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Synthesis and biological studies of 1, 2, 3, 4-tetrahydro pyrimidine derivatives

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ABSTRACT

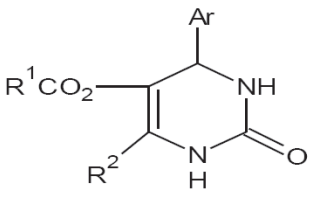
It has been found that several DHPM derivatives possess biological activity, which has led to their use as antiviral, antibiotic, anticarcinogenic, antihypertensive, antitubericular, anti mycobacterial or anticancer activity. Further more, DHPM s are chiral compounds and it has been discovered that the configuration at the steriogenic carbon C4 determines their biological properties. DHPMs Derivatives are synthesized via a multicomponent reaction of aldehyde derivative, urea or thiourea and 1,3-dicarbonyl compounds using Biginelli Reaction and microwave irradiation catalyzed by HCl. 1H NMR, IR, mass spectra and CHN analysis data established identification of the compounds are evaluated for their antiviral, antibiotic, anticarcinogenic, antihypertensive, antitubericular ,anti mycobacterial or anticancer activity.

Key words: Dihydropyrimidines, Antitubercular activity, Antimycobacterial activity.

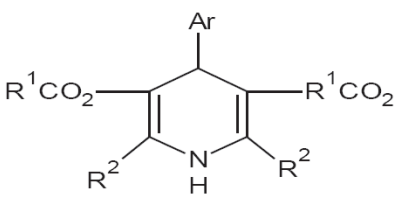
INTRODUCTION

The multicomponent reactions (MCRs) are one of the most important protocols in organic synthesis and medicinal chemistry. The diversity, efficiency and rapid access to small and highly functionalized organic molecules makes this approach of central current interest in the construction of combinatorial libraries and optimization in drug discovery process.

The 3, 4-dihydropyrimidin-2(1*H*)-ones (DHPM–1, Fig. 1) have recently emerged as important target molecules due to their therapeutic and pharmacological Properties such as antiviral, antimitotic, anticarcinogenic, antihypertensive and noteworthy, as calcium channel modulators. Additionally, their particular structure has been found in natural marine alkaloid batzelladine A and B which are the first low molecular weight natural products reported in the literature to inhibit the binding of HIV gp-120 to CD4 cells, so disclosing a new field towards the development of AIDS therapy. Also, due to the close related structure of DHPMs with the known dihydropyridine calcium channel modulators of the Hantzsch-type (DHP - 2, Fig. 1), an intensive research has been devoted to synthesize the dihydropyrimidinone nucleus and this subject was recently reviewed.



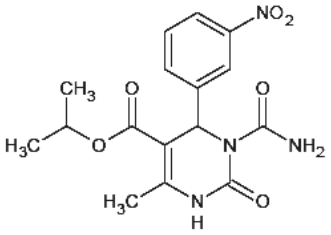
DHPM -1



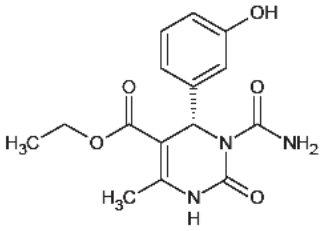
DHP -2

Fig. 1: The Biginelli (1) and Hantzch (2) compounds

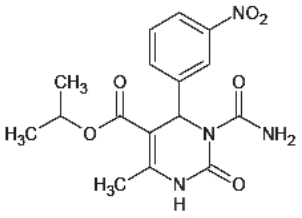
The following compound (i) exhibits an antihypertensive effect and only (S)-Monastrol (ii) and (R) - Mon- 97(iii) present potential anticancer activity



Compound (i)
antihypertensive



Compound (ii)
(S)-Monastrol



Compound (iii)
R)-Mon $_{97}$

[Anticancr agent]

The original one-pot synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones was firstly reported by Pietro Biginelli in 1893 performing the three-component cyclocondensation reaction of ethyl acetoacetate, benzaldehyde and urea under Brönsted acid catalysis. However, this reaction suffers from the harsh conditions, high reaction times and frequently low yields. Among the diversity of available methodologies in the literature that use lithium salts, TMSI, reactions performed under ionic liquids, solid phase, polymer-supported, heterogeneous catalysis by silica's and montmorillonites or activation by ultrasound and microwave energies as synthetic protocols to prepare DHPMs, special attention has been dedicated to Lewis acids catalysis. Recently, $BF_3.OEt_2$ complex was shown to be an excellent promoter of the three-component reaction but anhydrous conditions were required. High yields of DHPMs were obtained using metals halides, such as $NiCl_2.6H_2O$ and $FeCl_3.6H_2O$, $CoCl_2.6H_2O$, $BiCl_3$, In (III)-halides, and $ZrCl_4$, or lanthanide halides such as $LaCl_3.7H_2O$, and $CeCl_3.7H_2O$ as Lewis acid catalysts. Metal triflates, such as $Zn(OTf)_2$, $Cu(OTf)_2$, $Bi(OTf)_3$,and $Sc(OTf)_3$ or lanthanide triflates as $Yb(OTf)_3$, and $La(OTf)_3$. Were also reported.

