International Journal of Applied Chemistry.
ISSN 0973-1792 Volume 13, Number 1 (2017) pp. 135-144

http://www.ripublication.com

Synthesis a Number of Unimpeachable Pyrimidine Derivatives

Kaushik joshi and Haresh Ram

[1]DKV Arts & Science College, Jamnagar, Gujarat, India
[2]Tolani College of Arts & Science, Adipur (Kutch), Gujarat, India.

Abstract

An uncomplicated and efficient method for synthesis of 1,2,3,4-tetrahydropyrimidine derivatives was accomplished from N-(2,4-bis(trifluoromethyl)phenyl)-3-oxobutanamide, dissimilar aldehyde and urea using few drops of conc. HCl added and refluxed with ethanol with good yield and no auxiliary purification requirement for compound. The structures of the products were supported by FTIR, ^{1}HMR and mass spectral data and microbiological activity completed of all compounds.

Keywords: N-(2,4-bis(trifluoromethyl)phenyl)-3-oxobutanamide; HCl, urea only refluxed.

INTRODUCTION

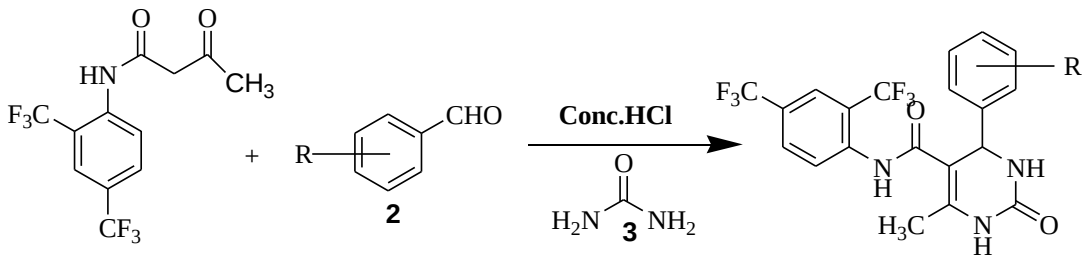
Recently, synthesis of tetrahydropyrimidine and their derivatives is of high interest in organic chemistry. The pyrimidine fragment is present in various biologically active compounds, many of which have been found use in medical practice1,2. Thus, recently, much attention has been paid to derivatives of pyrimidine, including their hydrogenation products.

Molecular docking of tetrhydropyrimidine derivatives have been studied by **Sun et al.[1].** Ghorai and co-workers have reported a convenient synthetic route to 2-aryl-

Ntosylazetidines and their ZnX_2 mediated regioselective nucleophilic ring opening reactions for the synthesis of tetrahydropyrimidine[2]. **Baltork and co-workers[3]** have synthesized chemo selective tetrahydropyrimidines using nano as reusable solid acid catalyst under microwave irradiation. Zhao et al. were synthesized fluoroalkylated multifunctional 1,2,3,4-tetrahydropyrimidines for the first time by the reaction of 3-fluoroalkyl-3-anilinoacrylic acid esters with primary amines and formaldehyde under mild conditions[4]. **Muravyova et al.** have carried out multicomponentreactions with ultrasonic activation used as key methods for the synthesis of tetrahydropyrimidine derivatives[5]. And few Fluoro Containing Pyrimidine Derivatives[6] synthesis 4-(2-chloro-6-fluorophenyl)-1,2,3,4-tetrahydro-6-iso-propyl-N-phenyl)-2-thithioxopyrimidine-5-carboxamide and this pyrimidine derivatives[7-11].

Literature survey shows that lots of work has been done for tetrahydropyrimidines. Many researchers have been synthesized tetrahydropyrimidines using different methods[12-14]. Recently, one-pot multicomponent reactions have emerged as a powerful tool in synthetic organic chemistry because of their significant advantages[15-18]. Polyethylene glycol -mediated facile one-pot synthesis of polysubstituted-tetrahydropyrimidines under mild and green reaction conditions have been developed by **Kidwai et al.[19].** Iodine catalyst one pot synthesis of tetrahydro pyrimidine derivatives have been reported by **Veerababurao et al.[20].**

We have developed a new modesty for the synthesis N-(2,4-bis(trifluoromethyl)phenyl)-4-(4-substitutedphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide ***(4a-h)*** with the advantage of fine yield and environmentally easiness (**Scheme-a**).



