ISSN 0975-6299 Vol 3/Issue 2/April – June 2012

International Journal of Pharma and Bio Sciences

RESEARCH ARTICLE MEDICINAL CHEMISTRY

SYNTHESIS AND BIOLOGICAL STUDIES OF 1, 2, 3, 4-TETRAHYDRO-6-METHYL- 2-OXOPYRIMIDINE-5-CARBOXAMIDE DERIVATIVE

PARTHIV KANTILAL CHAUDHARI

Shri R.R. Lalan College, Bhuj, Higher Education Department, Gujarat Government, Bhuj-Kutch, Gujarat, India

Corresponding author

ABSTRACT

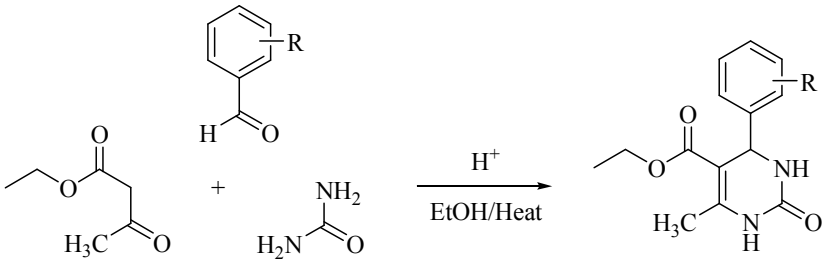
From various biomedical applications and pharmacological profile of pyrimidine derivative, the novel series of 1, 2, 3, 4-tetrahydro-6-methyl- 2-oxopyrimidine-5-carboxamide derivative (PK-101 to PK-110) are synthesized. The synthesis of these thirty compounds was achieved by the Biginelli reaction of acetoacetanilide, urea derivatives and corresponding aldehydes. The reaction is catalysed by concentrated hydrochloric acid (HCl). The products were characterized by various analytical techniques like FT-IR spectroscopy, mass spectrometry, ^{1}H NMR spectroscopy and elemental analysis. The newly synthesized compounds were subjected to various biological activities *viz*., antimicrobial, antimycobacterial.

KEYWORDS

Multicomponent reactions, Begineli reaction, Tetrahydro- 2-oxopyrimidine-5-carboxamide, Antimicrobial activity, Antimycobacterial activity, Antitubercular activity.

INTRODUCTION

Biginelli P. reported the synthesis of functionalized 3, 4-dihydropyrimidin-2(1*H*)-ones (DHPMs) via three-component condensation reaction of an aromatic aldehydes, urea and ethyl acetoacetate (Scheme 3.1). In the past decade, this multicomponent reaction experienced a remarkable revival, mainly due to the interesting pharmacological properties associated with this dihydropyrimidine scaffold.



Scheme 3.1

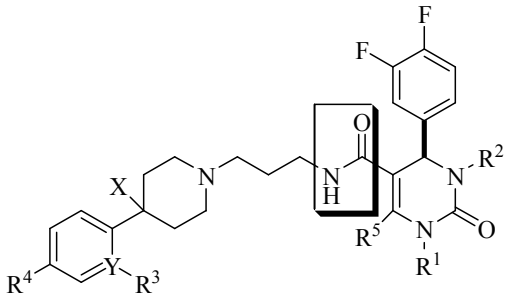
The classical three-component Biginelli condensation is usually carried out in alcoholic solution containing a few drops of concentrated hydrochloric or sulfuric acid as catalyst, although other systems such as tetrahydrofuran/hydrochloric acid (THF/HCl), dioxane/hydrochloric acid or acetic acid/hydrochloric acid were employed. Multicomponent reactions (MCRs) occupy an outstanding position in organic and medicinal chemistry for their high degree of atom economy, applications in combinatorial chemistry and diversity-oriented synthesis [1].

The venerable Biginelli reaction, one pot cyclocondensation of aldehyde, 1, 3-ketoester and urea or thiourea, is inarguably one of the most useful MCRs [2]. Polyfunctionalized dihydropyrimidines (DHPMs) represent a heterocyclic system of remarkable pharmacological activity.

