Khamgaonkar et al., 1:6
http://dx.doi.org/10.4172/scientificreports.326

Open Access Scientific Reports

Research Article Open Access

Microwave Assisted Synthesis of Novel Ethyl 2-(3,4-Dihydro-6-Methyl-2-oxo-4-Phenyl-5-Propionylpyrimidin-1(2H)-yl) Acetohydrazide Derivatives

Vishal D. Khamgaonkar*, Pradeep V. Kore, Mahesh M. Game-Patil and Sandip S. Kshirsagar

Department of Pharmaceutical Chemistry, JSPM'S Charak College of Pharmacy and Research, Pune-Nagar Road, Wagholi, Pune, India

Abstract

A new series of 2-(3,4-dihydro-6-methyl-2-oxo-4-substituted-5-propionylpyrimidin-1(2H)-yl) acetohydrazide have been synthesized by one pot three component cyclo condensation reaction using zinc metal and lead as a catalyst. The success of the reaction was observed by TLC and melting. The structures of these compounds were established on the basis of spectral data and elemental analysis. All compounds were evaluated for antibacterial activity by the broth microdilution assay method and found moderately active.

Keywords: DMHP; Microwave; Dihydropyrimidone; Biginelli reaction

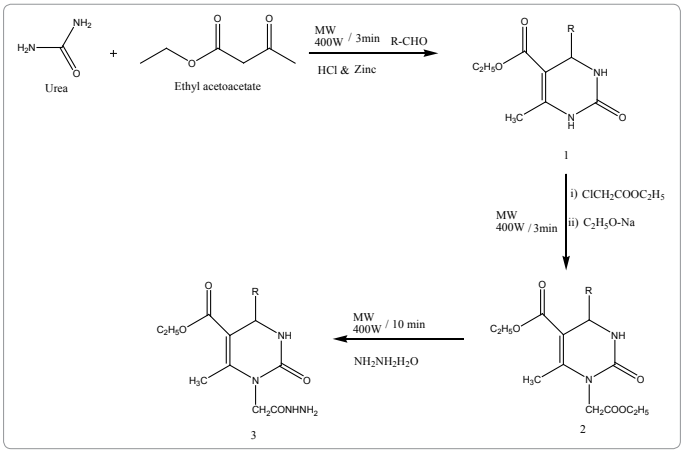
Introduction

In 1893, the synthesis of functionalize 3,4-dihydropyrmidine 2-(one H) ones (DHPMs) by a three compound condensation reaction of an aromatic aldehyde, urea and ethyl aceto acetate, was reported for first time by P. Biginelli. In post decade, such Biginelli type dihydropyrimidines have received a considerable amount of attention, due to interesting pharmacological property associated with calcium channel blocker activity, antihypertensive activity, antibacterial and antimicrobial activity. The use of microwave irradiation in organic synthesis has become increasingly popular within the pharmaceutical and academic arenas, because it is a new enabling technology for drug discovery and development [1]. By taking advantage of this efficient source of energy, compound libraries for lead generation and optimization can be assembled in a fraction of time required by classical thermal methods. In the past decade, dihydropyrimidine derivatives have exhibited important pharmacological properties, as the integral backbone of several calcium channel blocker, antihypertensive agents, alpha-la-antagonists and neuropeptide Y (NPY) antagonist [2-7]. One of the most potent drug synthesized was [4 substituted phenyl-5-ethoxycarbonyl-6-methyl]3,4-dihydroxypyrimidine 2(1 H) one, which has been found to be potent anti-hypertensive, calcium channel antagonism that is comparable with standard drug Nifedipine. A classical root to obtain [4 substituted phenyl-5-ethoxycarbonyl-6-methyl]3,4-dihydroxypyrimidine 2(1 H) one is by reaction of aldehyde, ethyl acetoacetate and urea along with refluxing with ethanol, hydrazine hydrate (for 24 hours) following Biginelli reaction was carried out [8-10]. However, in generality of the methods is limited and mostly required long time and hence, considering the importance of dihydropyrimidine moiety as pharmacophoric scaffold, we applied the application of microwave irradiation to the reaction using zinc metal and lead as a catalyst. Thus, it has accelerated the rate and yield of product [11-13].

Materials and Methods

The microwave assisted synthesis were carried out using a Synthos 300 monomode oven monitored manually and temperature maintained at a constant value 140°C within the power modulation of 200 W. Stirring was provided manually in intervals, while reactions were performed in open glass vessels within a ramp time of 10 sec to 2 min. All reagents were obtained from Merk Chemicals Limited. Solvents used were of analytical grade and when necessary, were purified and dried by standard methods.