1 **2** **3** **(4a-h)**

Scheme a

METHOD

To the mixture of N-(2,4-bis(trifluoromethyl)phenyl)-3-oxobutanamide, Different Aromatic aldehyde and urea in ethanol was added few drops of Conc. HCl with stirring for 17 hrs.. After 24 hrs reaction mass pour in water, Insoluble solid was generated, it is pyrimidine derivatives. Then filter and crystallization by ethanol.

RESULTS & DISCUSSION

N-(2,4-bis(trifluoromethyl)phenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxamide (4a)

Yield: 65%; mp 175ºC; Anal. Calcd. for C20H15F6N3O2: C, 54.18; H, 3.41; F, 25.71; N, 9.48; O, 7.22; Found: C, 54.20; H, 3.40; F, 25.70; N, 9.50; O, 7.20%; IR (cm-1): 3238 (N-H stretching of amide), 3105 (C-H stretching of aromatic ring), 2974 (C-H asymmetrical stretching of CH3 group), 2887 (C-H symmetrical stretching of CH3 group), 1637 (C=O stretching of amide), 1573, 1556 (C=O stretching of cyclic) 1508 (N-H deformation of pyrimidine ring), 1454 (C-H asymmetrical deformation of CH3 group), 1394 (C-H symmetrical deformation of CH3 group), 1294 (C-N-C stretching vibration of pyrimidine ring), 1084 (C-F stretching), 827 (para-substituted), 734 (C-H in out plane deformation of aromatic ring); ^{1}H NMR (DMSO-d6) δ ppm: 2.02 (s, 3H, H), 5.53 (s, 1H, H), 6.96-6.99 (d, 1H, H), 7.10-7.17 (dd', 2H, H), 7.26-7.28 (dd', 2H, H), 7.49-7.54 (m, 1H, H), 7.67 (s, 1H, H), 8.20-8.23 (d, 1H, H), 8.83 (s, 1H, H), 8.86 (s, 1H, H), 9.70 (s, 1H, H), MS: m/z 443.

N-(2,4-bis(trifluoromethyl)phenyl)-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxo pyrimidine-5-carboxamide (4b)

Yield: 60%; mp 179ºC; Anal. Calcd. for $C_{20}H_{14}ClF_6N_3O_2$: C, 50.28; H, 2.95; Cl, 7.42; F, 23.86; N, 8.79; O, 6.70; Found: C, 50.33; H, 2.90; Cl, 7.48; F, 23.80; N, 8.74; O, 6.75%; IR (cm^{-1}): 3266 (N-H stretching of amide), 3173 (C-H stretching of aromatic ring), 2966 (C-H asymmetrical stretching of CH_3 group), 2883 (C-H symmetrical stretching of CH_3 group), 1633(C=O stretching of amide), 1573 (C=O stretching of cyclic) 1550 (N-H deformation of pyrimidine ring), 1500 (C-H asymmetrical deformation of CH_3 group), 1450 (C-H symmetrical deformation of CH_3 group), 1297 (C-N-C stretching vibration of pyrimidine ring), 1087 (C-F stretching), 827 (para-substituted), MS: *m/z* 478.