4-Aryl-1, 4-dihydropyridines of the nifedipine type are the most studied class of organic calcium channel modulators and, since their introduction into clinical medicine in 1975 they have become almost indispensable for the treatment of cardiovascular diseases such as hypertension, cardiac arrhythmias or angina. In recent years, research interest has also been focused on aza-analogs such as dihydropyrimidines which shows similar pharmacological profile to this type of classical dihydropyridines calcium channel modulators [2].

PHARMACOLOGICAL PROFILE

Research interest in multifunctionalized DHPMs of privileged heterocyclic core is associated with several pharmacological properties. Small molecules targeting the mitotic machinery [3]. Notably, 4-aryldihydropyrimidinone heterocycles attached to an aminopropyl-4-piperidine moiety via a C5 amide linkage have proven to be excellent templates for selective α_{1a} receptor subtype antagonists to warrant further consideration for the treatment of Benign prostatic hyperplasia (BPH) [4]. In the synthesis of these DHPM-5-carboxamides, amide bond formation between the requisite amines and the corresponding DHPM acids was performed using standard solution phase amide coupling chemistry involving carbodiimide coupling reagents [4, 5].



Fragment based Approach

IMPROVED REACTION CONDITIONS

Previous reported protocols normally required prolonged reaction times and high temperature with moderate yields, so there has been a considerable interest to explore mild, rapid and higher yielding protocol. The toxicity and volatile nature of many organic solvents, particularly chlorinated hydrocarbons that are widely used in huge amounts for organic reactions have posed a serious threat to the environment. Thus, so many improved protocols have been designed for preparing these types of entities that have been developed to improve and modify this reaction by several catalysts.

Different catalysts have been employed for these types of reaction. They are

Ferric chloride (FeCl3)/tetraethyl orthosilicate [6], triflates [7,8] , metal bromide [9,10], polyoxometalate [11], strontium (II) nitrate [12], cerium (III) chloride [13], lithium trifluoromethanesulfonate or lithium triflate (LiOTf) [14], lanthanide triflates-Ln(OTf)3 [15], heteropolyacids [16-20], ion exchange resins, polymer based solid acid [21,22], L-proline [23,24], chiral phosphoric acid [25], trimethylsilyl chloride (TMSCl) [26], zirconium tetrachloride ZrCl4 [27], dowex [28], Boron trifluoride-etharate (BF3-etharate) [29], BF3-etharate/cuprous chloride (CuCl) [29], vanadium trichloride (VCl3) [30], lithium perchlorate (LiClO4) [31], stannous chloride (SnCl2.2H2O) [32a], AlCl3/KI [32b], CoCl2/MnCl2 [32c], AlCl3/AlBr3 [32d], P2O5 [33], Bismuth oxide perchlorate (BiOClO4.xH2O) [34], CaCl2 [35a], 1,3-Dibromo-5,4-dimethylhydantoin [35b], Zinc tetrafluoroborate [35c].

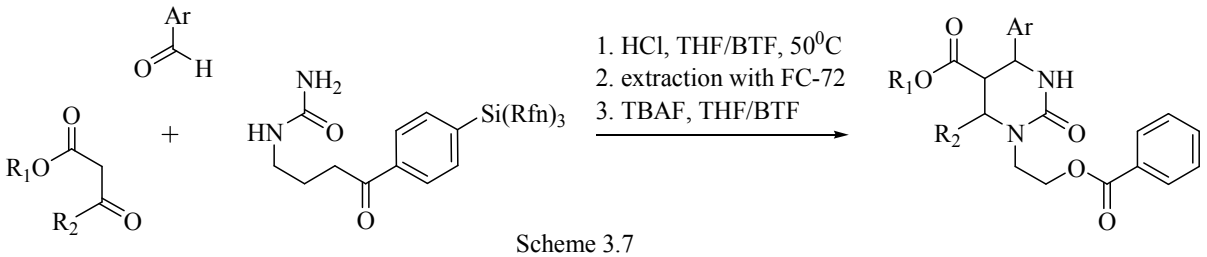
Numerous modifications on Lewis acid absorbed on mineral inorganic solid supports, silica, different clays are also reported and disclosed a simple modification of the Biginelli DHPM synthesis. Excellent yields enhanced reaction rates, compatibility with various functional groups, environmentally friendly procedure, time saving process, low cost and easy availability of the catalyst are some of the salient features of this reaction. This procedure will offer an easy access to substituted dihydropyrimidin-2(1H)-ones and thiones with different substitution patterns in high to excellent yields.

