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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NEW 3, 4-DIHYDROPYRIMIDINONES VIA NOVEL CHALCONE SERIES

Shahid Shaikh[a], Naziabegum P. Shaikh[b] S. D. Salunke [b] and M. A. Baseer[a*]

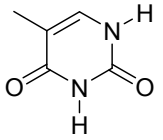
[a] *Organic Chemistry Research Laboratory, Yashwant Mahavidyalaya, Nanded -431 602, Maharashtra, India*
[b] *Research Centre in Chemistry, Rajarshi Shahu Mahavidyalaya, Latur-413512, Maharashtra, India*
Email: shahid245@rediffmail.com Phone No.: +91 8421331205

Abstract:
Calcium acetate is efficiently catalyzes one-pot, three component Biginelli reaction by condensation of aldehyde, acetyl acetone and urea or thiourea in ethanol to afford the corresponding 5-acetyl 4-substituted aryl-6-methyl-3, 4-dihydropyrimidine-2-(1*H*)-ones which are precursor of synthesis of novel chalcone series. All the newly synthesized compounds were tested for their antimicrobial activity.

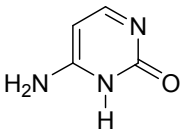
Keywords: Biginelli condensation, acetyl acetone, dihydropyrimidines, chalcone, antimicrobial activity.

1. Introduction

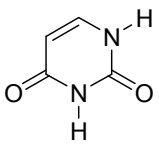
It is well known that the dihydropyrimidinones (DHPMs) or pyrimidinones and related compounds exhibit a wide range of biological activities. Furthermore, out of five major class of nucleic acid three are pyrimidine derivatives which comprises of Thymine **(1)** which is found in DNA, Cytocine **(2)** found in DNA and RNA, Uracil **(3)** in RNA. Pyrimidinones has received much attention because of their involvement as bases in DNA and RNA.



1
Thymine



2
Cytosine



3
Uracil

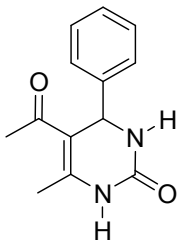
Other interesting pyrimidine containing compounds are 3, 4-dihydropyrimidine-2-(1*H*)-ones (DHPMs) called Biginelli compounds are the largest and most studied class of nitrogen containing heterocycles because of their promising biological and pharmaceutical properties such as anti-viral, anti-tumor, antibacterial and anti-inflammatory properties[1], α_{1a}-adrenrgic antagonists and neuropeptide Y (NPY) antagonists, potent calcium channel modulators, antihypertensive agents[2], and anti-HIV activity in some marine natural products, containing

DHPM skeleton such as the alkaloid batzelladine B[3]. The classical Biginelli reaction involves three component condensations of an aldehyde, β-keto ester and urea in presence of catalytic amount of HCl in ethanol at reflux temperature to afford desired DHPM[4]. The major drawback associate with this protocol is the low yield, particularly for aliphatic and substituted aromatic aldehydes. In connection with our previous work on synthesis of 3, 4-DHPMs by using calcium acetate catalyst. On this basis various 3, 4-dihydropyrimidine-(1*H*)-ones or thiones have been synthesized by using acetyl acetone/ethyl acetoacetate, aldehyde and urea or thiourea.

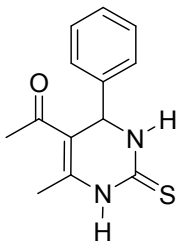
In this present work we report synthesis and antimicrobial activity of new 3, 4-dihydropyrimidine via novel chalcone series. The literature survey revealed that chalcone derivatives possess various biological activities such as cytotoxicity[5] antitumor[6] anti-inflammatory[7], antiplasmodial[8], immunosuppression[9], antioxidant[10]; antibacterial[11], antifungal[12], and antiprotozoal[13].They also possess antiviral[14], antimalarial[15], antiulcerative[16] and antihyperglycemic[17] activities.

