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Original article

Design, synthesis and QSAR study of certain isatin-pyridine hybrids as potential anti-proliferative agents

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ABSTRACT

A hybrid pharmacophore approach was adopted to design and synthesize new series of isatin–pyridine hybrids. All the newly prepared hybrids (**5a**–**o**, **8** and **11a**–**d**) were *in vitro* evaluated for their anti-proliferative activity against three human cancer cell lines, namely HepG2 hepatocellular carcinoma, A549 lung cancer and MCF-7 breast cancer. Compound **8** emerged as the most active member against HepG2 cell line (IC_{50} = 2.5 ± 0.39 μM), with 2.7-fold increased activity than the reference drug, doxorubicin (IC_{50} = 6.9 ± 2.05 μM). Whilst, compound **11c** was found to be the most potent counterpart against A549 and MCF-7 cell lines with IC_{50} values of 10.8 ± 1.15 and 6.3 ± 0.79, respectively. The weightiness of the utilization of non-cleavable linker, as the chalcone linker, and simplification of the first group, was explored *via* the SAR study. Furthermore, a QSAR model was built to explore the structural requirements controlling the cytotoxic activities. Notably, the predicted activities by the QSAR model were very close to those experimentally observed, hinting that this model could be safely applied for prediction of more efficacious hits comprising the same skeletal framework. Finally, a theoretical kinetic study was established to predict the ADME of the active hybrids.

1. Introduction

Molecular hybridization is a valuable structural modification approach that comprises the incorporation of two or more pharmacophores into a single entity. It is based on the recognition of pharmacophoric subunits in two or more biologically active molecules with subsequent fusion of these subunits in the molecular architecture of hybrid compounds combining pre-selected characteristics of the original templates [1]. These biologically active molecules could be acting through the same mechanism of action or different mechanisms of action [2]. Moreover, the connection between the two molecular entities could be carried out using cleavable or non-cleavable linkages. Utilization of the non-cleavable linker is based on the ability of the different molecules to retain their biological activity and specific affinity for their biological targets. While, the approach using cleavable bond is based on the release of the two parental molecular structures under physiological or the enzymatic conditions that prevail at site of activity aiming to either improve poor pharmacokinetic properties or improve the activity and selectivity of the drugs and to release the two substances directly in the targeted tissues [2]. Mostly, design of the hybrid drugs aims to circumvent the drug resistance, minimize the risk of drug–drug interactions, counterbalance the known side effects associated with the other hybrid part and amplify the activity through the interaction with multiple targets as one single molecule [3,4]. In the last few years, hybrid drug design has emerged as a prime tool for the discovery of innovative anticancer therapies that can potentially overcome most of the pharmacokinetic drawbacks encountered when using conventional anticancer drugs.

Isatin (1*H*-indole-2,3-dione), **I** (Fig. 1), is a privileged scaffold and one of the most promising class of heterocyclic systems that possesses many interesting activity profiles and well-tolerated in humans [5]. BIBF1120 **II** (Fig. 1), an isatin-based triple angiokinase inhibitor disclosed by Boehringer, is currently in phase III clinical trials in non-small cell lung cancer [6]. Sunitinib, **III** (Fig. 1), trade name Sutent, is a multikinase isatin-based inhibitor targeting

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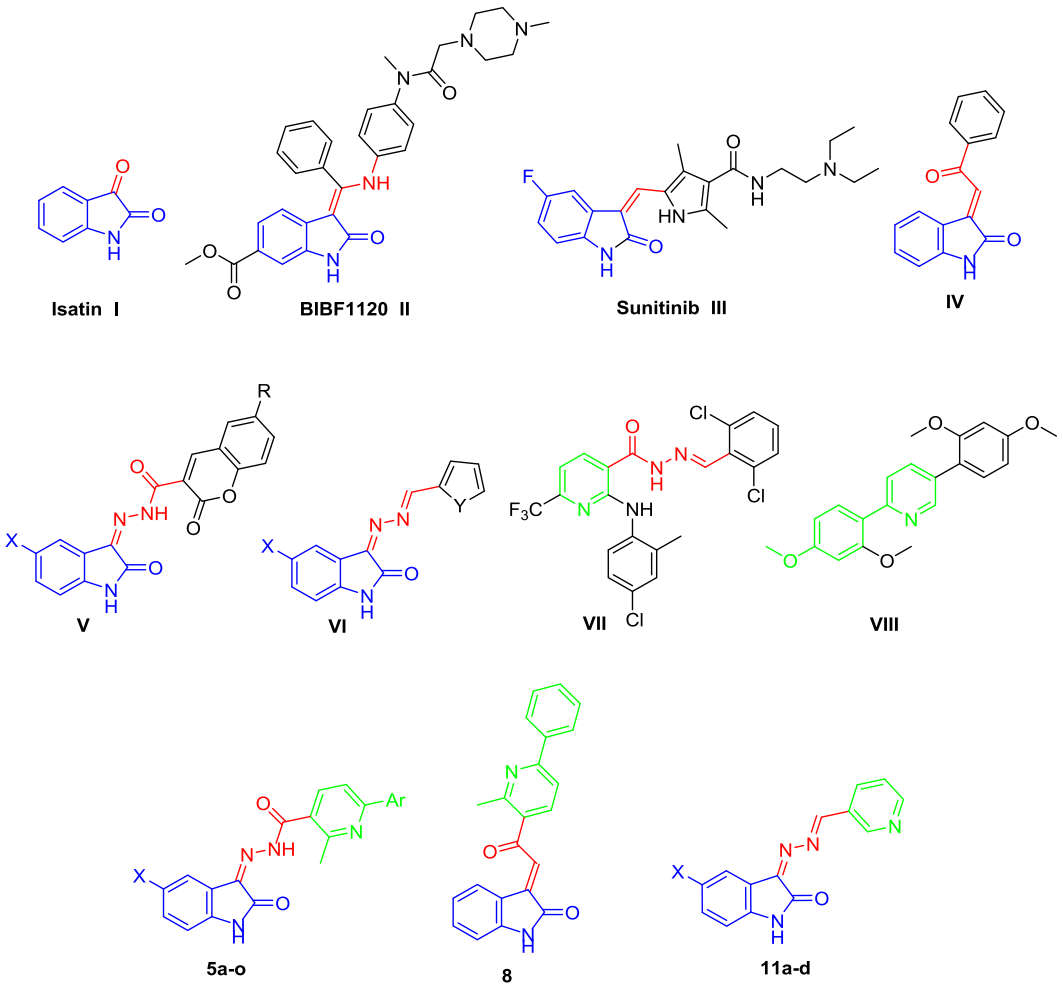