Antitubercular activity

Dihydropyrimidines are not represented in the current clinical antitubercular regiments, suggesting that this class of compounds may target new biochemical mechanisms potentially allowing treatment of MDR-TB and there are very few investigatory reports on dihydropyrimidines as antitubercular agents. Recognizing these facts and in constituents of work on pyrimidine derivatives. We set upon a programmed of making anti-tubercular agents, using the central dihydropyrimidie as the template and adding versatile constituents on the various positions of dihydropyrimidine ring.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. Reagent grade chemicals were purchased fro commercial source and used as received .IR spectra were recorded on Shimadzu-8400 FTIR spectrophotometer by DRS method. 1H NMR spectra were recorded in CDCl3 on a BRUKER AVANCE II 400 spectrometer using TMS as internal standard. The progress of reaction was monitored by TLC run on silica gel G (Merck)

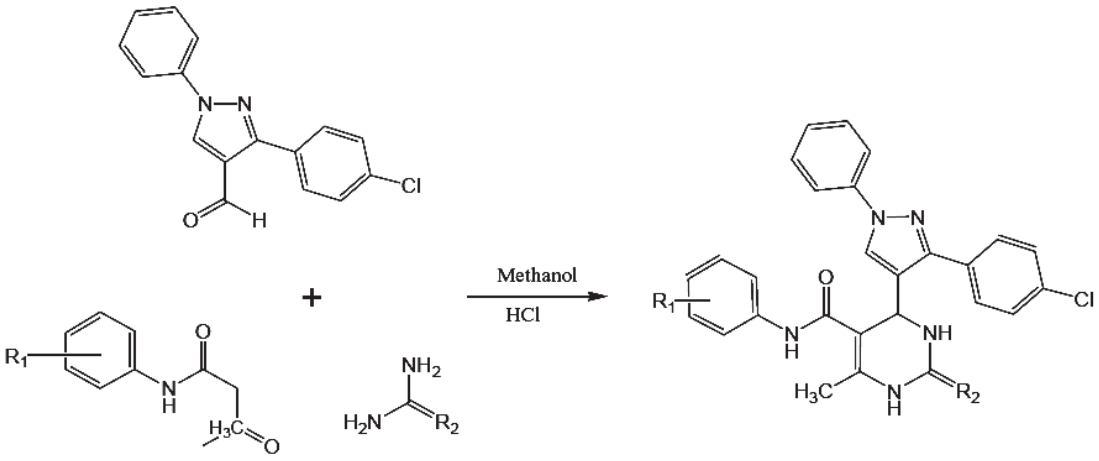
General experimental procedure

Conventional method

A mixture of aldehyder deri. (0.01mole),1,3 –dicarbonyl compound(0.01 mole), urea(0.01 mole)add in a 30ml methanol and add catalytic amount of Hydrochloric acid were placed in an round bottom flask and the mixture was refluxed for about 18 hrs till the reaction was complete(monitored by TLC). The mixture was then cooled to RT and poured into water with continuous stirring when the solid product separated out. The crude solid product was purified by repeated recrystallisation from alcohol or by column chromatography to give the pure products.

Microwave method

A mixture of aldehyde deri. (0.01mole), 1, 3 –dicarbonyl compound (0.01 mole), urea (0.01 mole) and catalytic amount of Hydrochloric acid were placed in an flask and irradiated in a microwave oven 220 W for the required duration [table I] After the completion of the mixture was cooled to room temperature and water was added with stirring when the solid product precipited out, which was filtered. The crude product was washed with water and



