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ORIGINAL ARTICLE

A facile microwave assisted one pot synthesis of novel xanthene derivatives as potential anti-inflammatory and analgesic agents

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Abstract Microwave assisted irradiation of resorcinol and substituted aryl aldehydes using sulfamic acid as catalyst afforded novel 9-aryl-9*H*-xanthene-3,6-diol derivatives (**1a–f**) in good yields. The newly synthesized compounds which were previously selected on the basis of PASS prediction were tested for anti-inflammatory activity using carrageenan-induced rat paw edema and analgesic activity using acetic acid induced writhing and formalin-induced paw edema in mice along with the estimation of gastric ulcerogenicity index. Compounds **1e** and **1f** exhibited significant anti-inflammatory and analgesic activities as compared to standard drug. The study also revealed that compounds (**1a–f**) showed minimum or no ulcerogenicity in mice as that of the standard drug.

1. Introduction

Inflammation is a defensive but exaggerated local tissue reaction in response to exogenous or endogenous insult. It is a complex phenomenon, comprising of biochemical as well as immunological factors. It is recognized by heat, redness, tumor and pain. Traditionally most treatment of inflammation is with non-steroidal anti-inflammatory drugs (NSAID's). The most important mechanism of anti-inflammatory action of NSAIDs is considered to be primarily by inhibition of prostaglandin synthesis (Hunashal et al., 2011). However long usage of NSAID's and selective cyclooxygenase-2 (COX-2) inhibitors give unacceptable side effects such as gastric ulcer (Bush and Imani, 1991) with NSAID's and cardiac toxicity with coxibs.

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So there is a constant need for discovery of novel and safer anti-inflammatory drugs.

Xanthene functionality is a key structural element of many biologically active compounds. Xanthene derivatives have been reported to possess various pharmacological properties such as antibacterial (Hideo, 1981), antiviral (Lambert et al., 1997), anti-inflammatory (Poupelin et al., 1978) and CCR1 antagonist (Naya et al., 2003). Xanthenes are of great interest in the lead optimization process of drug discovery. Some evidence has surfaced that suggests the xanthene core structure also may be useful in the design and development of pharmacological agents (Ornstein et al., 1998; Goodell et al., 2006). Thus synthesis of xanthene derivatives is of immense interest. As a result of our investigation using PASS (prediction of activity spectra for substances) studies, it was found that 9-aryl xanthene moiety do possess some anti-inflammatory activity influenced by the substitution pattern of these molecules. The compounds chosen for synthesis and activity determination were selected on the basis of their best prediction values as anti-inflammatory and analgesic as well as ease of their synthesis.

Reported synthetic methodologies involve harsh conditions or longer reaction time leaving considerable scope for development of further clean, facile and efficient process for the synthesis of these important molecules. The organic reactions taking place in aqueous media have recently attracted much attention in synthetic chemistry, not only because water is one of the most abundant, cheapest and environmentally friendly solvents but also because it exhibits unique reactivity and selectivity, which is different from those observed in conventional organic solvents (Demko and Sharpless, 2001; Li, 2005). Apart from this, to overcome the limitations from the catalysis point of view, we started to search for new catalysts having high catalytic activity, easy availability and short reaction time involving simple work-up procedure, and sulfamic acid attracted our attention as it is known to catalyze a number of organic transformations. Recently, sulfamic acid has emerged as a promising solid acid catalyst for acid catalyzed reactions, such as functional group protections and deprotections and the synthesis of isoamyl acetate and polymeric ethers. Moreover, some important organic transformations, including the Beckmann rearrangement (Wang et al., 2004 and Singh et al., 2004) and Bignelli condensations (Li et al., 2003) have been performed successfully in the presence of sulfamic acid. As a continuation of our research devoted to the development of green route methods (Thomas et al., 2009, 2010), herein we report an efficient and convenient method for microwave assisted synthesis of some novel 9-aryl xanthenes derivatives by condensation of aldehydes with resorcinol in the presence of sulfamic acid as catalyst followed by screening for *in vivo* anti-inflammatory and analgesic activities.

2. Experimental

2.1. Activity prediction

In an effort to optimize biological profile, a wide structural diversity of xanthenes possessing the 9-aryl moiety as a salient feature of the xanthene core have been virtually designed, synthesized and investigated for the foresaid pharmacological activity. In order to accelerate search for New Chemical Entities (NCEs), an internet version of the PASS (prediction of biological activity spectra) (http://www.ibmh.msk.su/PASS/Ref.html) was used to predict the anti-inflammatory and analgesic action of different 9-aryl xanthene derivatives.

The technique of PASS is based on the analysis of SARs for the training set currently including about 46,000 drugs, drug candidates and lead compounds whose biological activities are determined experimentally. The set of MNA (multilevel neighborhood atoms) descriptors are generated on the basis of structural formulas presented in the MOL-file (SDF-file) form. Since MNA descriptors are generated for each compound de novo, new descriptors can be obtained upon presentation of a novel structural feature in the compound under study.

Based on the statistics of MNA descriptors for active and inactive compounds from the training set, two probabilities are calculated for each activity: Pa—probability of compound being active and Pi—probability of compound is being inactive. Being probabilities, the Pa and Pi values vary from 0.000 to 1.000 and in general Pa + Pi < 1, since these probabilities are calculated independently.

The PASS predictions can be interpreted and used in a flexible manner-

(i) Only activities with Pa > Pi are considered as possible for a particular compound.
(ii) If Pa > 0.7—the substance is very likely to exhibit activity in experiment, but chance of the substance being analog of a known pharmaceutical agent is also high.
(iii) If 0.5 < Pa < 0.7—the substance is likely to exhibit the activity in the experiment, but the probability is less and the substance is unlike known pharmaceutical agents.
(iv) If Pa < 0.5—the substance is unlikely to exhibit the activity in the experiment. However if the presence of this activity is confirmed in the experiment, the substance might be an NCE.

2.1.1. Selection of possible cognition enhancers

Prediction of biological activity spectra was made for about 200 virtually designed variedly substituted structures from the theoretical calculations on the basis of PASS prediction. The compounds screened were the structures formed from the various combinations of R (H, 2-OH, 4-OH, 3-OCH_3-4-OH, 4-Cl and 4-NO_2) groups in the hydroxylated xanthene moiety. On the basis of prediction results from the database analysis, potential xanthenes were selected for testing their anti-inflammatory and analgesic activities. The compounds screened above were further subjected to 'Lipinski rules of five'. The MIPC (mol inspiration property calculator) program has been utilized (www.molinspiration.com) for calculating the Lipinski descriptors. The log *P* values and the associated parameters for the compounds under consideration have been provided in Table 1 and the probabilities of the test compounds for being active (Pa) are provided in Table 2. On the basis of the above-mentioned criteria, the chosen compounds were synthesized and experimentally tested as anti-inflammatory and analgesic agents.

2.2. Materials and reagents

All research chemicals were purchased from Across organics (NY, USA), Sigma–Aldrich (St. Loius, Missiouri, USA) and

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