N-(2,4-bis(trifluoromethyl)phenyl)-4-(3-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxo pyrimidine-5-carboxamide (4c)

Yield: 68%; mp 187ºC; Anal. Calcd. for $C_{20}H_{14}ClF_6N_3O_2$: C, 50.28; H, 2.95; Cl, 7.42; F, 23.86; N, 8.79; O, 6.70; Found: C, 50.34; H, 2.97; Cl, 7.40; F, 23.87; N, 8.70; O, 6.72%; IR (cm^{-1}): 3386 (N-H stretching of amide), 3163 (C-H stretching of aromatic ring), 2983 (C-H asymmetrical stretching of CH_3 group), 2877 (C-H symmetrical stretching of CH_3 group), 1637 (C=O stretching of amide), 1541(C=O stretching of cyclic) 1501 (N-H deformation of pyrimidine ring), 1497 (C-H asymmetrical deformation of CH_3 group), 1451 (C-H symmetrical deformation of CH_3 group), 1297

(C-N-C stretching vibration of pyrimidine ring), 1080 (C-F stretching), 824 (para-substituted); MS: *m/z* 478.

N-(2,4-bis(trifluoromethyl)phenyl)-4-(2-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxo pyrimidine-5-carboxamide (4d)

Yield: 64%; mp 184ºC; Anal. Calcd. for $C_{20}H_{14}ClF_6N_3O_2$: C, 50.28; H, 2.95; Cl, 7.42; F, 23.86; N, 8.79; O, 6.70; Found: C, 50.36; H, 2.95; Cl, 7.42; F, 23.80; N, 8.75; O, 6.70%; IR (cm^{-1}): 3376 (N-H stretching of amide), 3167 (C-H stretching of aromatic ring), 2983 (C-H asymmetrical stretching of CH_3 group), 2873 (C-H symmetrical stretching of CH_3 group), 1677 (C=O stretching of amide), 1547 (C=O stretching of cyclic) 1503 (N-H deformation of pyrimidine ring), 1497 (C-H asymmetrical deformation of CH_3 group), 1457 (C-H symmetrical deformation of CH_3 group), 1293 (C-N-C stretching vibration of pyrimidine ring), 1100 (C-F stretching), 869 (C-Cl stretching), 837 (para-substituted); MS: *m/z* 478.

N-(2,4-bis(trifluoromethyl)phenyl)-4-(4-fluorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxo pyrimidine-5-carboxamide (4e)

Yield: 59%; mp 181ºC; Anal. Calcd. for $C_{20}H_{14}F_7N_3O_2$: C, 50.28; H, 2.95; Cl, 7.42; F, 23.86; N, 8.79; O, 6.70; Found: C, 50.36; H, 2.97; Cl, 7.40; F, 23.82; N, 8.70; O, 6.77%; IR (cm^{-1}): 3356 (N-H stretching of amide), 3165 (C-H stretching of aromatic ring), 2985 (C-H asymmetrical stretching of CH_3 group), 2872 (C-H symmetrical stretching of CH_3 group), 1677 (C=O stretching of amide), 1542 (C=O stretching of cyclic) 1505 (N-H deformation of pyrimidine ring), 1490 (C-H asymmetrical deformation of CH_3 group), 1457 (C-H symmetrical deformation of CH_3 group), 1290 (C-N-C stretching vibration of pyrimidine ring), 1083 (C-F stretching), 837 (para-substituted); MS: *m/z* 478.

N-(2,4-bis(trifluoromethyl)phenyl)-4-(3-fluorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxo pyrimidine-5-carboxamide (f)

Yield: 68%; mp 188ºC; Anal. Calcd. for $C_{20}H_{14}F_7N_3O_2$: C, 50.28; H, 2.95; Cl, 7.42; F, 23.86; N, 8.79; O, 6.70; Found: C, 50.43; H, 2.90; Cl, 7.42; F, 23.80; N, 8.73; O, 6.74%; IR (cm^{-1}): 3374 (N-H stretching of amide), 3145 (C-H stretching of aromatic ring), 2984 (C-H asymmetrical stretching of CH_3 group), 2874 (C-H symmetrical stretching of CH_3 group), 1647 (C=O stretching of amide), 1544 (C=O stretching of cyclic) 1500 (N-H deformation of pyrimidine ring), 1474 (C-H asymmetrical deformation of CH_3 group), 1454 (C-H symmetrical deformation of CH_3 group), 1284 (C-N-C stretching vibration of pyrimidine ring), 1074 (C-F stretching), 834 (para-substituted); MS: *m/z* 461.