2. Results and discussion

In this work four aldehydes used for Biginelli condensation reaction include benzaladehyde, 4-chloro, 2-chloro and 4-nitro banzaldehyde. The reaction was carried out by refluxing mentioned aldehyde (2 mmol), acetyl acetone (2 mmol) and ureaor thioures (2 mmol) in ehanol solvent by using 10mole % of the catalyst to obtained corrosponding DHPMs **4a-e** in good yield. Considering the importance of chalcones derivatives as the active therapeutic agents, in particular, as



4a



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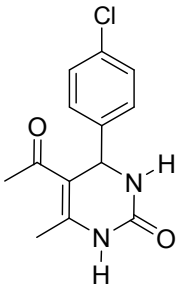

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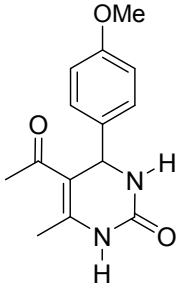

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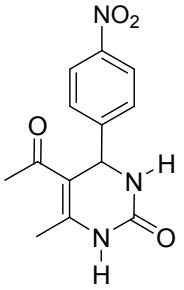
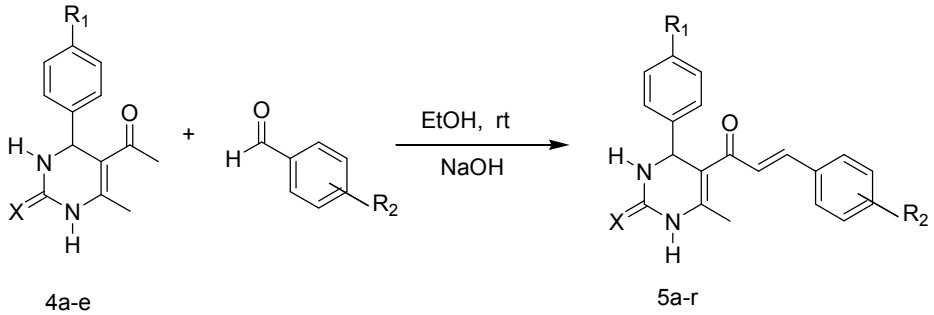


4e

antifungals ,antidiabetic, anticancer and chalcones as biologically important scaffolds due the properties associated with them, herein we wish to report synthesis of various substituted new chalcones by reacting 5-acetyl-4-(substituted phenyl)-6-methyl-3,4-dihydropyrimidones with appropiate aromatic aldehyde to get 1[6-methyl-4-(substitutedphenyl)- 2-oxo or thio-1,2,3,4 tetrahydropyrimidin-5-yl]-3-(substitutedphenyl)-prop-2-en-1-one (**5a-r**) by Claisen-Schmidt condensation between substituted 3, 4-dihydropyrimidones (**4a-e**) and aromatic aldehyde in sodium hydroxide in ethanol at room temperature **(Scheme 1)** and the result are summarized in **Table 1.**



4a-e 5a-r

Scheme 1: Synthesis a series of new 3, 4-dihydropyrimidinones via novel chalcone series

Table 1: Synthesis of new 3, 4-dihydropyrimidinones via novel chalcone series

Product	R_1	R_2	X	Yield (%)	M.P. (^oC)
5a	4-H	4-Cl	O	80	157
5b	4-Cl	4-Cl	O	83	159-160
5c	4-OMe	4-Cl	O	78	166
5d	3-NO_2	4-Cl	S	66	150-151
5e	4-H	4-Cl	S	87	169-170
5f	4-H	2-Cl	O	60	174-175
5g	4-Cl	2-Cl	O	60	166-167
5h	4-OMe	2-Cl	O	45	172-173
5i	3-NO_2	2-Cl	S	58	168
5j	4-H	2-Cl	S	86	155-156
5k	4-H	3,4,5-$(OCH_3)_3$	O	86	182-183
5l	4-Cl	3,4,5-$(OCH_3)_3$	O	47	163
5m	4-OMe	3,4,5-$(OCH_3)_3$	O	60	157-159
5n	3-NO_2	3,4,5-$(OCH_3)_3$	S	45	166-167
5o	4-H	3,4,5-$(OCH_3)_3$	S	48	158-159
5p	4-H	3,4-$(OCH_3)_2$	O	82	163-164
5q	4-Cl	3,4-$(OCH_3)_2$	O	49	161-162
5r	4-OMe	3,4-$(OCH_3)_2$	O	57	164

