



Synthesis of Acetylated Dihydropyrimidine Analogues Under Solvent Free Conditions and their Evaluation as Calcium Channel Blockers

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ABSTRACT

One pot condensation of ethylacetoacetate with various para and ortho substituted aldehydes and urea or thiourea by $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ affords eight different substituted 3,4-dihydropyrimidine ones/thiones. Further we prepared acetylated 3,4-dihydropyrimidine ones/thiones, on treatment of 3,4-dihydropyrimidine ones/thiones with acetic anhydride using zinc chloride as a catalyst. Calcium channel blocker activity shows that synthesized compounds have moderate activity.

Key words: Biginelli reaction, microwave irradiation, acetylated 3,4-dihydropyrimidine ones/thiones, calcium channel blocking activity.

INTRODUCTION

Biginelli reaction is one of the most useful multicomponent cyclo condensation reaction. It is an acid catalysed cyclocondensation reaction of a α -ketoester with an aldehyde and urea/thiourea to yield 3,4-dihydropyrimidine 2(1H)-ones/thiones in quantitative amounts¹. Various Lewis acids and protic acid promoters like FeCl_3 and HCl , $\text{BF}_3 \cdot \text{OEt}_2$, and ytterbium triflate², zirconium(IV) chloride³, indium bromide⁴, lanthanum chloride, $\text{Cu}(\text{OTf})_3$ ⁵, H_2SO_4 ⁶, AcOH ⁷, Polypyrophosphate ester (PPE)⁸, ammonium chloride⁹, $\text{CuCl}_2 \cdot 2\text{H}_2\text{O} \cdot \text{HCl}$ ¹⁰,

$\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ ¹¹, $\text{CoCl}_2(\text{OAc})_2$ ¹² were used as catalysts.

Dihydropyrimidines (DHPMs) represent heterocyclic systems of remarkable pharmacological efficacy and many exhibit antiviral, antitumor, antibacterial, anti inflammatory activity. Several marine natural products containing the dihydropyrimidine -5-alkaloids were found to be potent HIV gp-120-CD4 inhibitors.¹³ Polyfunctional dihydropyrimidines are used as calcium channel blockers, antiviral and antitumor agents, and α_{1a} antagonists¹⁴⁻¹⁷. Owing to the immense therapeutic

and medicinal significance of dihydropyrimidines, exploring convenient and efficient methods for their synthesis with readily available reagents is of prime importance.

Calcium channel blockers are widely used for treating the disorders of cardiovascular system. They have a variety of pharmacological effects and are active not only against hypertension, angina pectoris, metabolism incompetence and arrhythmias but also for prevention of arterial sclerosis. Most commonly used calcium channel blockers include nifedipine, verapamil etc. 4-aryl-1,4-dihydropyridines of nifedipine type serve as an important tool for study of Calcium channel structure and function.

Metabolic oxidation to form inactive pyridine derivative frequently results in short duration of action of these drugs. In recent years interest has been focused on aza analogues such as dihydropyrimidines, which show very similar pharmacological profile to classical dihydropyridine calcium modulators.

Generally in case of dihydropyridine with an ortho nitro group on phenyl ring (eg. nifedipine), dihydropyridine skeleton is light sensitive because a nitroso radical generated from a nitro group by light irradiation removes a proton from phenyl group causing aromatization. The transposition of nitro group from ortho substitution to meta substitution (eg. nifedipine) prevented the oxidation of dihydropyridine ring, although the pharmacological activity of meta substituted compound is usually less potent than that of ortho substituted compounds.

However in case of dihydropyrimidines with an ortho nitro group, aza analogue of dihydropyridines, this problem could theoretically be overcome.

In the present work one pot condensation of aromatic aldehydes, ethylacetoacetate and urea/thiourea in the presence of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ has been done to get corresponding 3,4- dihydropyrimidine ones/thiones 1-8 (DHP ones/thiones 1-8).

Treatment of DHP ones/thiones 1-8 with acetic anhydride and ZnCl_2 yield acetylated 3,4-

dihydropyrimidine ones/thiones 1-8 (ADHP ones/thiones 1-8).