In an interesting variation of this protocol, the Biginelli reaction was also adapted to fluorous-phase conditions by the Wipf P. et al. [36,37]. In fluorous synthesis, an organic molecule was rendered soluble in fluorocarbon solvents by attachment to a suitable fluorocarbon group (“fluorous tag”). Fluorocarbon solvents are usually immiscible with organic solutions and fluorous molecules partition out of an organic phase and into a fluorous phase by standard liquid-liquid extraction.

At the desired stage of the synthesis, the fluorous label is cleaved and the product is rendered “organic” again [38]. In the fluorous Biginelli reaction, the fluorous urea derivative was prepared by attachment of a suitable fluorous tag to hydroxyethylurea. The fluorous urea was then condensed with 10 equivalents each of the corresponding acetoacetates and aldehydes in tetrahydrofuran (THF)-benzotrifluoride (BTF) containing hydrochloric acid (HCl). After extraction of the fluorous DHPMs with fluorous solvent (perfluorohexanes, fluorocarbon: FC-72),

desilylation with tetrabutylammonium fluoride (TBAF) followed by extractive purification provided the "organic" Biginelli products DHPMs in good overall yields.

Considering the simple experimental techniques used in this fluorous chemistry, automation should be feasible, thus allowing the preparation of DHPM libraries (Scheme 3.7) [38].



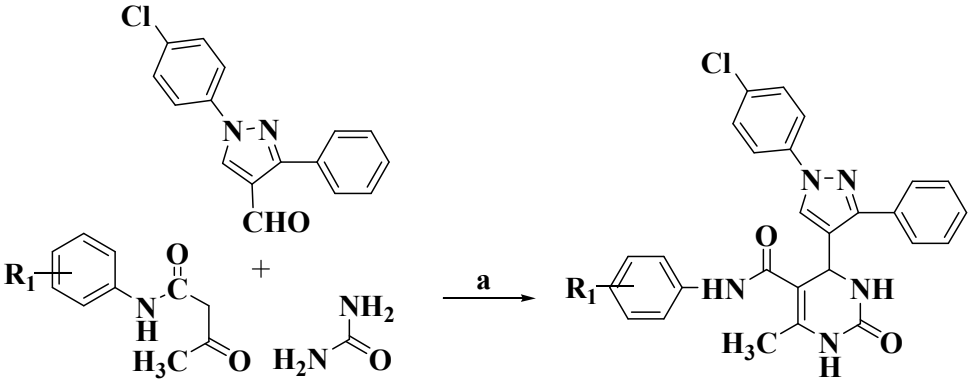
Scheme 3.7

CURRENT WORK

The chemistry of pyrimidines and its derivatives have been studied for over a century due to their diverse biological activities. The 1, 2, 3, 4-tetrahydropyrimidine ring system is of special biological interest because it has numerous pharmacological and medicinal applications *viz*, antitumor, antiviral, antimalarial, antitubarcular etc.

Keeping in mind various biomedical applications and with a view to further assessment, the pharmacological profile of these class of compounds, three novel series of 1,2,3,4-tetrahydropyrimidine (PK-101 to PK-110) are synthesized. The synthesis of these ten compounds was achieved by the Biginelli reaction of acetoacetanilide, urea derivatives and corresponding aldehydes. The reaction is catalysed by concentrated hydrochloric acid (HCl). The products were characterized by various analytical techniques like FT-IR spectroscopy, mass spectrometry, ^{1}H NMR spectroscopy and elemental analysis. The newly synthesized compounds were subjected to various biological activities *viz*., antimicrobial, antimycobacterial.