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2	p-OCH3	O	1-B	72	245-50	10
3	o-F	O	1-C	65	192-94	7
4	p-F	O	1-D	82	214-20	12
5	m-F	O	1-E	56	208-10	15
6	o-Cl	O	1-F	78	156-60	8
7	p-Cl	O	1-G	65	211-22	5
8	m-Cl	O	1-H	88	255-60	9
9	o-No2	O	1-I	74	201-10	3
10	p-No2	O	1-J	80	245-25	5
11	m-No2	O	1-K	73	235-47	7
12	H	S	2-A	78	179-88	5
13	p-OCH3	S	2-B	69	200-11	12
14	o-F	S	2-C	83	268-77	9
15	p-F	S	S-D	71	260-74	4
16	m-F	S	2-E	77	206-17	6
17	o-Cl	S	2-F	73	178-89	9
18	p-Cl	S	2-G	82	209-20	8
19	m-Cl	S	2-H	85	235-38	6
20	o-No2	S	2-I	85	200-05	4
21	p-No2	S	2-J	70	250-55	7
22	m-No2	S	2-K	89	190-95	9

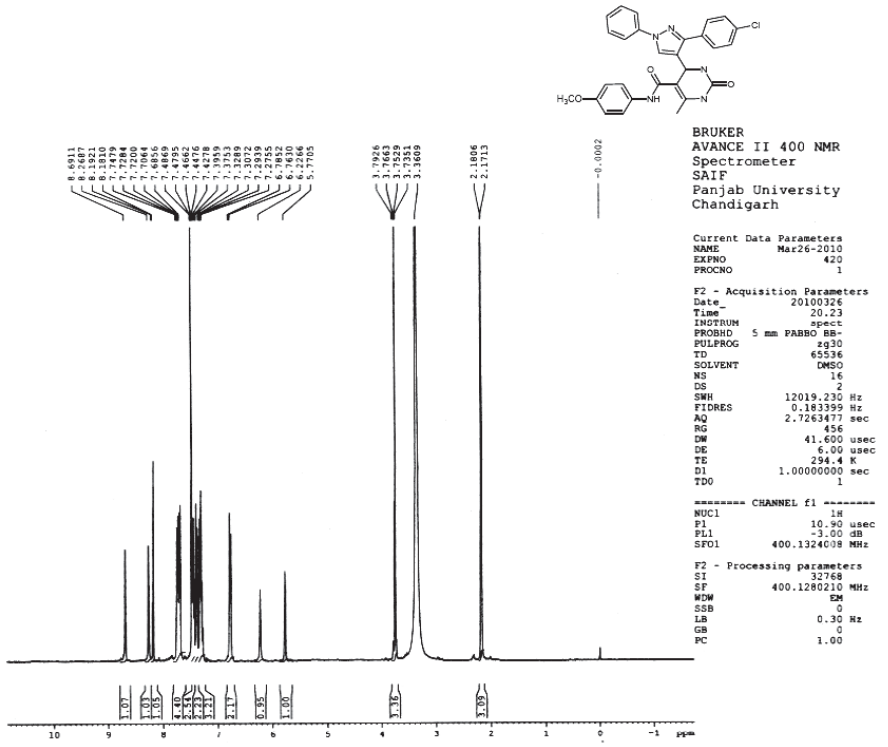
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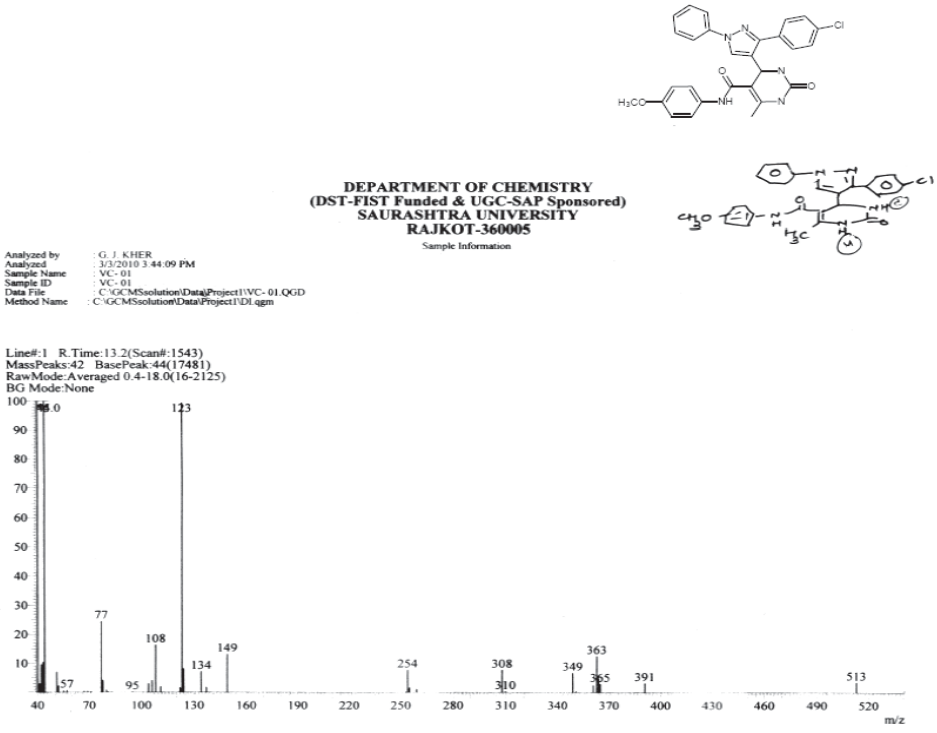
Fig. 1:


