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Novel pyrimidine-pyridine hybrids: Synthesis, cyclooxygenase inhibition, anti-inflammatory activity and ulcerogenic liability

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ABSTRACT

Some derivatives containing pyrido[2,3-*d*:6,5*d*′]dipyrimidine-4,5-diones (**9a-f**), tetrahydropyrido[2,3-*d*] pyrimidine-6-carbonitriles (**11a-c**) and 6-(4-acetylphenyl)-2-thioxo-2,3,5,6,7,8-hexahydro-1*H*-pyrimido [4,5-*d*]pyrimidin-4-one (**12**) were synthesized from 6-amino-2-thioxo-2,3-dihydro-*1H*-pyrimidin-4-one (**8**). The anti-inflammatory effect of these candidates was determined and the ulcer indices were calculated for active compounds. 7-Amino-5-(3,4,5-trimethoxyphenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyr ido[2,3-*d*] pyrimidine-6-carbonitrile (**11c**) exhibited better edema inhibition than celecoxib. Moreover, compounds **9b**, **9d** and **11c** revealed better COX-2 inhibitory activity in a range (IC_{50} = 0.25–0.89 μM) than celecoxib (IC_{50} = 1.11 μM). Regarding ulcerogenic liability, all of the compounds under the study were less ulcerogenic than indomethacin. Molecular docking studies had been carried on active candidates **9d** and **11c** to explore action mode of these candidates as leads for discovering other anti-inflammatory agents.

1. Introduction

Inflammation is a biological response to a defective tissue homeostasis in which body defense cells and defense chemicals like plasma proteins, leukocytes and fluid enter the perturbed tissue leading to vasodilation, increasing a blood flow and vascular permeability [1–4]. Anti-inflammatory drugs non-steroidal (NSAIDs) are important drugs for pain and inflammation relieving, which produce their effect through cyclooxygenase (COX) enzymes suppression [5–7]. COX enzymes have two isoforms, inducible COX-2 and constitutive COX-1 [8]. The constitutive COX-1 has many physiological roles as protecting gastric mucosa, vascular homeostasis and platelet aggregation, but the inducible COX-2, the other isoform, is concerned with prostaglandins supporting the inflammatory progress and mediating pain [9–12].

The suppression of two isoenzymes is the main factor of gastrointestinal adverse effects produced by the administration of traditional NSAIDs [13,14]. In an attempt to decrease these side effects, a current approach consists of preparing selective inhibitors for COX-2 with improved gastric safety profile [15,16]. But unfortunately, some adverse changes in the biochemical COX pathway caused by selective COX-2 inhibitors such as increased incidences of myocardial infarction and high blood pressure result in withdrawal of both rofecoxib and valdecoxib from market [17–20]. So there is a still great need for design of selective and potent COX-2 suppressors for relieving inflammation without side effects. Although many studies attributed rofecoxib's cardiac toxicity not due to its COX-2 inhibition but rather an intrinsic chemical property related to its metabolism [21,22]. These studies revealed that under physiological conditions, rofecoxib ionizes to an anion that yields in the presence of oxygen a reactive maleic anhydride capable of reacting with various biological targets thereby contributing to mechanisms of atherothrombosis. The pyrimidine nucleus is reported as an essential scaffold that possess a huge biological activities including an anti-inflammatory effect [23–27]. 6-Hydroxy-1-[2-(1*H*-imidazol-4-yl)ethyl]-4,4,6-trimethyl-tetrahydropyrimidine-2-thione (**1**) had been mentioned in literature to reduce inflammation by 65% at 100 mg/kg [28]. Moreover, a new candidates containing pyrimidine ring was prepared and evaluated as anti-inflammatory candidates by Venu et al [29]. From this set, compound **2** recorded higher inflammation suppression than aspirin and phenyl butazone as standards at all tested doses.

In addition 1,2,3,4-tetrahydropyrimidine derivative **3**, having 4-chlorophenyl group at the 6th position of pyrimidine nucleus, showed high anti-inflammatory effect (edema inhibitory percent 70.7%) [30] (see Fig. 1).