N-(2,4-bis(trifluoromethyl)phenyl)-4-(2-fluorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxo pyrimidine-5-carboxamide (4g)

Yield: 57%; mp 170ºC; Anal. Calcd. for $C_{20}H_{14}F_7N_3O_2$: C, 50.28; H, 2.95; Cl, 7.42; F, 23.86; N, 8.79; O, 6.70; Found: C, 50.44; H, 2.91; Cl, 7.43; F, 23.85; N, 8.75; O, 6.66%; IR (cm^{-1}): 3366 (N-H stretching of amide), 3166 (C-H stretching of aromatic ring), 2988 (C-H asymmetrical stretching of CH_3 group), 2874 (C-H symmetrical stretching of CH_3 group), 1647 (C=O stretching of amide), 1544 (C=O stretching of cyclic) 1508 (N-H deformation of pyrimidine ring), 1474 (C-H asymmetrical deformation of CH_3 group), 1458 (C-H symmetrical deformation of CH_3 group), 1286 (C-N-C stretching vibration of pyrimidine ring), 1088 (C-F stretching), 837 (para-substituted); MS: *m/z* 461.

N-(2,4-bis(trifluoromethyl)phenyl)-4-(4-methoxyphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine -5-carboxamide *(4h)*

Yield: 59%; mp 178ºC; Anal. Calcd. for $C_{21}H_{17}F_6N_3O_3$: C, 50.28; H, 2.95; Cl, 7.42; F, 23.86; N, 8.79; O, 6.70; Found: C, 50.45; H, 2.90; Cl, 7.49; F, 23.91; N, 8.70; O, 6.60%; IR (cm^{-1}): 3363 (N-H stretching of amide), 3154 (C-H stretching of aromatic ring), 2966 (C-H asymmetrical stretching of CH_3 group), 2874 (C-H symmetrical stretching of CH_3 group), 1666 (C=O stretching of amide), 1534 (C=O stretching of cyclic) 1557 (N-H deformation of pyrimidine ring), 1513 (C=C stretching of aromatic ring), 1475 (C-H asymmetrical deformation of CH_3 group), 1406 (C-H symmetrical deformation of CH_3 group), 1344 (C-NO2 symmetrical deformation of NO2 group), 1311 (C-N-C stretching vibration of pyrimidine ring), 1241 (C-N stretching), 1153 (C-F stretching), 831 (para-substituted), 760 (C-H in out plane deformation of aromatic ring); MS: *m/z* 473.

Antimicrobial evaluation

Total of the Prepared compounds **(4a-h)** were experienced for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method [17-19] 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 regular drugs.

The minimal inhibitory concentration (MIC) values for all the newly synthesized compounds, definited as the lowly concentration of the compound preventing the

observable growth, were determined by using micro dilution broth method according to NCCLS standards [30].