Antimicrobial activity

Antimicrobial activity was determined using agar cup diffusion method [18]. The tested organism were subcultured on nutrient agar medium (HI media laboratories Ltd. Mumbai, India) for bacteria and potato-dextrose agar (PAD) medium (HI media laboratories Ltd. Mumbai, India) for fungi. Ampicillin was used as reference drug for bacterial strain. Griseofulvin was used as positive control for fungi.Bacterial culture was incubated at 37 ^{0}C for *Escherichia coli*, at 27+ 2 ^{0}C for other bacteria for 24 h while fungal culture was incubated at 25-30 ^{0}C for 4-5 days. The minimum inhibitory concentration of the sample was estimated for each of the test organism in triplicates. The solution of the test compounds were prepared by dissolving 5mg each in 5mL of dimethylsulfoxide at a concentration of 1000 □g/ mL. The cups each of 10 mm in diameter were made by scooping out medium with a sterilized cork borer in a Petri dish which was streaked with the organism. The solutions of each test compound (0.1 mL) were added separately in the cups and petri dishes were subsequently incubated incubated at 37 ^{0}C for *Escherichia coli*, at 27+ 2 ^{0}C for other bacteria for 24 h while fungal culture was incubated at 25-30 ^{0}C for 4-5 days.. Zone of inhibition produced by each compound was measured in mm.The medium used for the antibacterial study has the following composition [g/L]:Peptone, 5; Beef extract, 3; yeast extract, 1.5; sodium chloridr, 8; and distilled water, 1L; pH was adjusted at 7.6.

Compounds 5a-r was screened for their antifungal and antibacterial activities. Most of the compounds 5a-r exhibited good to excellent antimicrobial activity with respect to the reference drugs. The results of antifungal and antibacterial activities are outline in Table 2 and 3, respectively. The result obtained showed that most of the compounds 5a-r showed variable range of inhibition zones against the tested microorganism.

Antifungal activity

The result of antifungal screening of 1[6-methyl-4-(substituted phenyl)- 2-oxo or thio-1, 2, 3, 4 tetrahydropyrimidin-5-yl]-3-(substituted phenyl)-prop-2-en-1-one 5a-r against [*Aspergillus niger, Aspergillus oryzae ,Aspergillus fumigatus, and Candida parapsilosis]* are reported in Table 2, in coparison with those of reference drud geiseofulvin. The inhibition zone of compounds **5a-r** good to excellent activity ranged from 10 mm-22 mm against all the tested fungal microorganism. Compound **5a, 5e, 5g** and **5k** showed moderate inhibition zone 11 mm, 10 mm, and 5p showed excellent inhibition zone of 20 mm respectively against *Aspergillus niger* compared with 25mm of the reference drug. Compound **5h, 5n, 5q** and **5r** exhibited good to excellent inhibition zone 19 mm, 15 mm, 18 mm and 20 mm respectively against *Aspergillus oryzae.* Intrestingly, compounds **5k, 5l** and **5q** were more potent antifungal than the refrrence Griseogulvin showing hghier inhibition zones 22 mm, 23 mm and 23 mm against *Aspergillus fumigatus* than Griseofulvin 25 mm. Furthermore, compound **5c, 5d and 5p** showed highest antifungal activity than the reference drug against *Candida parapsilosis* with inhibition zone 20 mm, 22 mm and 20 mm comparing with the Griseofulvin 25 mm. However, compound **5e, 5f, 5g, 5i, 5j** and **5m** were inactive against the *Aspergillus oryzae* and *Candida parapsilosis* microorganism. Among the all the derivatives **5a-r** the 4-chloro and dimethoxy and trimethoxy compounds are more active with respect to 2 chloro derivatives.

Antibacterial activity

The antibacterial activity of against 1[6-methyl-4-(substituted phenyl)- 2-oxo or thio-1, 2, 3, 4 tetrahydropyrimidin-5-yl]-3-(substituted phenyl)-prop-2-en-1-one 5a-r against Gram positive [*Bacillus subtilis*, *Staphylococcus aureus] and Gram negative [Salmonella typhi, Escherichia coli]* bacteria are reported in Table 3, The result were compared with

antibacterial activity of reference drug ampicillin. The inhibition zones of the compounds **5a-r** varied from 10 mm-24 mm against the all tested microorganism. However, compounds **5a-r** showed good to excellent inhibition zones against Gram positive [*Bacillus subtilis*, *Staphylococcus aureus]*. Furthermore, these compounds were active in antibacterial effect against *Gram negative [Salmonella typhi, Escherichia coli]* bacteria. While among the all the compounds 5a-r, the 4-chloro, 2- chloro, and dimethoxy and trimethoxy compounds are more active against all the tested microorganism

Table 2: Antifungal activity of compounds 5a-r.

