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SHORT COMMUNICATION

Quinoline based furanones and their nitrogen analogues: Docking, synthesis and biological evaluation

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Abstract A small library of twenty-four quinoline based butenolides also known as furanones and their nitrogen analogues was prepared by using two different aroylpropionic acids, viz. 3-(2-naphthoyl)propionic acid (**3**) and 3-(biphenyl-4-yl)propionic acid (**4**), as starting materials. The 3-aroylpropionic acids were reacted with different 6-substituted-2-chloroquinolin-3-carbalde hydes (**2a–d**) to obtain the corresponding furan-2(3*H*)-ones (**5a–h**). The purified and characterized furanones were then converted into their corresponding 2(3*H*)-pyrrolones (**6a–h**) and *N*-benzyl-pyrrol-2(3*H*)-ones (**7a–h**). The antimicrobial activities of the title compounds were evaluated against two strains of each Gram +ve (*Staphylococcus aureus* and *Bacillus subtilis*), Gram −ve bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) and against fungal strains of *Aspergillus niger* and *Aspergillus flavus*. *In vivo* anti-inflammatory potential of the title compounds was investigated by standard method. Majority of the compounds showed significant antibacterial activity against both the Gram +ve strains. Eight most potent anti-inflammatory compounds (**5b, 5d, 5h, 6b, 7b, 7d, 7f, 7h**) which exhibited >53% inhibition in edema, were also screened for their *in vivo* analgesic activity. All the tested compounds were found to have significant reduction in ulcerogenic action but only three compounds (**5d, 5h** and **7h**) showed comparable analgesic activity to standard drug, diclofenac. The results were also validated using *in silico* approach and maximum mol doc score

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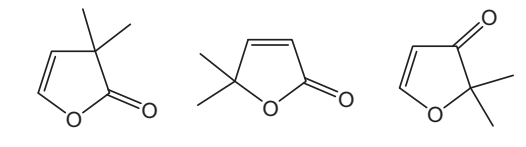
was obtained for compounds **7a–h**. On comparing the *in vivo* and *in silico anti-inflammatory* results of synthesized compounds, *N*-benzyl pyrrolones (**7a–h**) emerged as the potent anti-inflammatory agents. It was also observed that compounds that possess electron withdrawing group such as —Cl or NO_2 are more biologically active.

1. Introduction

Butenolides, also known as butyrolactones, are five membered heterocyclic compounds occurring naturally in many medicinal plants (Mao et al., 2011). Natural products containing butenolide ring system have been known to exhibit a wide range of useful and significant biological actions. Chemically these are oxidized furans, which are considered as an important scaffold to synthesize compounds of biological and pharmaceutical importance. In recent years, a large number of synthetic compounds containing butenolide nucleus were prepared and studied for various interesting biological actions in search of potent therapeutic agents (Lattmann et al., 2004; Rossi et al., 1998; Hashem et al., 2014). Butenolides consist of four carbon unsaturated γ-lactone ring and occur in numerous phytochemicals in three different forms (Fig. 1) depending upon the relative positions of the carbonyl group and the double bond in the hetero ring such as 2,3-dihydrofuran-2-ones or furan-2(3*H*)-ones, 2,5-dihydrofuran-2-ones or furan-2(5*H*)-ones and 3,2-dihydrofuran-3-ones or furan-3(2*H*)-ones (Allison et al., 1992).

Furanones and their open ring (acyclic) products serve as precursors for the syntheses of large number of physiologically active heterocyclic compounds vis-a-vis can also be fused or combined with other heterocyclic moieties (Allison et al., 1992; Flower, 2003). A number of nitrogen containing heterocyclic systems which exhibit promising biological activities and are prepared from butenolides include pyrrolones, pyridazinones, pyrazoles, isothiazolones, oxadiazoles, triazoles, etc (Bekhit and Abdel-Azeim, 2004; Bailly et al., 2008; Hashem et al., 2014). Several research studies conducted elsewhere have shown that butenolides (furanones) possess wide spectrum of biological activities such as antibacterial, antifungal, antiviral, antioxidant, antimalarial, anticonvulsant, anti-inflammatory, COX-II inhibition, analgesic, antitumor, and anticancer properties (Albrecht et al., 2008; Moosavi-Movahedi et al., 2003; Levy et al., 2003; Lattmann et al., 2004; Hashem et al., 2014). Recently, there has been a great interest in preparing arylidene butenolides, which have a large spectrum of important and potential biological activities (Lattmann et al., 2005; Khan and Husain, 2002; Leite et al., 1999). The γ-lactone ring of butenolides is quite reactive and therefore employed as a building block to construct diverse classes of nitrogen heterocyclic compounds possessing significant pharmacological activities (Black et al., 2003; Zarghi et al., 2007; Hashem et al., 2007; Husain et al., 2005).



2(*3H*)-furanone 2(*5H*)-furanone 3(*2H*)-furanone

Figure 1 Various isomeric forms of furanone ring.

Quinoline ring system is present in number of bioactive natural products and quite a few are used therapeutically. Quinolines and their synthetic derivatives are reported to exhibit anti-inflammatory and analgesic activities (Husain et al., 2013) in addition to other useful pharmacological activities (Jashim Uddin et al., 2004; Pohle et al., 2001).

Biphenyl based furanones and pyrrolones show interesting antimicrobial and anti-inflammatory activities (Khan and Husain, 2002). Naproxen and Nabumetone are examples of naphthalene containing NSAIDs which are usually indicated in the management of pain and inflammatory conditions. Also it has been reported that several other naphthalene derivatives inhibit cyclooxygenase enzyme, block the synthesis of inflammatory mediators and therefore, display good anti-inflammatory activities (Harrak et al., 2007).

Prompted by these findings, and as a part of our current research interest on furanone derivatives, we thought to prepare compounds having three biological moieties in one i.e. biphenyl and naphthalene based furanones or pyrrolones having quinoline moiety in search of potent lead/drug molecules for anti-inflammatory or antimicrobial therapy. A total of twenty-four title compounds viz. eight furan-2(3*H*)-ones, eight pyrrol-2(3*H*)-ones and eight *N*-benzyl-pyrrol-2(3*H*)-ones were prepared and screened for antibacterial, antifungal, *in vivo* analgesic and anti-inflammatory activities.

2. Experimental

2.1. General

The reagents and solvents used in all experiments were obtained from Merck (Mumbai, India), S.D. Fine (Mumbai, India), CDH (New Delhi) and Qualigens (India). Melting points were recorded in open end capillary tubes using MR-VIS Visual melting point apparatus (LAB India) and are uncorrected. The IR spectra were recorded on Hitachi 150–200 spectrophotometer using KBr. ^{1}H NMR spectra were recorded on Bruker spectrospin DPX-300 MHz in $CDCl_3$ or DMSO using tetramethylsilane (TMS) as an internal reference. Chemical shift (δ) values are reported in parts per million (ppm) while splitting patterns of peaks as singlets, doublet or triplet in proton NMR spectra are indicated by abbreviations *s*, *d*, *t* and *m*, respectively. Mass spectrometry for title compounds was performed on a JEOL JMS-D 300 instrument. Perkin-Elmer 240 analyzer was used to perform elemental analyses (C, H, N) and was found in the range of ±0.4% for each analyzed element. Progress of reaction was monitored on thin-layer chromatography using silica gel G as stationary phase in the solvent system-Toluene:Ethyl acetate:Formic acid (5:4:1, v/v/v) or Petroleum ether:Toluene:Ethyl acetate (5:4:1,