DEPARTMENT OF CHEMISTRY
(DST-FIST Funded & UGC-SAP Sponsored)
SAURASHTRA UNIVERSITY
RAJKOT-360005
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Analyzed : 3/3/2010 3:44:09 PM
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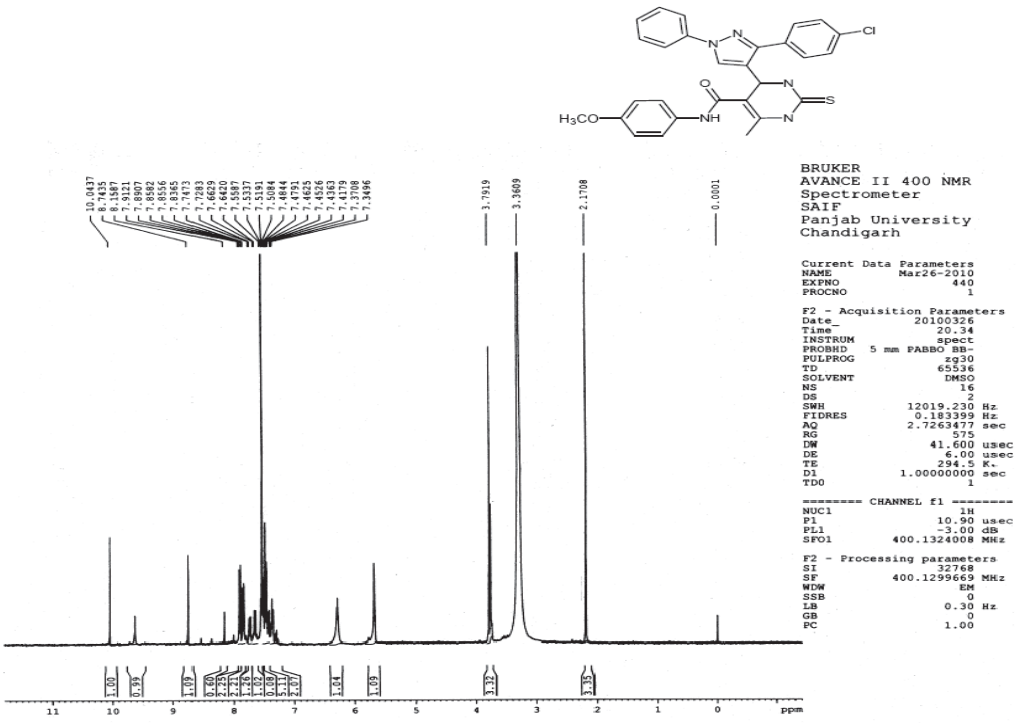
m/z