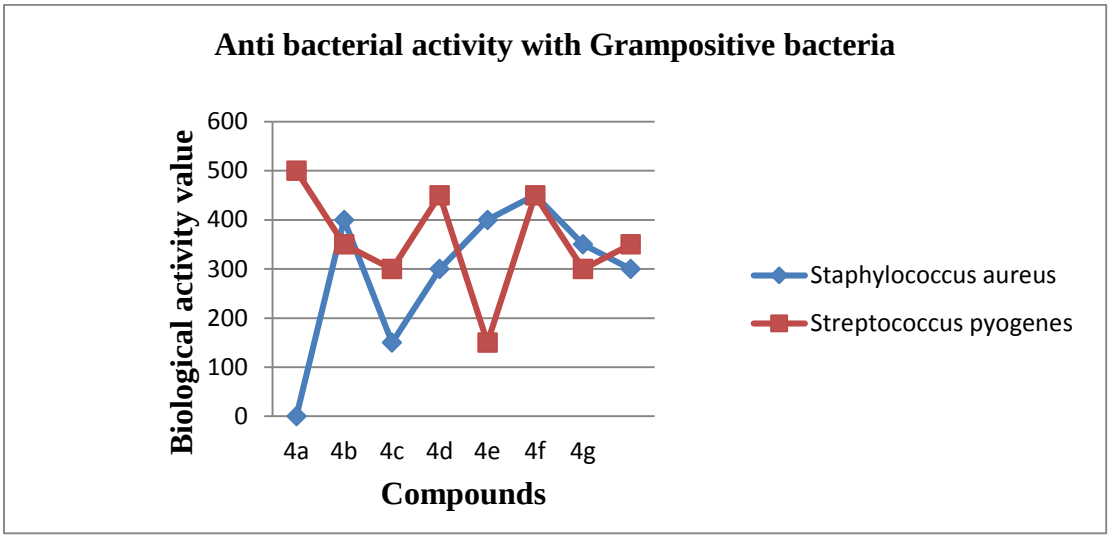
Minimal Inhibition Concentration [MIC]:-

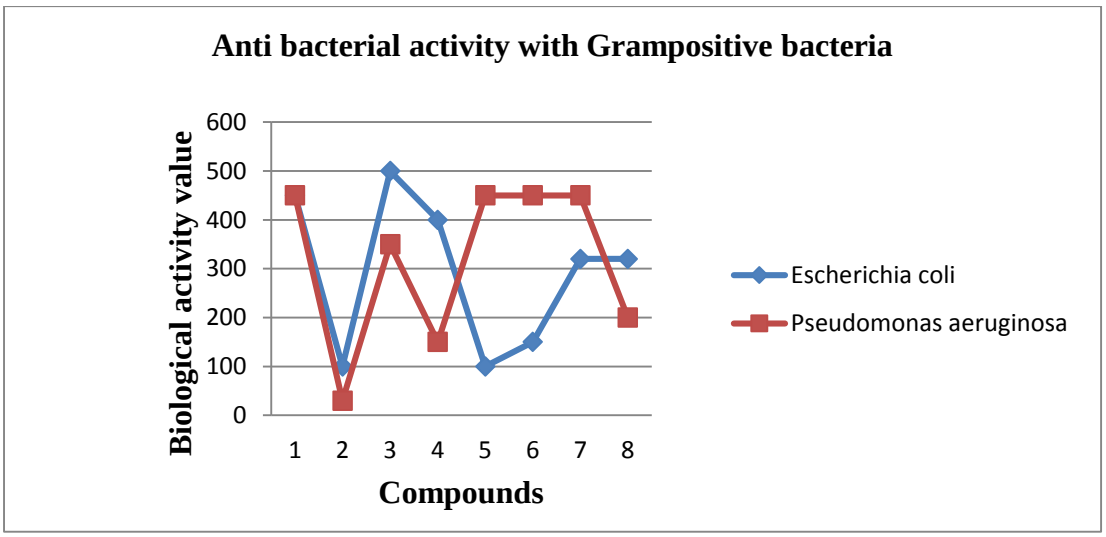
The main advantage of the 'Broth Dilution Method' for MIC determination lies in the fact that it can readily be converted to determine the MIC as well.