REACTION SCHEME:-



PK 101 TO 110

Reagents and conditions: (a) Conc. HCl, MeOH, Reflux, 20-22h.

Table-1

Code	R_1	M.F.	M.W.	M.P. ºC	Yield %	R_{f1}	R_{f2}
PK-101	H	$C_{27}H_{22}ClN_5O_2$	483	218-220	66	0.42	0.66
PK -102	4-OCH_3	$C_{28}H_{24}ClN_5O_3$	513	191-193	64	0.50	0.69
PK -103	4-F	$C_{27}H_{21}ClFN_5O_2$	501	226-228	63	0.49	0.73
PK -104	4-NO_2	$C_{27}H_{21}ClN_6O_4$	528	237-239	76	0.46	0.68
PK -105	4-Cl	$C_{27}H_{21}Cl_2N_5O_2$	517	220-226	80	0.54	0.75
PK -106	3-Cl	$C_{27}H_{21}Cl_2N_5O_2$	517	189-191	69	0.50	0.70
PK -107	3-NO_2	$C_{27}H_{21}ClN_6O_4$	528	210-212	65	0.53	0.72
PK -108	2-Cl	$C_{27}H_{21}Cl_2N_5O_2$	517	227-229	79	0.50	0.65
PK -109	2-NO_2	$C_{27}H_{21}ClN_6O_4$	528	240-242	58	0.55	0.67
PK -110	2-F	$C_{27}H_{21}ClFN_5O_2$	513	206-208	62	0.48	0.77

TLC Solvent system R_{f1}: Hexane: Ethyl acetate – 6:4,
TLC Solvent system R_{f2}: Chloroform: Methanol – 9:1.

EXPERIMENTAL
MATERIALS AND METHODS

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine. IR spectra were recorded Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. ^{1}H NMR was determined in DMSO-d_6 solution on a Bruker Ac 400 MHz spectrometer. Elemental analysis of the all the synthesized compounds was carried out on Elemental Vario EL III Carlo Erba 1108 model and the results are in agreements with the structures assigned.

General procedure for the synthesis of 4-(1-(4-chlorophenyl)-3-phenyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydro-N-(aryl)-6-methyl-2-oxopyrimidine-5-carboxamide (PK 101-110)

A mixture of *N*-(aryl)-3-oxobutanamides (0.01 mol), 1-(4-chlorophenyl)-3-phenyl-1H-pyrazole-4-carbaldehyde (0.01 mol), urea (0.015 mol) and catalytical amount of concentrated hydrochloric acid in ethanol (30 ml) was heated under reflux condition for 20 to 22 hrs. The reaction mixture was kept at room temperature for 24 hrs. The product obtained was isolated and recrystallized from ethanol.

4-(1-(4-chlorophenyl)-3-phenyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydro-N-(4-methoxyphenyl)-6-methyl-2-oxopyrimidine-5-carboxamide (PK-102)

Yield: 64%; mp 191-193 ºC;
IR (cm^{-1}): 3498 (N-H stretching of primary amide), 3230 (N-H stretching of pyrimidine ring), 3115 (C-H symmetrical stretching of CH_3 group), 2937 (C-H asymmetrical stretching of CH_3 group), 1712 (C=O stretching of amide), 1641 (N-H deformation of pyrimidine ring), 1525 and 1483 (C=C stretching of aromatic ring), 1435 (C-H asymmetrical deformation of CH_3 group), 1408 (C-N-C stretching of pyrimidine ring), 1340 (C-H symmetrical deformation of CH_3 group), 1276 (C-N stretching of pyrimidine ring), 1240 (C-O-C asymmetrical stretching of ether linkage), 1174 (C-H in plane deformation of aromatic ring), 1062 (C-O-C symmetrical stretching of ether linkage), 866 (C-H out of plane deformation of 1,4-disubstitution);

