid leukemia). Upon screening of the library compounds, it was determined that these compounds were less cytotoxic than were the clinical agents ellipticine and doxorubicin. Compound **(ii)**, however, had selective cytotoxicity for myeloid leukemic cancer cells (IC_{50} 20 nM). Many compounds proved to have topo II inhibitory activity, with **(ii)** being one of the most potent found with an IC_{50} of 72 μM. Topo II is an important nuclear enzyme controlling DNA topology through catalysis of a transient breakage of double-stranded DNA in an ATP-dependent fashion, enabling the passage of double-stranded DNA followed by a resealing of the DNA [4]. In summary, this work has produced compound **(ii)** with topo II inhibitory activity comparable to the antitumour agent etoposide, which was also a potential selective cytotoxicity agent against myeloid leukemic cancer cells and further work in this area is warranted.



(i)



(ii)

High-affinity ligands to the $\alpha_2\delta$ subunit of voltage-gated calcium channels

Gabapentin **(iii)** is an anticovulsant agent used in the clinical treatment of epilepsy [5]. Clinical studies have recently demonstrated that gabapentin is efficacious in reducing neuropathic pain in humans and suggested that gabapentin and related gamma amino acids are promising new therapeutics for the treatment of neuropathic pain [6] and anxiety [7]. It has been postulated that the efficacy of gabapentin in reducing neuropathic pain is a consequence of its interaction with the $\alpha_2\delta$ subunit of the voltage-dependant calcium channel (VDCC) [8]. Recent work [9] has probed the $\alpha_2\delta$ binding hypothesis to discover a compound superior to gabapentin. The approach taken involved high-throughput parallel synthesis in solution, in tandem with rapid purification techniques. This formed the basis for the synthesis of a focused library of 576 pyrrolopyridazine derivatives, of general structure **(iv)**.

The key to the synthesis was the parallel Sn2Ar coupling methodology, which enabled the rapid generation of a 1-aminopyrrolopyridazine library [transformation **(v)** to **(iv)** in the Scheme]. The library was screened in a [^{3}H]gabapentin binding assay against human A710 cell membranes. Several active compounds were obtained, of which one of the most potent was **(vi)** with an $\alpha_2\delta$ binding affinity (IC_{50}) of 30 nM.

This work is of interest because it has demonstrated the use of a high-throughput parallel Sn2Ar reaction, which enabled rapid SAR generation of lead compounds. The library targeted a series of leads with improved or equal potencies compared with those of the initial lead compound used in this study. Further profiling of the leads such as **(vi)** is warranted.

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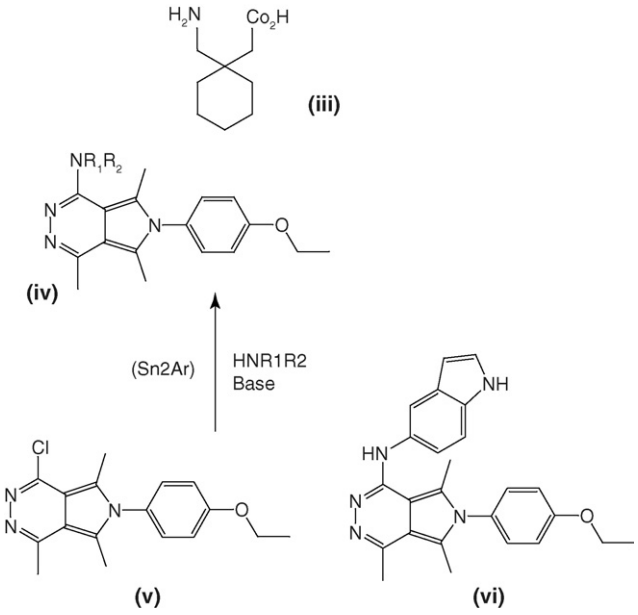

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