Scheme of Reaction



Experimental Part

Synthesis of ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate (1a)

To a mixture of urea (0.1 mole), benzaldehyde (0.1 mole) and ethylacetoacetate (0.1 mole) in ethanol, 4 drops of concentrated hydrochloric acid was added and was refluxed under microwave for 3 min at 200 W. The reaction mixture was poured into ice water (100 ml) with stirring and left overnight at room temperature. Filtered and residue was dried at room temperature, recrystallised from ethanol. IR: 1648 cm^{-1} (amide C=O); 1703 cm^{-1} (C=O ester); 3244 cm^{-1} (NH) 1H NMR Spectral Data of compound: δ ppm, CDCl3,1.15(t, 3H, CH_3 ester); 2.25 (s, 3H, dihydropyridyl CH_3); 4.05 (q, 2H, CH_2 ester); 6.8(s,

***Corresponding author:** Vishal D. Khamgaonkar, Department of Pharmaceutical Chemistry, JSPM'S Charak College of Pharmacy and Research, Pune-Nagar Road, Wagholi, Pune-412207, India, E-mail: sanpals24@rediffmail.com

Received August 31, 2012; **Published** September 22, 2012

Citation: Khamgaonkar VD, Kore PV, Game-Patil MM, Kshirsagar SS (2012) Microwave Assisted Synthesis of Novel Ethyl 2-(3,4-Dihydro-6-Methyl-2-oxo-4-Phenyl-5-Propionylpyrimidin-1(2H)-yl) Acetohydrazide Derivatives. 1:326. doi:10.4172/scientificreports.326

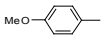
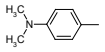
Sr. No	R	% yield	M.p. ºC	Mol. Formula	Mol.weight	Elements
3a		89%	207ºC	$C_{16}H_{20}N_4O_3$	316	C, 59.60; H,6.20; N,17.53; O, 14.84
3b		75%	210ºC	$C_{16}H_{19}ClN_4O_3$	359	C, 54.60; H,5.10; N,15.51; O, 13.97; Cl, 9.98
3c		78%	116ºC	$C_{17}H_{22}N_4O_4$	346	C, 58.90; H,6.58; N,16.53; O, 17.81
3d		71%	115ºC	$C_{18}H_{25}N_5O_3$	359	C, 61.01; H,7.20; N,19.40; O, 13.34
3e		72%	121ºC	$C_{16}H_{19}N_5O_5$	361	C, 55.60; H,5.40; N,19.33; O, 20.24
3f		64%	114ºC	$C_{16}H_{20}N_4O_5$	332	C, 57.80; H,6.01; N,16.98; O, 19.24
3g		68%	132ºC	$C_{17}H_{22}N_4O_4$	346	C, 58.60; H,6.40; N,16.13; O, 18.44

Table 1: Physiochemical Parameters of Synthesised Compounds (3a-3g).

SR .No	Compound	Staphylococcus aureus (+ve)	Escherichia coli (-ve)		
		50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml
1	Procaine penicillin	20	22	-	-
2	Streptomycin	-	-	17	23
3	3a	10	09	17	15
4	3b	05	11	13	17
5	3c	14	16	09	13
6	3d	13	14	08	08
7	3e	09	07	16	15
8	3f	12	13	09	07
9	3g	09	10	14	13

Table 2: Zone of Inhibition.

1H, dihydropyridyl-CH); 7.2-7.3 (m, 4H, Ar H) 7.4 (s, 1H, 3 NH); 8.9 (s, 1H, 1 NH). Mass (FAB):237(M+, 12%), 189(Base peak 100%).

Synthesis of Ethyl 1-[(ethoxycarbonyl)methyl]-1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate (2a)

The compound 1 (0.1 mol) was dissolved in a solution prepared by reacting Na (0.1 mol) with 200 ml of absolute ethanol. The solution was kept in microwave for 10 min at 200 W. Ethyl chloroacetate (0.1 mol) was added in three portions over a period of 2 min. The reaction mixture was filtered while hot to remove precipitated sodium chloride; the solvent was removed on a rotary vacuum evaporator. The crude product was collected and recrystallised from ethanol. Compounds 2b-2g has been synthesized in above manner. Spectral data of 2a- IR (KBr) 1648 cm^{-1} (CONH), 1701 cm^{-1} (C=O of ring carbonyl), 1725 cm^{-1} (C=O ester), 2978 cm^{-1} (aromatic proton stretching), 3116 cm^{-1} (CONH), 3245 cm^{-1} (NH stretching), 1H NMR δ ppm $CDCl_3$, 1.1 (t,6H,CH_3), 2.45 (s,3H,CH_3), 4.13 (s,3H,CH_3) 4.2 (q,4H,CH_2), 4.45 (d,2H,CH_2), 5.2 (s,1H,dihydropyridyl-CH), 7.3-7.4 (m,10 H Ar), 7.9 (S,1H,NH). Mass (FAB): 265 (M+, 12%), 178 (Base peak 100%).