Pharmacological screening

The Calcium channel blocking activity was evaluated by inducing contractions using KCl. This method was reported earlier by Mahmoudian *et al*¹⁵ for screening newer calcium channel blockers. All the synthesised compounds (ADHP 1-8) were screened by inducing contractions using KCl on guinea pig ileum using Verapamil HCl as standard. Potassium chloride in different concentrations produced dose-dependent effect. Addition of verapamil HCl reduced the Potassium chloride induced contractions. The compounds were dissolved in DMSO, as they were not soluble in water. DMSO on its own didn't produce any effect on Potassium chloride contractions. PA_2 value which is negative log molar concentration of antagonist required to reduce the response of agonist by 50% was determined. Higher PA_2 value, more potent is the antagonist. All the synthesized compounds showed moderated calcium channel blocker activity against the KCl induced contractions.

MATERIAL AND METHODS

Melting points were determined by capillary tube method. TLC plates checked purity of the compounds. NMR spectral analysis was carried in a Bruker spectropin-200 NMR spectrophotometer at IISC, Bangalore. IR spectral analysis was carried out by using KBr pellet method.

Synthesis of 3, 4- dihydropyrimidine-2(1H)-ones/thiones 1-8 (DHP ones/thiones 1-8):

A mixture of benzaldehyde (0.01 moles), ethylacetoacetate (1.30g, 0.01mole), urea/thiourea (0.6g, 0.01moles) and stannous chloride (0.60g) were taken in a borosil beaker and heated in a microwave oven at (160W). At the end of irradiation after completion of the reaction, it was monitored by TLC (ethyl acetate: pet-ether 3: 2). The contents were cooled at room temperature and ice-cold water was added. The solid product was filtered and recrystallized by using ethanol as a solvent to afford the pure 3,4- dihydropyrimidine-2(1H)-ones/thiones 1-8.

DHP ones 1-5 showed IR (KBr) bands

3238(NH str), 3132(Ar-CH), 2980, 2920(Aliphatic-CH), 1500 (C=C Ar-Str), 1706(C=O Str), 1305(C-N Str)

NMR:7.63 δ (s,1H,NH), 9.13 δ (s,1H,NH), 5.98 δ (s,1H,CH), 2.38 δ (s,3H,CH₃), 1.09 δ (t,3H,CH₃), 4.08 δ (q,2H,CH₂), 7.10-7.325 δ (m,5H,Ar-H),

DHP Thiones 6-8 showed IR (KBr) bands 3229(NH str), 3130(Ar-CH), 2975, 2915(Aliphatic-CH), 1490 (C=C Ar-Str), 1702(C=O Str), 1310(C-N Str)

NMR:7.60 δ (s,1H,NH), 8.93 δ (s,1H,NH), 5.95 δ (s,1H,CH), 2.39 δ (s,3H,CH₃), 1.08 δ (t,3H,CH₃), 4.05 δ (q,2H,CH₂), 7.12-7.425 δ (m,5H,Ar-H),

Synthesis of Acetylated 3,4-dihydropyrimidine-2(1H)-ones/thiones 1-8 (ADHP ones/thiones 1-8):

A mixture of 3,4-dihydropyrimidine-2(1H)-ones/thiones(0.306g), acetic anhydride(1.3824g) and anhydrous zinc chloride(0.9548g) were taken in a borosil beaker and irradiated at 160-640 W. The progress of the reaction was monitored by TLC (ethyl acetate: pet-ether1: 1).Then 5% hydrochloric acid (10ml) was added to the reaction mixture. After cooling, the solution was filtered to give the solid product. The crude product was recrystallized using ethyl acetate as solvent to afford the acetylated product of 3,4- dihydropyrimidine-2(1H)-ones/ thiones 1-8.

Table 1: SnCl₂.2H₂O catalyzed synthesis of 3,4-dihydropyrimidine-2(1H)-ones/thiones in a microwave oven at 160 W

S. No.	Compound Code	R	X	Time (sec)	Yield (%)	m.p. (°C)
1.	DHP-1	H	O	40	95	201-203
2.	DHP-2	4-Cl	O	40	93	211-212
3.	DHP-3	4-OH	O	40	90	227-228
4.	DHP-4	2-Cl	O	35	93	217-218
5.	DHP-5	4-OCH ₃	O	20	94	200-201
6.	DHP-6	H	S	40	95	209-210
7.	DHP-7	4-Cl	S	35	92	192-194
8.	DHP-8	4-OCH ₃	S	25	94	151-152

Table 2: Acetylation of the corresponding 3,4-dihydropyrimidine-2(1H)-ones/thiones in a microwave oven at 160 W

