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Research paper

Synthesis of α-santonin derived acetyl santonous acid triazole derivatives and their bioevaluation for T and B-cell proliferation

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ABSTRACT

A new series of α-santonin derived acetyl santonous acid 1,2,3-triazole derivatives were synthesised using Huisgen 1,3-dipolar cyclo-addition reaction (click chemistry approach) and evaluated for their *in vitro* inhibition activity on concanavalin A (ConA) induced T cell proliferation and lipopolysaccharide (LPS) induced B cell proliferation. Among the synthesised series, compounds **2-10** and **19** exhibited significant inhibition against ConA and LPS stimulated T-cell and B-cell proliferation in a dose dependent manner. More significantly compounds **4, 9-10** and **19** exhibited potent inhibition activity with remarkably lower cytotoxicity on the mitogen-induced T cell and B cell proliferation at 1 μM concentration. The compound **6** displayed potent immunosuppressive effects with ~89% against LPS induced B-cell and ~83% against ConA stimulated T-cell proliferation at 100 μM concentration without cytotoxicity. Compound **10** was more selective against B cell proliferation and exhibited 81% and 69% suppression at 100 and 1 μM concentration respectively. The present study led to the identification of several santonin analogs with reduced cytotoxicity and strong inhibition activity against the cell proliferation induced by the mitogens.

1. Introduction

Despite the immense synthetic diversity of combinatorial chemistry and high-throughput screening, natural products (NPs) and the related analogs are attractive sources of new clinical candidates for drug discovery and development for the treatment of human diseases [1,2]. A broad range of chemical and structural diversity, biochemical specificity, pharmacological and other molecular properties make NPs favourable leads for drug discovery [3].

Immunosuppresants form an important class of clinical drugs that are essential pre-requisite for successful organ transplantation and treatment of various autoimmune diseases like rheumatoid arthritis, systemic lupus, multiple sclerosis, myasthenia gravis, pemphigus and psoriasis [4–6]. With the knowledge that T-lymphocytes play a key role in transplant rejection and other cell-mediated autoimmune diseases [7,8], the major break-through in the field of chemical immunosuppression for transplantation came with the discovery of cyclosporine [6], since then field has grown tremendously and currently a number of immunosuppressive drugs such as glucocorticoids (e.g. cortisol), cyclosporin A, tacrolimus, sirolimus (rapamycin) and rituximab, etc. are available. These drugs act by inhibiting T or B cell proliferation during an immune response [9,10]. Rapamycin for instance acts by suppressing T-cell activation, mainly by inhibiting proliferation induced by growth-promoting lymphokines [11]. Rituximab binds CD20 receptor primarily found on the surface of B-cells, and stimulates B-cell apoptosis [12]. In spite of irrefutable clinical advantages, these immunosuppresants possess some inevitable and severe side effects, such as renal and liver toxicity, infection, malignancy and other cosmetic effects [13,14]. Thus, there is a significant unmet requirement for the development of new, efficient and safe

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