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Original article

Synthesis and pharmacological investigation of 3-(substituted 1-phenylethanone)-4-(substituted phenyl)-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylates

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ABSTRACT

Fifteen new ethyl 6-methyl-2-methoxy-3-(substituted 1-phenylethanone)-4-(substituted phenyl)-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylates (**6a**–**o**) have been synthesized in a two step reaction. In first step ethyl acetoacetate, *s*-methylisourea and appropriate benzaldehydes reacted in a single step reaction to obtain ethyl 6-methyl-2-methoxy-4-(substituted phenyl)-1, 4-dihydropyrimidine-5-carboxylates (**4a**–**e**). Second step involves synthesis of reaction between substituted phenacyl bromides and 1-4-dihydropyrimidine-5-carboxylates (**6a**–**o**). Their structures are confirmed by IR, ^{1}H NMR, mass and elemental analyses. The compounds were tested for antihypertensive activity by non-invasive tail-cuff, and evaluated by carotid artery cannulation method for determining the diastolic blood pressure. Hypertension was induced by DOCA-salt. Anti-inflammatory activity was carried out by carrageenan induced rat-paw oedema method. Test compounds **6b**, **6c**, **6e**, **6f**, **6j**, **6h**, **6k**, **6l**, **6m**, **6n** and **6o** exerted comparative antihypertensive activity at 10 mg/kg dose level compared to nifedipine. Compounds **6j**, **6m** and **6o** showed excellent results on evaluation by direct method. Test compounds **6a**–**6h**, **6l**, **6m**, **6n** and **6o** exerted moderate to comparative anti-inflammatory activity at the 100 mg/kg dose level compared to indomethacin. Their further investigation for analgesic activity and acute ulcerogenesis was carried out, compounds **6m**, **6f**, **6k**, **6o** showed excellent to good analgesic activity and low ulcerogenic activity.

1. Introduction

Similar groups/structures often exhibit similar biological activities. However, they usually exhibit different potency. The traditional structure–activity relationship (SAR) is a useful tool in the search for new drugs. However, SAR is usually determined by making minor changes to the structure of the existing compound and assessing the effect on its biological activity. Similarly, structural analogy has played vital role in designing compounds with higher potency. One of such structural analogy is seen between 4-aryl-1, 4-dihydropyridines (DHPs) of the nifedipine type and dihydropyrimidines (DHPMs). In 1893 Italian chemist Pietro Biginelli reported on the acid-catalyzed cyclocondensation reaction of ethyl acetoacetate, benzaldehyde and urea. The reaction was carried out simply by heating a mixture of three components dissolved in ethanol with a catalytic amount of hydrochloric acid at reflux temperature. The product of this novel one pot, three-component synthesis that precipitated on cooling of the reaction mixture was identified correctly by Biginelli as 3, 4-dihydropyrimidine-2(1*H*)-one [1].

The synthetic potential of this new heterocyclic synthesis remained unexplored for quite some time. In the 1970s and 1980s interest slowly increased, and the scope of the original cyclocondensation reaction was gradually extended by variation of all three building blocks, allowing access to a large number of multifunctionalized dihydropyrimidines [2].

In the past decades, a broad range of biological effects, including antiviral [3], antitumor [4], antibacterial [5] and anti-inflammatory [6] activities have been ascribed to these partly reduced pyrimidine derivatives. More recently, DHPMs have emerged as, for e.g., orally active antihypertensive agents [7]. A very recent highlight in this context been the identification of the structurally rather simple DHPM monastrol as a mitotic kinesin motor protein inhibitor and potential new lead for the development of anticancer drugs [8]. Appropriately functionalized DHPM derivatives have emerged as potent calcium channel modulators [9]. Apart from synthetic DHPM derivatives several marine natural products with interesting biological activities containing the dihydropyrimidine-5-carboxylate core have recently been isolated. Most among these are the batzelladine alkaloids A and B which inhibit the binding of HIV

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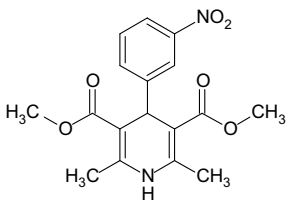
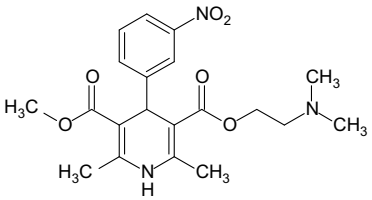
envelop protein gp-120 to human CD4 cells and therefore, are potential new leads for AIDS therapy [10].

2. Chemistry

The chemistry of pyrimidine-5-carboxylates has been of great interest. 4-Aryl-1, 4-dihydropyridines of the nifedipine type (I, II) are most studied class of organic calcium channel modulators, since their introduction. They have become drugs of immense importance for the treatment of hypertension, cardiac arrhythmias, etc. In recent years, interest has also been focused on aza-analogues such as dihydropyrimidines of types III and IV which show similar pharmacological profile to classical dihydropyridine calcium channel modulators, the reported lead compounds show superiority in potency and duration of activity.