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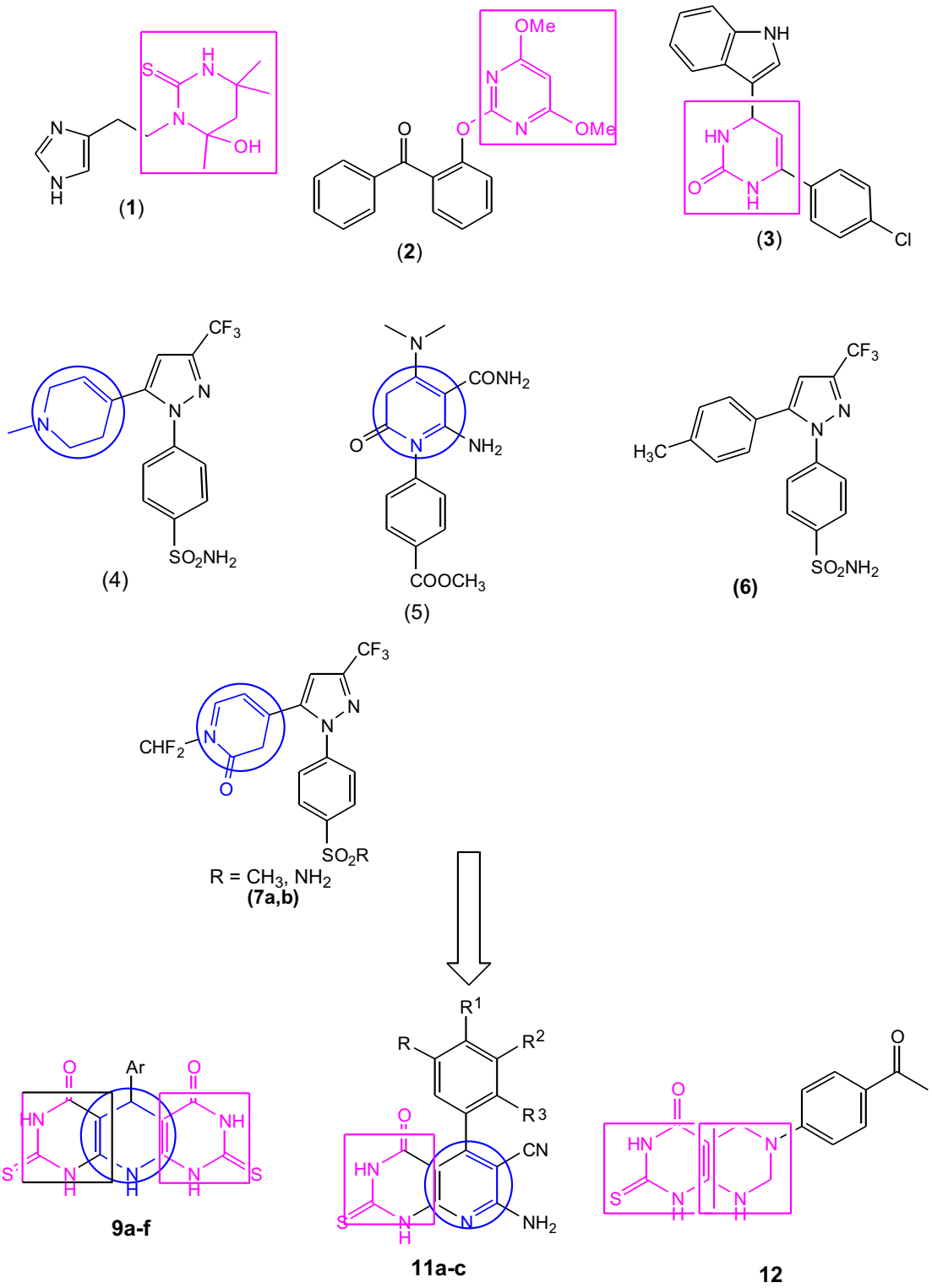

Fig. 1. Chemical structures of reported pyrimidine derivatives (**1**–**3**), some pyridine derivatives (**4, 5, 7a, b**) and celecoxib (**6**) as anti-inflammatory agents.

Moreover, pyridine ring is main scaffold in literature as promising anti-inflammatory agents [31–35].

For example, 4-[5-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-3-trifluoromethylpyrazol-1-yl]benzene-sulfonamide (**4**) showed an anti-inflammatory activity (ED_{50} = 61.2 mg/kg po) between that of aspirin (ED_{50} = 128.7 mg/kg po) and celecoxib (ED_{50} = 10.8 mg/kg po) [36]. Also, the pyridone derivative (**5**) exhibited anti-inflammatory activity in the same range of the reference indomethacin drug [37].

Furthermore, Chowdhury et al [38] detected that the substitution of tolyl ring present in celecoxib (**6**) by *N*-difluoromethyl-1,2-dihydropyrid-2-one moiety provided compounds **7a,b** which exhibited dual selective COX-2/5-LOX inhibitory activities. Prompted by the aforementioned facts and as a continuation of