European Journal of Medicinal Chemistry xxx (2014) 1–9

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

# Heterocyclic scaffolds as promising anticancer agents against tumours of the central nervous system: Exploring the scope of indole and carbazole derivatives

Chris Sherer, Timothy J. Snape*

*School of Pharmacy and Biomedical Sciences, University of Central Lancashire, Preston, Lancashire, PR1 2HE, UK*

ARTICLE INFO

*Article history:*
Received 7 September 2014
Received in revised form
30 October 2014
Accepted 3 November 2014
Available online xxx

*Keywords:*
Indole
Carbazole
Indolocarbazole
CNS
Cancer
Heterocycle

ABSTRACT

Tumours of the central nervous system are intrinsically more dangerous than tumours at other sites, and in particular, brain tumours are responsible for 3% of cancer deaths in the UK. Despite this, research into new therapies only receives 1% of national cancer research spend. The most common chemotherapies are temozolomide, procarbazine, carmustine, lomustine and vincristine, but because of the rapid development of chemoresistance, these drugs alone simply aren't sufficient for long-term treatment. Such poor prognosis of brain tumour patients prompted us to research new treatments for malignant glioma, and in doing so, it became apparent that aromatic heterocycles play an important part, especially the indole, carbazole and indolocarbazole scaffolds. This review highlights compounds in development for the treatment of tumours of the central nervous system which are structurally based on the indole, carbazole and indolocarbazole scaffolds, under the expectation that it will highlight new avenues for research for the development of new compounds to treat these devastating neoplasms.



## 1. Introduction

Despite continued research efforts, cancer remains one of the biggest threats to human health, and it was estimated to be responsible for 15% of all deaths internationally in 2010 [1]. More recently, in 2014 in the USA, it is expected that there will be 1,665,540 new incidences of cancer, of which 23,380 would be of the “brain and other nervous system” (1.4%), yet such cancers would result in 14,320 of the 585,720 cancer-related deaths (2.4%) [2]. Tumours of the brain and central nervous system, unlike many other tumour types, can occur in people regardless of sex, race and age, as well as generally being unpreventable [3]. This means that continued research, specifically into curative therapies, is paramount.

In particular, tumours of the central nervous system (CNS) are intrinsically more dangerous than tumours at other sites. In the case of brain tumours, they are responsible for 3% of cancer deaths in the UK, yet research into cures receives only 1% of national cancer research spend [4]. Current treatment for brain tumours generally involves surgical resection (if possible), followed by radiotherapy and chemotherapy, with the most common chemotherapies, according to Cancer Research UK, being temozolomide, procarbazine, carmustine, lomustine and vincristine. Because of the rapid chemoresistance developed by many brain cancers, these drugs alone simply aren't sufficient for long-term treatment [5].

The indole moiety has been described as a privileged structure [6] as it is a structure that appears extensively in many unrelated areas of biology and medicine, and depending on substituents can have a diverse range of effects. The indole nucleus can be found in compounds as diverse as the hormone serotonin, the amino acid tryptophan, the psychedelic drug LSD and the antimigrane drug rizatriptan (Fig. 1). It is believed by many to be the most ubiquitous and important privileged structure known [6,7].

Just as indoles can be diverse in structure, there are a wide range of biological targets that indoles have been shown to affect. This review discusses ways in which indoles have been shown to prevent cell signalling (PKC inhibitors, PDGF signal transduction inhibitors), prevent normal cell cycle progression (G2/M abrogators, CK2 inhibitors, Trk inhibitors, topoisomerase inhibitors), induce oxidative stress to cells (reactive oxygen species generators), prevent vascularisation in tumours (angiogenesis inhibitors), prevent DNA repair (PARP inhibitors, CK2 inhibitors), and induce the form of cell death known as methuosis.

This review focuses on the development of drugs for the treatment of tumours of the central nervous system which are

* Corresponding author.
*E-mail address:* tjsnape@uclan.ac.uk (T.J. Snape).

http://dx.doi.org/10.1016/j.ejmech.2014.11.007
0223-5234/

**Acronyms/initialisms**

| | |
|---|---|
| AML | Acute myeloid leukaemia |
| CK2 | Casein kinase 2 |
| CNS | Central nervous system |
| PARP | Poly ADP ribose polymerase |
| PDGF | Platelet-derived growth factor |
| PKC | Protein kinase C |
| ROS | Reactive oxygen species |
| VEGF | Vascular endothelial growth factor |

structurally based on the indole, carbazole and indolocarbazole scaffolds (Fig. 2). In doing so, the literature was searched using Thomson Reuters' Web of Knowledge™ for articles containing both a classification of tumours of the central nervous system and either the term "*indol*" or "*carbazol*", and no restraint on publication date was used. In the interest of ensuring comprehensiveness, this review focuses solely on indole-based structures, so related structures such as isoindoles, indolenes, indazoles and azaindoles are not included, but will be the focus of a separate review. As this is a review of the effect of the indole moiety on biological activity, molecules where the inclusion of an indole moiety does not appear to be the important structural factor, such as in large natural products, are also not included.