Fig. 1. Structures of compounds **I**–**VIII** and the target hybrids (**5a**–**o**, **8** and **11a**–**d**).

VEGFR-1, VEGFR-2, PDGFRβ and c-Kit. Sunitinib was approved in 2006 by the FDA for the treatment of advanced renal cell carcinoma (RCC) and gastrointestinal stromal tumors (GIST) [7–9]. The FDA approval of sunitinib paved the way to design and synthesis of various isatin-based molecules with diverse activities against cancer. In this context, many synthetic isatin-based derivatives were developed to inhibit diverse tyrosine and serine/threonine kinases, to name just a few, c-Met kinase [10], c-Src kinase [11], RET kinase [12], FLT3 kinase [13], cyclin-dependent kinases (CDKs) [14], glycogen synthase kinase 3β (GSK-3β) [15], Aurora B kinase [16], p38α MAP kinase [17], JNK3 MAP kinase [18], p90 ribosomal S6 protein kinase 2 (RSK2) [19] and Polo-like kinase 4 (PLK4) [20,21].

Over the last decade, numerous studies pointed out the importance of isatin based anticancer hybrids as promising chemotherapeutic agents. Several research groups adopted hybridization approach for the design of isatin-thiazolidine/thiazolidinone hybrid analogs as potent anti-proliferative agents [22–26]. Lee and co-workers reported two studies about the design, synthesis and cytotoxicity evaluation of two different series of isatin–benzothiazole and isatin-linked chalcones analogs against three human breast cancer cell lines. Compound **IV** (Fig. 1), elicited excellent activity with IC_{50} values of 14.99, 5.26 and 4.23 μM against MDA-MB231, MDA-MB468 and MCF7 cancer cells, respectively [27,28]. Also, A. T. Taher et al. [29] explored the anti-breast cancer activity of isatin-thiazoline and isatin-benzimidazole conjugates against breast cancer cell line MCF7. Besides, the cytotoxic activities of isatin-arylsulfoanilide [30], isatin-4-piperazinylquinoline [31], isatin-benzoxazole [32], isatin-quinazoline-4(3*H*)-one [33] and isatin-pyrazoline [34] hybrids were reported. Moreover, we reported the anticancer activity of two series of isatin-based hydrazones **V** and **VI** (Fig. 1) [35,36].

On the other hand, non-fused pyridines constitute another important class of heterocycles, which displayed interesting biological activities including anticancer activity [37–39]. Sorafenib, Regorafenib, Vismodegib and Crizotinib are examples for the clinically approved pyridine-containing anticancer drugs [40–42]. Interestingly, the pyridine-based hydrazone **VII** (Fig. 1), inhibited the growth of all tested cancer cell lines with nanomolar potency at the NCI, USA and did not show animal toxicity. Moreover, it has been selected by the Biological Evaluation Committee of NCI for testing in vivo Hollow Fiber Assay [43]. Recently, Zheng and co-workers developed a novel series of pyridine-bridged analogs of combretastatin-A4 as potential anticancer agents. Among these derivatives compound **VIII** (Fig. 1), displayed modest activities against A549 lung cancer, MDA-MB-231 breast cancer and Hela cervical cancer cell lines [44].

The present study is an extension of our ongoing efforts towards developing potent isatin-based anticancer agents [35,36,45–47], utilizing a hybrid pharmacophore approach. In view of the previous findings, we decided to design and synthesize three different set of isatin-pyridine hybrids **5a**–**o**, **8** and **11a**–**d** (Fig. 1), with the prime aim of developing potent anticancer agents. Our strategy adopted