S. No.	Compound Code	Molecular formula	Molecular weight	Yield (%)	R _f value	Melting point(°C)	Pharmacological Activity (PA ₂ value)
1.	ADHP-1	C ₁₆ H ₁₈ N ₂ O ₄	302.0	95.5	0.716	160	5.62
2.	ADHP-2	C ₁₆ H ₁₇ N ₂ O ₄ Cl	336.5	91.74	0.754	159	5.4
3.	ADHP-3	C ₁₆ H ₁₈ N ₂ O ₅	318.0	90.11	0.72	180	5.7
4.	ADHP-4	C ₁₆ H ₁₇ N ₂ O ₄ Cl	336.5	96.83	0.813	168	5.54
5.	ADHP-5	C ₁₇ H ₂₀ N ₂ O ₅	332.0	85.2	0.58	140	5.42
6.	ADHP-6	C ₁₆ H ₁₈ N ₂ O ₃ S	318.0	94.16	0.92	170	6.06
7.	ADHP-7	C ₁₆ H ₁₇ N ₂ O ₃ SCI	352.5	92.23	0.76	158	5.6
8.	ADHP-8	C ₁₇ H ₂₀ O ₄ N ₂ S	348.0	93.5	0.65	153	5.54

ADHP ones 1-5 showed IR (KBr) bands 3235(NH str), 3129(Ar-CH), 2974, 2911(Aliphatic-CH), 1494(C=C Ar-Str), 1700(C=O Str), 1303(C-N Str)

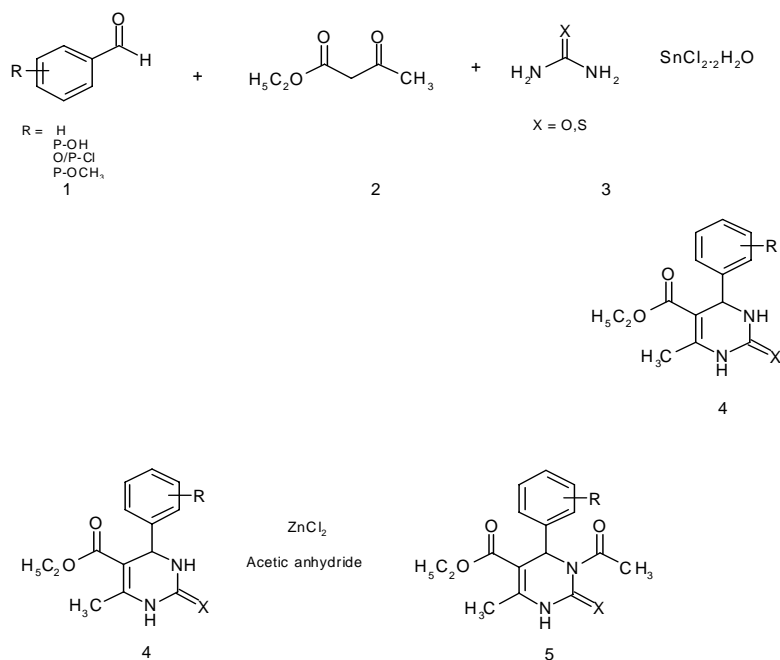
NMR: 8.43 δ (s,1H,NH), 6.64 δ (s,1H,CH), 2.56 δ (s,3H,CH₃), 1.12 δ (t,3H,CH₃), 4.23 δ (q,2H,CH₂), 2.39 δ (s,3H,CH₃), 7.253-7.412 δ (m,5H,Ar-H),

ADHP Thiones 6-8 showed IR (KBr) bands 3234(NH str), 3131(Ar-CH), 2969, 2909(Aliphatic-CH), 1511(C=C Ar-Str), 1699(C=O Str), 1304(C-N Str)

NMR: 8.38 δ (s,1H,NH), 6.57 δ (s,1H,CH), 2.54 δ (s,3H,CH₃), 1.22 δ (t,3H,CH₃), 4.13 δ (q,2H,CH₂), 2.28 δ (s,3H,CH₃), 6.799-7.277 δ (m,5H,Ar-H),

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4 = DHPones/thiones,

X=O DHP ones,

R = H (DHP-1), p-chloro(DHP-2),

hydroxy(DHP-3),

o-chloro(DHP-4), p-methoxy (DHP-5),

X=S DHP thiones,

R= H(DHP-6), p-chloro(DHP-7), p-p-

methoxy(DHP-8),

5 = ADHPones/thiones,

X=O ADHP ones,

R= H(ADHP-1), p-chloro(ADHP-2), p-hydroxy p-

(ADHP-3), o-chloro(ADHP-4), p-methoxy(ADHP-5),

X=S ADHP thiones,

R = H (ADHP-6), p-chloro(ADHP-7),

methoxy (ADHP-8).

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