Compd.	***Zone of inhibition in mm***			
	A.niger	***A.oryzae***	***A.fumi***	***C.para***
5a	11	14	19	17
5b	16	10	13	13
5c	19	--	12	20
5d	12	10	10	22
5e	10	--	--	12
5f	16	--	12	14
5g	**10**	**10**	**13**	**--**
5h	**12**	**19**	**15**	**10**
5i	**14**	**14**	**12**	**--**
5j	**12**	**17**	**14**	**--**
5k	**10**	**12**	**22**	**14**
5l	**12**	**10**	**23**	**19**
5m	**15**	**14**	**14**	**--**
5n	**12**	**15**	**12**	**15**
5o	**19**	**10**	**17**	**12**
5p	**20**	**14**	**12**	**20**
5q	**14**	**18**	**23**	**19**
5r	**12**	**20**	**16**	**14**
Griseofulvin	**25**	**25**	**25**	**25**

------Indicates no zone of inhibition.

Table 3: Antbacterial activity of compounds 5a-r.

Compd.	**Zone of inhibition in mm**			
	B.S	***E.coli***	***S.aur***	***S.Typhi***
5a	13	10	14	11
5b	14	16	15	13
5c	19	14	22	20
5d	12	10	14	19
5e	15	16	19	--
5f	12	10	15	--
5g	12	--	14	13
5h	--	23	12	14
5i	24	19	16	12
5j	19	24	14	17
5k	10	14	12	20

5l	14	--	14	10
5m	11	22	20	11
5n	12	14	19	16
5o	15	12	14	10
5p	19	18	22	19
5q	12	14	23	14
5r	10	16	17	16
Ampicillin	**27**	**26**	**28**	**25**

--- Indicates no zone of inhibition.

3. Experimental

Melting points of the compounds were determined in open capillary tubes and are uncorrected, IR Spectra were recorded on Shimadzu FT-IR Spectrometer using potassium bromide pellets, ^{1}H NMR was determined on a Bruker Avance II 400 Spectrometer against TMS as internal standard. Mass spectra were recorded on waters Micromass Q-Tof Micro spectrometry. The purity of the compounds was checked by thin layer chromatography (TLC).

3.1. General experimental procedure for the synthesis of 5-acetyl-4-substituted phenyl-6-methyl-3, 4-dihydropyrimidine-2-(1*H*)-ones:

A mixture of appropriate aldehyde (10mmol), acetyl acetone (15 mmol), ureaor thiurea (25 mmol) and the catalyst, calcium acetate (10 mol %) in ethanol (20 mL) was refluxed for the time 5-12 hrs**.** The reaction was monitored by TLC. After completion of reaction, the solvent was removed under reduced pressure and the residue was treated with water, filtered off, washed with water, dried and recrystallized from methanol to afford Biginelli reaction product **(4a-e)** in excellent purity.

5-acetyl-4-phenyl-6-methyl-3, 4-dihydropyrimidine-2-(1H)-one (4a):

IR (KBr, cm^{-1}): 3286 (NH), 3257 (N-H), 2978(CH_3), 1702-1675 (C=O), 1598, 1455, 1416 (ArH). ^{1}HNMR ($CDCl_3$, δ ppm): 2.10 (s, 3H, $COCH_3$); 2.34 (s, 3H, CH_3); 5.32 (s, 1H, C^4H); 7.22 (m, 4H, ArH); 7.27-7.31(m, 4H, ArH); 7.52 (s, 1H, NH); 9.02 (s, 1H, NH). Mass: Mass (m/z) 231(M+1).

3.2. General experimental procedure for the synthesis of 1[6-methyl-4-sbstituted phenyl-2-oxo-1, 2, 3, 4 tetrahydropyrimidin-5-yl]-3-(4-substituted phenyl)-prop-2-en-1-one:

A mixture of acetyl derivatives of (**4a-e**) **(**(10 mmol) and aldehyde (10 mmol) in ethanol (30 mL) was added 30% solution of sodium hydroxide (12mL). The reaction mixture was then stirred at room temperature for 24 hr. the reaction mixture was poured on to ice cold water, and acidified with dilute HCl. The solid obtained was filtered, washed with water and recrystallized from dilute ethanol to get chalcone **(5a-r).**

All the remaining derivatives were synthesized by adopting the same experimental procedure and their structures were established on the basis of spectral analysis data (IR, ^{1}H NMR and Mass).

Conclusion

In conclusion, we have successfully synthesized new 3, 4-dihydropyrimidine derivatives via novel chalcone series. We studied the biological importance of synthesized compounde 5a-r by screening their antimicrobial activity against four fungal and bacterial microorganism. All the synthesized compound **5a-r** showed good antibacterial activity against all the test microorganism while compounds **5c, 5d, 5k, 5l, 5p and 5q** exhibited most potent antifungal showing highest inhibition zone against *Aspergillus fumigatu* and *Candida parapsilosis*

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