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Original article

Synthesis of cyanopyridine and pyrimidine analogues as new anti-inflammatory and antimicrobial agents

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ABSTRACT

A new series of substituted benzylidene acetophenone (Ia-Ih), 2-amino-4, 6- substituted diphenylpyridine-3-carbonitrile (IIa-IIh) and 4, 6-substituted diphenylpyrimidin-2-amine (IIId-IIIg) were synthesized and evaluated for anti-inflammatory and antimicrobial activities. Four compounds (Ie, If, IIh and IIId) have shown good anti-inflammatory activity when compared to standard drug indomethacin. Two compound (Ie and IIh) displayed significant activity against gram -ve bacteria (*E. Coli*) and three compounds (IId, IIf and IIIh) displayed good activity against gram +ve bacteria (*S. aureus*) on comparison with the standard drug ofloxacin.

1. Introduction

Chalcones are a class of naturally occurring benzylidene acetophenone (Fig. 1) with diverse pharmacological properties, such as anti-inflammatory, [1] bactericidal, [2,3] fungicidal, [4] germicidal, [5,6] carcinogenic, [7] analgesic [8] and insecticidal activities. Recently, they have been recognized as compounds with potent biological activities that may be active in prevention of diseases such as inflammation.

The aim of the present work is to evaluate the anti-inflammatory and antimicrobial activity of the chalcones derivatives like cyanopyridine and pyrimidine. The derivatives of chalcone like: cyanopyridine, (Fig. 2) have proven to be of great importance in exhibiting and enhancing great antimicrobial activities.

Pyrimidine (Fig. 3) six membered heterocycles that contain two, three and four ring nitrogen atoms are named systematically as diazines, triazines, tetrazines. Pyrimidine being integral part of DNA and RNA impart diverse pharmacological properties such as effective bactericides, fungicides, meticides, insecticides, anticancer and herbicidal agents [9,10]. Certain pyrimidine derivatives are also known to display antiviral, antimicrobial, antifilarial and antileshmanial activities [11].

Since disease characterized by inflammation is an important cause of morbidity and mortality in humans, the processes involved in the host defense in inflammation have been and continue to be the object of several experimental studies. In the need of this, we envisaged a research to synthesize a new series of pharmaceutically important compounds like cyanopyridines and pyridines, as they play an important role in medicinal chemistry and possess therapeutic effectiveness against inflammation and diseases spread by microbes.

Chalcone derivatives were easily obtained through the Claisen–Schmidt condensation of aromatic benzaldehyde and derivertized acetophenones using catalyst. In our search, new chalcones (Fig. 4), cyanopyridine (Fig. 5) and pyrimidine (Fig. 6) were synthesized and evaluated for anti-inflammatory and antimicrobial activities.

2. Material and methods

All derivatives of chalcones, cyanopyridines and pyrimidines were synthesized as shown in Fig. 4, Fig. 5 and Fig. 6 respectively. These methods allowed the preparation of a variety of chalcones derivatives, cyanopyridines and pyrimidine compounds.

2.1. General synthesis

2.1.1. Step 1: general synthesis of chalcone compounds

The reaction involves the condensation of equimolar quantities of substituted acetophenone with substituted aromatic aldehyde in presence of aqueous alcoholic alkali resulting in the formation of α, β–unsaturated ketones (*i.e.* chalcones) was carried out by clasien-schmidt condensation reaction.

The substituted chalcone derivatives were prepared by stirring a solution of 2.75 gm of sodium hydroxide (NaOH) in 25 ml water and 20 ml ethanol in a round bottom flask. The flask was immersed in crushed ice and 0.043 mole (4.99 ml) of freshly distilled

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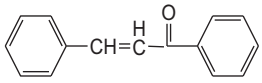


Fig. 1. Chalcone.

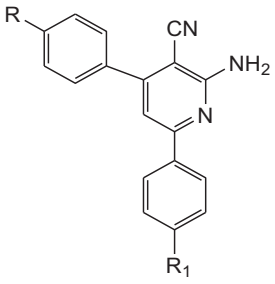


Fig. 2. Cyanopyridine.

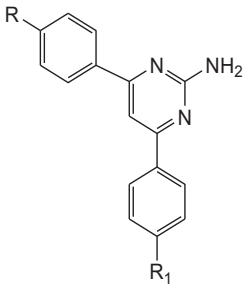


Fig. 3. Pyrimidine.

substituted acetophenone was poured. Exactly 0.043 mole of substituted aromatic aldehyde was added with stirring at below 25 °C for 7–8 hours. All the crude products were washed first with cold water until washings were neutral to litmus paper and then with 20 ml of cold rectified spirit, and recrystallised from ethanol (Fig. 4) (Table 1).