^{1}H NMR (DMSO-d_6) δ ppm: 2.17-2.18 (s, 3H, H_a), 3.73-3.79 (s, 3H, H_b), 5.77 (s, 1H, H_c), 6.22 (s, 1H, H_d), 6.76-7.74 (m, 13H, $H_{ee'-mm'}$), 8.18-8.19 (s, 1H, H_n), 8.26 (s, 1H, H_o), 8.69 (s, 1H, H_p); MS: *m/z* 513;
Anal. Calcd. For $C_{28}H_{24}ClN_5O_3$: C, 65.43; H, 4.71; N, 13.63. Found: C, 65.32; H, 4.63; N, 13.55%.

4-(1-(4-chlorophenyl)-3-phenyl-1H-pyrazol-4-yl)-N-(4-fluorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (PK-103)
Yield: 63%; mp 226-228 ºC
IR (cm^{-1}): 3290 (N-H stretching of primary amide), 3192 (N-H stretching of pyrimidine ring), 3099 (C-H symmetrical stretching of CH_3 group), 2874 (C-H asymmetrical stretching of CH_3 group), 1662 (C=O stretching of amide), 1589 (N-H deformation of pyrimidine ring), 1523 and 1471 (C=C stretching of aromatic ring), 1433 (C-H asymmetrical deformation of CH_3 group), 1338 (C-N-C stretching of pyrimidine ring), 1290 (C-H symmetrical deformation of CH_3 group), 1242 (C-N stretching of pyrimidine ring), 1031 (C-H in plane deformation of aromatic ring), 758 and 721 (C-H out of plane deformation of mono substituted benzene ring);
^{1}H NMR (DMSO-d_6) δ ppm: 2.35 (s, 3H, H_a), 5.80 (s, 1H, H_b), 6.65 (s, 1H, H_c), 7.28-7.73 (m, 13H, $H_{dd'-ll'}$), 7.86 (s, 1H, H_m), 7.96 (s, 1H, H_n), 8.66 (s, 1H, H_o); MS: *m/z* 501;
Anal. Calcd. For $C_{27}H_{21}ClFN_5O_2$: C, 64.61; H, 4.22; N, 13.95. Found: C, 64.52; H, 4.13; N, 13.84%.

4-(1-(4-chlorophenyl)-3-phenyl-1H-pyrazol-4-yl)-N-(4-fluorophenyl)-1, 2, 3, 4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (PK-106)
Yield: 69%; mp 189-191 ºC;
IR (cm^{-1}): 3363 (N-H stretching of primary amide), 3319 (N-H stretching of pyrimidine ring), 3099 (C-H symmetrical stretching of CH_3 group), 2966 (C-H asymmetrical stretching of CH_3 group), 1672 (C=O stretching of amide), 1566 (N-H deformation of pyrimidine ring), 1516 and 1481 (C=C stretching of aromatic ring), 1415 (C-H asymmetrical deformation of CH_3 group), 1388 (C-H symmetrical deformation of CH_3 group), 1340 (C-N-C stretching of pyrimidine ring), 1280 (C-N stretching of pyrimidine ring), 954 (C-H in plane deformation of aromatic ring), 804 (C-H out of plane deformation of 1,4-disubstitution);
^{1}H NMR (DMSO-d_6) δ ppm: 2.16-2.17 (s, 3H, H_a), 5.78 (s, 1H, H_b), 6.28 (s, 1H, H_c), 6.97-8.18 (m, 13H, H_{d-n}), 8.24 (s, 1H, H_o), 8.34 (s, 1H, H_p), 9.00 (s, 1H, H_q); MS: *m/z* 517;
Anal. Calcd. For $C_{27}H_{21}Cl_2N_5O_2$: C, 62.56; H, 4.08; N, 13.51. Found: C, 62.46; H, 3.97; N, 13.39%.

SPECTRAL DISCUSSION

MASS SPECTRAL STUDY

Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique.

