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Research paper

Repurposing a polymer precursor: Synthesis and *in vitro* medicinal potential of ferrocenyl 1,3-benzoxazine derivatives

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ABSTRACT

Cancer and malaria remain relevant pathologies in modern medicinal chemistry endeavours. This is compounded by the threat of the development of resistance to existing clinical drugs in use as first-line option for treatment of these diseases. To counter this threat, strategies such as drug repurposing and hybridization are constantly adapted in contemporary drug discovery for the expansion of the drug arsenal and generation of novel chemotypes with potential to avert or delay resistance. In the present study, a polymer precursor scaffold, 1,3-benzoxazine, has been repurposed by incorporation of an organometallic ferrocene unit to produce a novel class of compounds showing *in vitro* biological activity against breast cancer, malaria and trypanosomiasis. The resultant ferrocenyl 1,3-benzoxazine compounds displayed high potency and selectivity against the investigated diseases, with IC_{50} values in the low and sub-micromolar range against both chloroquine-sensitive (3D7) and resistant (Dd2) strains of the *Plasmodium falciparum* parasite. On the other hand, antitrypanosomal (*Trypanosoma brucei brucei*) potencies were observed between 0.15 and 38.6 μM. The majority of the compounds were not active against breast cancer cells (HCC70), however, for the toxic compounds, IC_{50} values ranged from 11.0 to 30.5 μM. Preliminary structure-activity relationships revealed the basic oxazine sub-ring and lipophilic benzene substituents to be conducive for biological efficacy of the ferrocenyl 1,3-benzoxazines reported in the study. DNA interaction studies performed on the most promising compound **4c** suggested that DNA damage may be one possible mode of action of this class of compounds.

1. Introduction

Benzoxazines are an eminent class of heterocyclic compounds endowed with appealing chemical and physical properties, placing them in the spotlight for various applications over the years [1,2]. The versatility of benzoxazines spans a diverse spectrum of industrial applications, from fabrication of polymers to biological applications as potential therapeutic drugs [1,2]. Since its conception, the benzoxazine scaffold has been a subject of extensive study for pharmaceutical applications due to its array of biological activities. Investigation of compounds containing this scaffold as chemotherapeutics, particularly 3,4-dihydro-2*H*-1,3-benzoxazines, dates as far back as the 1950s [3]. Urbański and colleagues were among the first to unveil the pharmaceutical potential of simple 1,3-benzoxazines such as **A** possessing antitumour efficacy (Fig. 1) [3,4]. Subsequent studies on the biological relevance of this scaffold, including the isolation of plant-based 2,4-dihydroxy-7-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one (DIMBAO) (**B**) as the first naturally occurring benzoxazine [5], unearthed a multitude of other biological activities possessed by this class of compounds.

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