I



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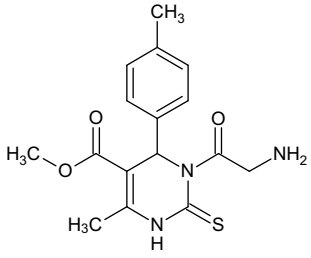
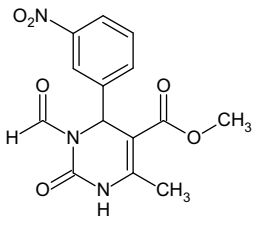


III



IV

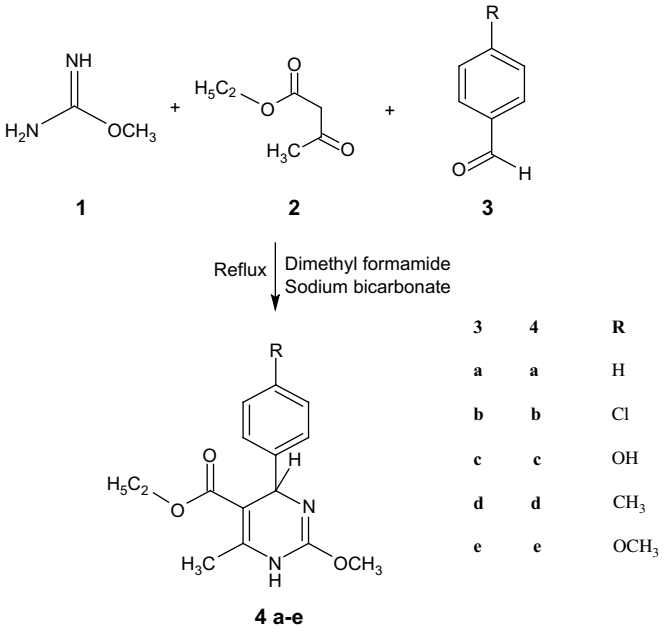
The pyrimidine-5-carboxylate substituted at third position, i.e., on nitrogen in the pyrimidine ring gives antihypertensive activity similar to nifedipine-type calcium channel modulator, substitution at the third nitrogen is possible and the resultants can be strong contenders of anti-inflammatory, antihypertensive activities [11–18]. It involves the application of Biginelli reaction and its modifications.

In the first step three-component reaction involving *o*-methylisourea hydrogensulfate, ethyl acetoacetate and substituted benzaldehydes (**3a**–**e**) reacted in the presence of sodium bicarbonate and dimethylformamide to form the substituted ring nucleus compounds (**4a**–**e**) (Scheme 1).

On reaction with various substituted phenacyl bromides **5a**–**c**, they undergo nucleophilic substitution reaction in the presence of a base such as pyridine, to form their respective derivatives (**6a**–**o**) (Scheme 2).

3. Pharmacology

Antihypertensive activity of synthesized compounds was carried out by model or method of Deoxycorticosterone Acetate salt (DOCA-salt) induced hypertension in rats [19–21]. The non-invasive method to determine systolic blood pressure (SBP), invasive method to determine diastolic blood pressure (DBP) and mean arterial blood pressure (MAP) for determining the changes in blood



3	4	R
a	a	H
b	b	Cl
c	c	OH
d	d	CH_3
e	e	OCH_3

1 2 3

4 a-e

Scheme 1.

pressure were performed using Power Lab/4SP with ML135 Dual Bio Amp computerized BP monitor automatic cardiovascular system (AD instruments Pvt. Ltd., Australia). Anti-inflammatory activity of synthesized compounds was carried out by carrageenan induced rat-paw oedema [22] method using UGO BASTILE Plethysmometer 7140. Analgesic activity was carried out by acetic acid induced writhing method [23]. Acute ulcerogenesis test was done according to Cioli et al. [24].

4. Results and discussion

All the compounds synthesized are novel. These derivatives were obtained from the two step synthesis, their structures were confirmed by IR, NMR and elemental analyses. We have shown that 2-hetero-1, 4-dihydropyrimidines can be synthesized with selective substitution of the *para*-substituted electrophiles at N3 position. This selectivity is believed to be due to electron density at N3 and N1. The former being richer in electron density is more reactive and produces products of exclusive functionalization at N3. Fifteen derivatives were synthesized, antihypertensive activity was carried out initially for all the test compounds, those compounds which were found out to show significant activity by non-invasive (Tail-cuff method) technique were further evaluated for antihypertensive activity by direct cannulation method. Anti-inflammatory activity was carried out followed by analgesic and acute ulcerogenesis studies.

4.1. Antihypertensive activity

Antihypertensive activity carried out by the non-invasive method gave the systolic blood pressure (SBP), from which the observations are summarized in Table 1. For structure–activity studies we choose the aromatic substitutions that are commonly employed in dihydropyridines. 4-Methoxy derivative **6n** has remarkable antihypertensive activity. 3, 4-Disubstituted methoxy derivative **6o** has shown good antihypertensive activity at 10 mg/kg. Although 3-methoxy 4-hydroxy derivative (**6i**) is less potent than the corresponding **6n** and **6o**. 3, 4-Dichloro analogues are moderately potent than **6n** and **6o**. Data are presented as