IR SPECTRAL STUDY

IR spectra were recorded on Shimadzu FT-IR-8400 model using KBr pellet method. Various functional groups present in molecule were identified by characteristic frequency obtained for them. For compounds PK-101 to 110, confirmatory band for amidic linkage of acetoacetanilide fragment was found in the range of 3215-3530 cm^{-1} and pyrimidine nucleus (C-N-C stretching, C-N stretching) were found in the range of 1320-1410 cm^{-1} and 1260-1425 cm^{-1} respectively. Another characteristic carbonyl stretching band of pyrimidine was observed at 1662-1712 cm^{-1} suggesting formation of desired products PK-101 to 110.

^{1}H NMR SPECTRAL STUDY

^{1}H NMR spectra were recorded in DMSO-d_6 solution on a Bruker Ac 400 MHz spectrometer using TMS as an internal standard. Number of protons and their chemical shifts were found to support the structure of the synthesized compounds.
For PK-101 to 110, characteristic singlets were observed for methyl group of acetoacetanilide fragment at 2.16-2.44 δ ppm. Another characteristic methine proton peak was observed at 5.69-5.80 δ ppm which confirmed the cyclisation. For PK-101 to 110, singlets were observed at 6.18-6.65 δ ppm

corresponding to NH group of pyrimidine.. In addition, the aromatic ring protons were observed at 6.82-8.70 *δ* ppm. All these frequencies suggested formation of desired products PK-101 to 110.

BIOLOGICAL EVALUATION

ANTIMICROBIAL EVALUATION

All of the synthesized compounds (PK-101 to 110) were tested for their antibacterial and antifungal activity (MIC) in vitro by broth dilution method [39-41] with two Gram-positive bacteria Staphylococcus aureus MTCC-96, Streptococcus pyogenes MTCC 443, two Gram-negative bacteria Escherichia coli MTCC 442, Pseudomonas aeruginosa MTCC 441 and three fungal strains Candida albicans MTCC 227, Aspergillus Niger MTCC 282, Aspergillus clavatus MTCC 1323 taking gentamycin, ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin and greseofulvin as standard drugs. The standard strains were procured from the Microbial Type Culture Collection (MTCC), Institute of Microbial Technology, and Chandigarh, India.

The minimal inhibitory concentration (MIC) values for all the newly synthesized compounds, defined as the lowest concentration of the compound preventing the visible growth, were determined by using micro dilution broth method according to NCCLS standards [39].

Table-2

In vitro Antimicrobial Screening Results for PK-101 to 110

Code	Minimal inhibition concentration (μg mL^{-1})						
	Gram-positive		Gram-negative		Fungal species		
	S.a.	*S. p.*	*E.c.*	*P.a.*	*C. a.*	*A. n.*	*A.c.*
PK- 101	250	500	250	250	500	1000	1000
PK -102	500	500	200	200	1000	500	1000
PK -103	100	62.5	250	250	>1000	500	1000
PK -104	100	500	62.5	250	500	>1000	1000
PK -105	200	500	250	250	>1000	>1000	>1000
PK -106	200	250	200	100	500	1000	1000
PK -107	250	500	250	500	>1000	1000	1000
PK -108	250	250	100	250	500	1000	500
PK -109	200	200	100	100	500	>1000	1000
PK -110	250	500	62.5	200	>1000	500	>1000
Gentamycin	0.25	0.5	0.05	1	-	-	-
Ampicillin	250	100	100	100	-	-	-
Chloramphenicol	50	50	50	50	-	-	-
Iprofloxacin	50	50	25	25	-	-	-
Norfloxacin	10	10	10	10	-	-	-
Nystatin	-	-	-	-	100	100	100
Greseofulvin	-	-	-	-	500	100	100

ACKNOWLEDGEMENT

Author is thankful to Shri R.R. Lalan Gujarat Government College, Bhuj for providing laboratory facilities. To carry out this research work

