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Improved anticancer and antiparasitic activity of new lawsone Mannich bases

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ABSTRACT

Substituted lawsone Mannich bases **2a-e**, **3a-e** and **4a-e** were prepared and tested for their biological activities. The new fatty alkyl substituted compounds **2a-c** exhibited strong and selective growth inhibitory activities in the low one-digit micromolar and sub-micromolar range against a panel of human cancer cell lines associated with ROS formation. In addition, compounds **2a-c** revealed sub-micromolar anti-trypanosomal activities against parasitic *Trypanosoma brucei brucei* cells via deformation of the microtubule cytoskeleton. The *N*-hexadecyl compound **2c** was also highly active against locally isolated *Entamoeba histolytica* parasite samples exceeding the activity of metronidazole.

1. Introduction

Naphthoquinones feature a large group of secondary plant and lichen metabolites with a broad range of properties including antioxidant, anti-inflammatory, anticancer, antibacterial, and trypanocidal activities [1-5]. Lawsone, 2-hydroxy-1,4-naphthoquinone (Fig. 1), is a constituent of the Henna plant (*Lawsonia inermis*) applied mainly for the treatment of skin diseases in Ayurveda and Unani medicine in South Asia [3-7]. Its biological properties are only fragmentarily explored, and in contrast to other natural naphthoquinones such as plumbagin and juglone, lawsone only showed weak toxicity both to hepatocytes and to various tumor cell lines [8-12]. Lawsone is a potentially useful starting material for the preparation of other *p*-quinones with proven or conceivable bioactivity such as atovaquone or lapachol [3, 4]. The readiness with which naphthoquinone derivatives undergo redox reactions and chelation of metal ions is presumably responsible for the greater part of their biological activities [4]. Ferrocenic aminohydroxynaphthoquinones derived from lawsone were reported to inhibit the growth of *Toxoplasma gondii* parasites [13]. *O*-Allyl and *C*-allyl lawsone derivatives and the naphthofuranquinone cyclization products of the latter showed distinct activity against *Trypanosoma cruzi* parasites [14, 15]. Some phenyl ethers of lawsone exhibited potent activity against *Trypanosoma brucei rhodesiense* and *Leishmania donovani* [16]. Fatty alkyl substituted lawsones revealed trypanocidal activity against the infective blood stream form of *T. cruzi* [17]. Pronounced anti-plasmodial activity against *Plasmodium falciparum* was observed for phenylsulfanylmethyl naphthoquinones based on lawsone [18]. A series of anticancer active 3-aminomethyl-naphthoquinones readily obtained from lawsone via a one-pot Mannich reaction was disclosed recently (e.g., **1**, Fig. 1) [19-22]. We now refined the structural motif of **1** by elongation of the *N*-alkyl side chain since long-chained alkyl residues were frequently found to confer enhanced bioactivity [23]. In addition, we explored the feasibility of other molecular fragments such as the vanillyl moiety that occurs in many bioactive natural products (e.g., in curcumin and ferulic acid), and the isosteric 3,4-difluorophenyl moiety. It was recently disclosed that certain naphthoquinone derivatives possessed multi-targeting properties including potent anticancer, anti-Alzheimer's and anti-trypanosomal activities [24-26]. Thus, the anticancer and antiparasitic activities of the new lawsone derivatives were evaluated on a panel of human cancer cell lines, in parasitic *Trypanosoma brucei brucei* cells that differ strongly from *T. cruzi* parasites concerning cell surface structure, and in *Entamoeba histolytica* samples isolated from amoebiasis patients.

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