Fig. 2: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Spectrometer
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RG 575
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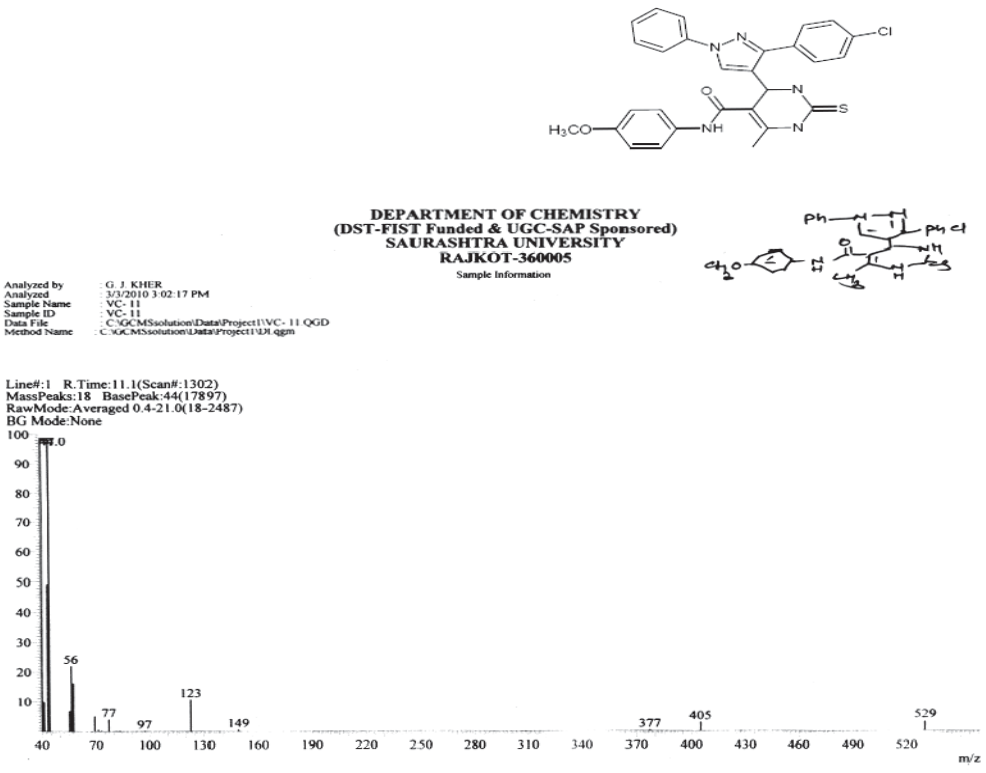
Fig. 3:


DEPARTMENT OF CHEMISTRY
(DST-FIST Funded & UGC-SAP Sponsored)
SAURASHTRA UNIVERSITY
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BG Mode:None
m/z

Fig. 4:

recrystallised from alcohol or purified by column chromatography to give the product in good to excellent yields.

All the product were characterized by melting point, 1H NMR, IR, mass spectra and CHN analysis

Spectral data

4-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydro-N-(4-methoxyphenyl)-6-methyl-2-oxopyrimidine-5-carboxamide, 1-B

A mixture of 3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (0.01mole), *N*-(4-methoxyphenyl)-3-oxobutanamide (0.01 mole), Urea (0.01 mole) and catalytic amount of Hydrochloric acid were placed in an flask and irradiated in a microwave oven 220 W for 10 min. After the completion of the mixture was cooled to room temperature and water was added with stirring when the solid product precipited out, which was filtered. The crude product was washed with water and recrystallised from alcohol or purified by column chromatography to give 69% yields.

M.P. 245-250 °C , IR-Aromatic 3047, C=O -1690, NH-1596 & 3400,-0CH_3-2830-2810 and 1460-1440,-CH_3-2920- and 1470-1430,-Cl-761 cm^{-1}, ^{1}H NMR($CDCl_3$)δ 3.73 (S,6H,-0CH_3), 5.71(d,1H,-CH),2.16(d,2H,-NH),8.0,(d,1H,-NH) 1.71(3H,-CH_3), 6.83-7.65(13H,ArH)

MF- $C_{28}H_2$ ClN_5O_3

M.W.-513.16

C=65.16%, H=4.71%, Cl=6.90%, N=13.63%, O=9.34%

4-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydro-N-(4-methoxyphenyl)-6-methyl-2-thiopyrimidine-5-carboxamide , 2-B

A mixture of 3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (0.01mole), *N*-(4-methoxyphenyl)-3-oxobutanamide (0.01 mole), Thiourea (0.01 mole) and catalytic amount of Hydrochloric acid were placed in an flask and irradiated in a microwave oven 220 W for 12 min. After the completion of the mixture was cooled to room temperature and water was added with stirring when the solid product precipited out, which was filtered. The crude product was washed with water and recrystallised from alcohol or purified by column chromatography to give 72% yields.

M.P. 200-211 °C , IR-Aromatic 3037, C=O -1690, NH-1650-1550,-SH-2590-2550,-0CH_3-2830-2810 and 1460-1440,-CH_3-2882-2862 and 1470-1430,-Cl-600-800 cm^{-1}, ^{1}H NMR($CDCl_3$)δ 3.73 (S,3H,-0CH_3), 5.77 (d,1H,-CH),6.22 (d,1H,-NH), 8.18 (d,1H,- NH) 1.71(3H,-CH_3), 6.22-8.69 (14H,ArH)

MF- $C_{28}H_{24}$ N_5 ClO_2S

M.W.-530.04

C=65.97%, H=4.96%, Cl=6.71%, N=13.26%, O=9.09%

ACKNOWLEDGMENTS

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