REFERENCE

[1] (a) Ramo´n, D. J.; Yus, M. *Angew. Chem., Int. Ed.* 2005, *44*, 1602. (b) Ramachary, D. B.; Barbas, C. F., III. *Chem. Eur. J.* 2004, *10*, 5323. (c) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* 2003, *125*, 7825. (d) Andreana, P. R.; Liu, C. C.; Schreiber, S. L. *Org. Lett.* 2004, *6*, 4231. (e) Cozzi, P. G.; Rivalta, E. *Angew. Chem., Int. Ed*. 2005, *44*, 3600. (f)

[2] Janis, R. A.; Silver, P. J.; Triggle, D. J. *Adv.Drug.Res*. 1987, *16*, 309.

[3] (a) Mayer, T. U.; Kapoor, T. M.; Haggarty, S. J.; King, R. W.; Schreiber, S. L.; Mitchison, T. J. *Science* 1999, *286*, 971; (b) Haggarty, S. J.; Mayer, T. U.; Miyamoto, D. T.; Fathi, R.; King, R. W.; Mitchison, T. J.; Schreiber, S. L. Chem. Biol. 2000, *7*, 275; (c) Maliga, Z.; Kapoor, T. M.; Mitchison, T*. J. Chem. Biol.* 2002, *9*, 989.

[4] (a) Lagu, B.; Tian, D.; Chiu, G.; Nagarathnam, D.; Fang, J.; Shen, Q.; Forray, C.; Ransom, R.; Chang, R. S. L.; Vyas, K. P.; Zhang, K.; Gluchowski, C. *Bioorg. Med. Chem. Lett.* 2000, *10* (2) 175-178; (b) Barrow, J. C.; Nantermet, P. G.; Selnick, H. G.; Glass, K. L.; Rittle, K. E.; Gilbert, K. F.; Steele, T. G.; Homnick, C. F.; Freidinger, T. W.; Ransom, R. W.; Kling, P.; Reiss, D.; Broten, T. P.; Schorn, T. W.; Chang, R. S. L.; O'Malley, S. S.; Olah, T. V.; Ellis, J. D.; Barrish, A.; Kassahun, K.; Leppert, P.; Nagarathnam, D.; Forray, C. *J. Med. Chem*. 2000, *43*, 2703.

[5] Zhang, L.; Rana, T. M*. J. Comb. Chem*. 2004, *6*, 457.

[6] Cepanec, I.; Litvic, I.; Bartolincic, A.; Lovric, M. *Tetrahedron* 2005, *61*, 4275.

[7] Lu, J.; Bai, Y. *Synthesis* 2002, *47*, 466.

[8] Adapa, S. R.; Anan, M.M.; Varala, R. *Synlett* 2003, *67*.

[9] Hojatollah, S.; Guo, Q. *Synth. Commun*. 2004, *34*, 171.

[10] Martins, M. A. P., Teixeira, M. V. M., Cunico, W. Scapin, R. E., Mayer, Pereira, C.M.P., Zanatta, N., Bonacorso, H. G. C., Peppe, Y. F. Yuan, *Tetrahedron Lett.* 2004, *45*, 8991.

[11] Fazaeli, R. S., Tangestaninejad, H. Aliyan, M. Moghadam, *Appl. Catal. A: Gen.* 2006, *309*, 44.

[12] Liu, C.; Wang, J.; Li, Y. *J. Mol. Catal A: Chem.* 2006, *258*, 367.

[13] Bose, D. S.; Fatima, L.; Mereyala, H. B. *J. Org. Chem*. 2003, *68*, 587.

[14] Lusch, M. J.; Tallarico, J. A. *Org. Lett.* 2004, *6*, 3237.

[15] Huang Y. J., Yang F.Y., Zhu, C. J. *J. Am. Chem. Soc*. 2005, *127*, 16386.

[16] Rafiee, E.; Jafari, H. *Biol. Med. Chem. Lett*. 2006, *16*, 2463.

[17] Amini, M. M.; Shaabani, A.; Bazgir, A. *Catal. Commun*. 2006, *7*, 843.