2.1.2. Step 2: synthesis of cyanopyridine compound

Chalcone compound synthesized from series I (2.08 gm, 0.01 mol), malanonitrile (0.66 gm, 0.01 mol) and ammonium acetate (6.16 gm, 0.08 mol) were dissolved in absolute ethanol (25 ml) was heated under reflux for 8 hours, cooled and poured into crushed ice. The crude products were separated and recrystallised from ethanol (Fig. 5) (Table 2).

2.1.3. Step 3: synthesis of pyrimidine compounds

A mixture of chalcone series II (2.53 gm, 0.01 mol), guanidine hydrochloride (0.995 gm, 0.01 mol) and dimethylformamide (20 ml) was taken and refluxed for about 5–7 hours, and kept overnight. The reaction mixture was poured into ice, crude products separated. Recrystallisation was brought out from methanol and later was washed with petroleum ether (Fig. 6) (Table 3).

Table 1
Different substitution of Chalcone derivatives.

Compounds	R	R_1	Yield (%)
Ia	–H	–H	58
Ib	–H	–Cl	49
Ic	–H	$-CH_3$	54
Id	–H	$-NO_2$	51
Ie	$-OCH_3$	–H	67
If	$-OCH_3$	–Cl	54.5
Ig	$-OCH_3$	$-NO_2$	56.6
Ih	$-OCH_3$	$-CH_3$	61

2.2. Pharmacological screening

2.2.1. Anti-inflammatory activity: (Winter et al.) [12]

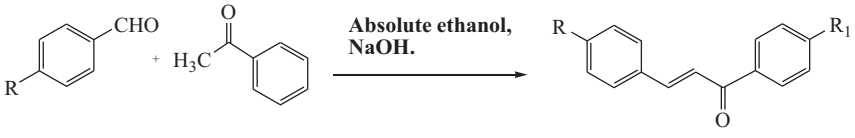
Anti-inflammatory activity of synthesized compounds was determined *in vivo* by acute carrageenan-induced paw oedema method in rats. The drug used as standard was indomethacin in dose of 10 mg/kg body weight. The doses of test compounds were 10 mg/kg body weight. The standard and test compounds were administered through oral route in the form of (0.1% CMC) suspension. The control group was administered 0.2 ml of normal saline orally. Carrageenan was injected subcutaneously, 0.1 ml of a 1% w/v carrageenan suspension (in 0.5% CMC) to hind paw of each rats. The study was carried out on healthy rats weighing 150–250 gm, divided in different groups of six animals each and housed in propylene cages. They were fed on standard pellet diet, water *ad. Libitum*. The volume was measured after 0, 1 and 3 hours after carrageenan injection with a plethysmometer (Fig. 7).

The mean increase in the paw volume in each group was calculated. Indomethacin used as standard drugs for comparison [13]. The paw volume was measured by mercury displacement method (plethysmometer) after 1 and 3 hours. Thus, paw oedema volume in control group (Vc) and test group (Vt) was measured and the percentage inhibition of oedema was calculated using the formula: % inhibition = [(Vc-Vt)/Vc] × 100.

2.2.2. Antimicrobial activity: (cup-plate diffusion method)

MIC value of the tested compounds will screened *in vitro* for their antimicrobial activities against various strains of bacteria by the agar diffusion technique or by tube dilution technique. The solvents DMSO/DMF will use as negative controls. The bacteria and fungi will maintain on nutrient agar and Czapek's-Dox agar media, respectively. The agar media will incubate with different microorganisms [14].

All synthesized compounds were tested by cup plate method for their antimicrobial activity against gram +ve (*S. aureus*) and gram –ve (*E. Coli*) organisms. Ofloxacin was taken as standard drug (50 μg/ml), inoculum's of test organism was mixed with nutrient agar (1%v/v) and after mixing 20 ml of this seeded medium was poured in 100 mm Petri dishes. After the setting of the medium, four holes were made in each plate and concentration of 50 μg/ml



(**Ia-Ih**)

Fig. 4. Synthesis of substituted chalcones derivatives: reagents and conditions: (a) absolute ethanol, NaOH.