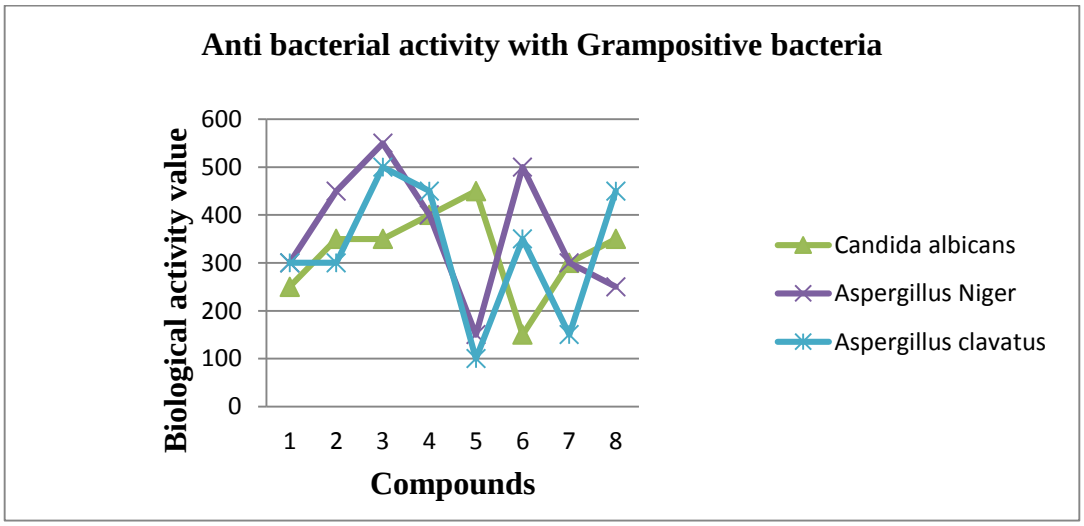
- Serial dilutions were prepared in primary and minor screening.
- The control tube containing no antibiotic is immediately subcultured by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37 ^{0}C overnight.
- The MIC of the control organism is read to check the accuracy of the drug concentrations.
- The lowest concentration inhibiting growth of the organism is recorded as the MIC.
- The amount of growth from the control tube before incubation (which represents the original inoculums) is compared.

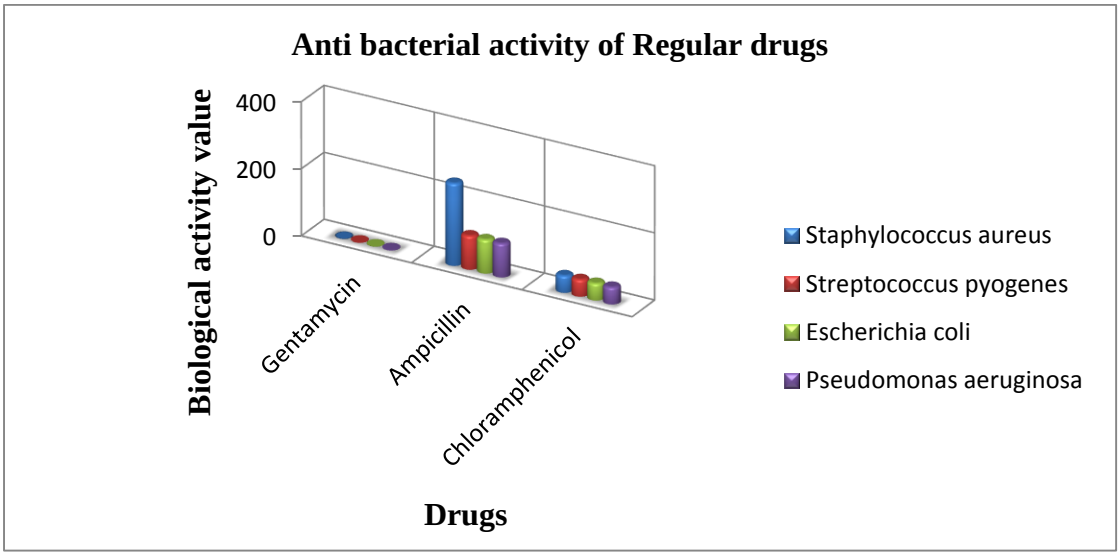
In vitro Antimicrobial Screening Results for (4a-h)