[18] Maradur, P. S.; Gokavi, G. S. *Catal. Commun*. 2007, *8*, 279.

[19] Heravi, M. M.; Bakhtiari, K. Bamoharam, F. F. *Catal. Commun*. 2006, *7*, 373.

[20] Rafiee, E.; Shahbazi, F. *J. Mol. Catal. A: Chem*. 2006, *250*, 57.

[21] Joseph, J. K.; Jain, S. L.; Sain, B. *J. Mol. Catal. A: Chem.* 2006, *247*, 99.

[22] Palaniappan, S., John, A., *J. Mol. Catal. A: Chem*. 2005, *233*, 9.

[23] Gohain, M., Prajapati, D., Sandhu, J. S., *Synlett* 2004, *235*.

[24] Mabry, J.; Ganem, B. *Tetrahedron Lett.* 2006, *47*, 55.

[25] Chen, X. H.; Xu, X. Y.; Liu, H.; Cun, L. F.; Gong, L. Z. *J. Am. Chem. Soc*. 2006, *128*, 14802.

[26] Zhu, Y. L.; Huang, S. L.; Wan, J. P.; Yan, L.; Pan, Y. J.; Wu, A. *Org. Lett.* 2006, *8*, 2599.

[27] Reddy, C. V.; Mahesh, M.; Raju, P.V.K.; Babu, T.R.; Reddy, V. V. N. *Tetrahedron Lett.* 2002, *43*, 2657.

[28] Singh, K.; Arora, D.; Singh, S. *Tetrahedron.Lett.* 2006, *47*, 4205-4207.

[29] Hu, E. H.; Sidler, D. R.; Dolling, U. H. *J. Org. Chem*. 1998, *63*, 3454.

[30] Salitha, G.; Reddy, G. S. K.; Reddy, K. B.; J. S. Yadav, *Tetrahedron Lett.* 2003, *44*, 6497.

[31] Yadav, J. S.; Reddy, B. V. S.; Srinivas, R.; Venugopal, C.; Ramalingam, T. *Synthesis* 2001, 1341.
[32] (a) Kumar S., Saini A. & Sandhu J. S., *Indian J. Chem., 43*B, 1485 (2004). (b) *ibid, 44*B, 762 (2005). (c) *ibid, 45*B, 684 (2006). (d) *ibid*, *46*B, 1690 (2007).
[33] Deshmukh M. B., Anbhule V., Prashant S. D., Jadhev A. R., Mali S. S., Jagtap and Deshmukh A., *Indian J. Chem., 46*B, 1545 (2007).
[34] Reddy Y. T. and Reddy, P. N., *Indian J. Chem., 44*B, 1304 (2005).
[35] (a) Misra, A. K., Geetanjali A. & Madhusudan, *Indian J. Chem.,* 43B, 2018 (2004). (b) Alibek, M. A., Zaghaghi, Z., *Chemical papers 63* (1), 97 (2009). (c) Kundu, S. K., Majee A., & Hajra A. *Indian J. Chem., 48*B, 408 (2009).
[36] Wipf, P.; Cunnigham, A. *Tetrahedron Lett*. 1995, *36*, 7819-7822.
[37] Studer, A.; Hadida, S.; Ferritto, R.; Kim, S.; Jeger, P.; Wipf, P.; Curran, D. P. *Science* 1997, *275*, 823-826.
[38] Studer, A.; Jeger, P.; Wipf, P.; Curran, D. P. *J. Org. Chem*. 1997, 62, 2917-2924.
[39] National Committee for Clinical and Laboratory Standards, Method for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically Approved Standard, fourth ed. NCCLS, Villanova, Italy, 1997, Document M 100-S7. S100-S157.
[40] Isenberg, D. H. Essential Procedure for Clinical Microbiology, American Society for Microbiology, Washington, 1998.
[41] Zgoda, J. R.; Porter, J. R. *Pharm. Biol.* 2001, *39*, 221.