Synthesis of 2-(3,4-dihydro-6-methyl-2-oxo-4-phenyl-5-propionylpyrimidin-1(2H)-yl)acetohydrazide (3a)

A mixture of the appropriate compound 2 (0.1 mol), hydrazine hydrate (8 drops), and 10 ml of 95% ethanol was refluxed under microwave for 3 min at 200 W. The solvent was removed by evaporating the compound at the room temperature and the residue was poured into cold water. The solid that formed was collected, washed with ice-cold water, and recrystallized from ethanol. All derivatives have been synthesized in this manner. Spectral data of 3a- IR (KBr) 1608 cm^{-1} (amide C=O), 1647 cm^{-1} (ester C=O), 1706 cm^{-1} (carbohydrazide C=O), 3238 cm^{-1}(-NH) 1H NMR δ ppm, CDCl3, 1.14 (t, 3H, CH3 of C_2H_5), 1.5 (s,3H, dihydropyridyl CH_3), 4.04 (q,2H,CH_2 of C2H_5) 5.4 (s, NH_2); 5.6 (d, 1H, NH); 7.22-7.3 (m, 4H, Ar H), 7.8 (s, 1H, 1 NH) Mass (FAB):251(M+, 9%), 186(Base peak 100%) Elemental analysis: C, 59.60; H, 6.20; N, 17.53; O, 14.84 (Table 1).

Results

Antibacterial activity

All the newly synthesized compounds were evaluated for antibacterial activity by broth microdilution assay against Gram-positive bacteria *Staphylococcus aureus* (ATCC 11632), and Gram negative bacteria *Escherichia coli* (ATCC 10536). Serial dilutions of the test compounds and reference drugs were prepared in Mueller-Hinton agar. The tubes were inoculated with 10^5 cfu.ml^{-1} (colony forming unit/ml) and incubated at 37°C for 18 h. Procaine penicillin and streptomycin were used as standard drugs. The data of activity is summarized in table-2: Zone of inhibition.

Conclusion

Derivatives presented herein showed antibacterial activities. Compounds (3c, 3d, 3f) were highly active against Gram positive bacteria. Compounds (3a-3b) exhibited activity against pathogenic Gram-negative bacteria at higher concentration, while compounds (3e-3g) specifically exhibited excellent antibacterial activity even at lower concentration. Suitable molecular modification of these compounds may generate potent antimicrobial agents in future.

References

1. Kappe CO (2004) Controlled microwave heating in modern organic synthesis. Angew Chem Int Ed Engl 43: 6250-6284.

2. Hayes BL (2004) Recent advances in microwave assisted synthesis.CEM Publishing: Matthews NC 37: 66-68.

3. Atwal KS, Rovnyak GC, Kimball SD, Floyd DM, Moreland S, et al. (1990) Dihydropyrimidine calcium channel blockers. 2. 3-Substituted-4-aryl-1, 4-dihydro-6-methyl-5-pyrimidinecarboxylic acid esters as potent mimics of dihydropyridines. J Med Chem 33: 2629-2635.

4. Atwal KS, Swanson BN, Unger SE, Floyd DM, Moreland S, et al. (1991) Dihydropyrimidine calcium channel blockers. 3. 3-Carbamoyl-4-aryl-1,2,3,4-tetrahydro-6-methyl-5-pyrimidenecarboxylic acid esters as orally effective antihypertensive agents. J Med Chem 34: 806-811.

5. Atwal KS, Rovnyak GC, Schwartz J, Moreland S, Hedberg A, et al. (1990) Dihydropyrimidine calcium channel blockers: 2-heterosubstituted 4-aryl-1,4-dihydro-6-methyl-5-pyrimidinecarboxylic acid esters as potent mimics of dihydropyridines. J Med Chem 33: 1510-1515.

6. Atwal (1989) Substituted 1, 4-dihyropyrimidines. 3. Synthesis of selectively functionalized 2-Hetero-1, 4-dihydropyrimidines. J Org Chem 54: 5898-5907.

7. Atwal KS, O'reilly BC, Gougoutas JZ, Malley MF (1987) Synthesis of Substituted 1,2,3,4-tetrahydro-6-methyl-2-thioxo-5-primidinecarboxylic acid esters. Heterocycles 26: 1189-1192.

8. Hayes BL (2001) Microwave synthesis: chemistry at the speed of light. CEM Publishing: Matthews, NC 57: 9225.

9. Loupy AED (2001) Microwaves in organic synthesis. Tetrahedron 57: 9199.

10. Maynard BJ (1994) Sonochemistry. Ultrasonic Chemistry, Summer 2000, Suslick Research Group, Chicago 17: 138–155.

11. Bose DS, Madapa S, Chavan S (2005) New protocol for biginelli reaction-a practical synthesis of monastol. Bioorganic and Medicinal Chemistry Letters 12: 149-151.

12. Eynde JJV, Hecq N, Kataeva O, Kappe CO (2001) Microwave mediated regioselective synthesis of novel primido [1, 2-a] pyrimidines under solvent-free conditions. Tetrahedron 57: 1785-1791.

13. Kappe CO (2000) Biologicaly active dihydropyrimidones of the Bignelli type-a literature survey. Eur J Med Chem 35: 1043-1052.