## 2. Topoisomerase inhibitors

Topoisomerase enzymes regulate how wound the double helical structure of DNA is, since they are capable of changing the topology of a DNA strand. Topoisomerases work by binding to the DNA and clipping the phosphate backbone, then either overwinding or underwinding the helix before reforming the backbone. They are particularly active during DNA replication, when the DNA helix can become overwound and then relaxed by topoisomerases.

Topoisomerases are split into two main categories; type I and type II. Type I topoisomerase (often referred to as topo I) acts by clipping one of the two strands of DNA, underwinding or overwinding the strand once (i.e. changing the linking number by ±1) and then reannealing the strand. This differs to Type II topoisomerase (topo II), which simultaneously clips both strands of the DNA helix in order to undo tangles and supercoils, and in the process change the linking number by ±2.

Topoisomerase inhibitors have been of interest as anticancer agents for the past 30 years [8], and the first potential anticancer drug underwent Phase I clinical testing over 20 years ago [9]. They are of pharmacological interest because of the strand breaks that occur in the absence of topoisomerases. These strand breaks render the DNA irreparably damaged, leading to cell death. Indole-containing topoisomerase inhibitors have been worked on by multiple research groups (see below), and many of these

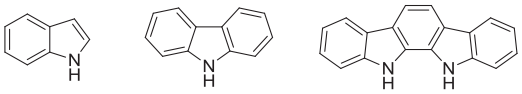

**Fig. 2.** From left to right: indole, carbazole and indolocarbazole.

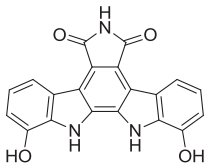

**Fig. 3.** The topoisomerase inhibitor BE-13793C.

compounds have strong structural similarities, in particular those containing an indolocarbazole group.

During a screening programme for antitumour substances at Banyu Pharmaceutical Company, a group lead by Suda discovered that the bacteria *Streptomyces mobaraensis* (strain BA13793) produced a topoisomerase I and II inhibitor which they named BE-13793C (Fig. 3) [10]. BE-13793C is an indolocarbazole, an indole fused to a carbazole (Fig. 2), which is a moiety that appears commonly in topoisomerase inhibitors [11].

Although initially BE-13793C wasn't tested on any brain tumour cell lines, it was shown to inhibit the growth of certain leukaemia cell lines, and was used as a lead compound for subsequently developed compounds, which ultimately were active against various brain tumour cell lines. During this lead development process one such compound identified was ED-110 (Fig. 4), a derivative first described in 1993 by many of the same people who discovered BE-13793C [12]. This analogue was found to induce topoisomerase I-mediated DNA cleavage, but not topoisomerase II-mediated cleavage [13]. ED-110 was produced by selectively glucosating one of the nitrogens of BE-13793C [12], and was tested on the tumour cell lines MKN-45 (human stomach), LS-180 (colon) and PC-13 (lung), and was found to have $IC_{50}$ values of 0.28 μg/mL, 1.65 μg/mL and 1.70 μg/mL respectively. It was also shown to help prevent metastases of the CNS tumour fibrosarcoma [14].

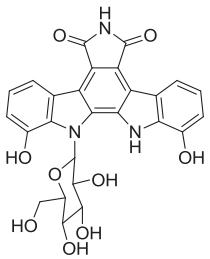

**Fig. 4.** The structure of ED-110.

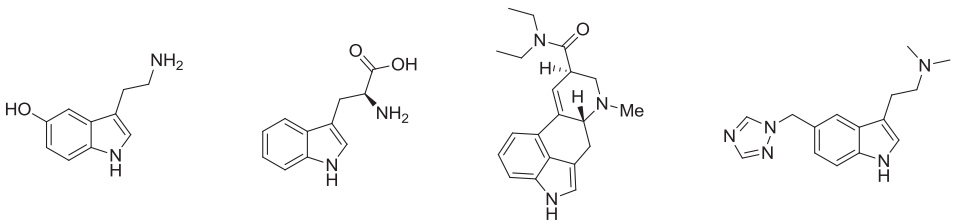

**Fig. 1.** From left to right: serotonin, tryptophan, LSD and rizatriptan.

Please cite this article in press as: C. Sherer, T.J. Snape, Heterocyclic scaffolds as promising anticancer agents against tumours of the central nervous system: Exploring the scope of indole and carbazole derivatives, European Journal of Medicinal Chemistry (2014), http://dx.doi.org/10.1016/j.ejmech.2014.11.007