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.***
4a	500	500	450	450	250	300	300
4b	400	350	100	30	350	450	300
4c	150	300	500	350	350	550	500
4d	300	450	400	150	400	400	450
4e	400	150	100	450	450	150	100
4f	450	450	150	450	150	500	350
4g	350	300	320	450	300	300	150
4h	300	350	320	2000	350	250	450
Gentamycin	0.25	0.5	0.05	1	-	-	-
Ampicillin	245	100	100	100	-	-	-
Chloramphenicol	50	50	50	50	-	-	-


Anti bacterial activity with Grampositive bacteria
Biological activity value
600
500
400
300
200
100
0
4a 4b 4c 4d 4e 4f 4g
Compounds
Staphylococcus aureus
Streptococcus pyogenes


Anti bacterial activity with Grampositive bacteria
Biological activity value
600
500
400
300
200
100
0
1 2 3 4 5 6 7 8
Compounds
Escherichia coli
Pseudomonas aeruginosa


Anti bacterial activity with Grampositive bacteria
Biological activity value
600
500
400
300
200
100
0
1 2 3 4 5 6 7 8
Compounds
Candida albicans
Aspergillus Niger
Aspergillus clavatus



CONCLUSION

In height, we include synthesized of novel 1,2,3,4-tetrahydropyrimidine derivatives using easy and proper method. This method produces these products in unparalleled yields and difficulty-free workup. Product is isolated by unproblematic filtration. The isolated products are very pure and do not need any column purification. This study opens up a new area of useful synthesis of potentially biologically active novel pyrimidine derivatives compounds.

ACKNOWLEDGEMENT

Authors are thankful to the department of chemistry, SHREE D. K. V. ARTS & SCIENCE COLLEGE, JAMNAGAR, India for providing laboratory facilities. One of us Dr Kaushik A. Joshi is thankful to UNIVERSITY GRANTS COMMISSION, BAHADUR SHAH ZAFAR MARG, NEW DELHI for providing a research project [(**47-654/13(WRO)** dated **12 MAR 2015**].

REFERENCES

[1] Sun, C; Yang, D; Xing, J; Wang, H; Jin, J. and Zhu, J; "Nitromethylene neonicotinoids analogues with tetrahydropyrimidine fixed cis-configuration: synthesis, insecticidal activities, and molecular docking studies" J. Agri. Food Chem. 2010, 58, 3415–3421. 23.

[2] Ghorai, M. K.; Das, K. and Kumar, A.; "An efficient synthetic route to substituted tetrahydropyrimidines by Cu(OTf)2-mediated nucleophilic ring-

opening followed by the [4+2] cycloaddition of N-tosylazetidines with nitriles" Tet. Lett. 2009, 50(10), 1105-1109.

[3] Baltork, M.; Moghadam, M.; Tangestaninejad, S.; Mirkhani, V.; Eskandari, Z. and Salavati, H. "Chemoselective synthesis of 2-aryloxazines and 2-aryltetrahydropyrimidines using nano-SiO2 as a reusable solid acid catalyst under thermal conditions and microwave irradiation" J. Iran. chem. soc. 2011, (8), 17- 27. 25.

[4] Zhao, F. L. and Jin-Tao, L.; "A novel and efficient synthesis of fluoroalkylated multifunctional 1,2,3,4-tetrahydropyrimidines." J. Fluor. Chem. 2004, 125(12), 1841-1845.

[5] Muravyova, E. A.; Desenko, S. M.; Musatov, V. I.; Knyazeva, I. V.; Shishkina, S. V.; Shishkin, O. V. and Chebanov, V. A.; "Ultrasonic-Promoted ThreeComponent Synthesis of Some Biologically Active 1,2,5,6-Tetrahydropyrimidines." J. Comb.Chem. 2007, 9(5), 797-803.

[6] Patel KN, Joshi KA, Ram HK, International Journal for Pharmaceutical Research Scholars (IJPRS), 2015; V-4; 210-214.

[7] Vora JH, Joshi KA, Ram HK, International Journal for Pharmaceutical Research Scholars (IJPRS), 2015; V-4; 163-167.

[8] Vora JH, Joshi KA, Ram HK, "A New Maneuver Etiquette For Synthesis of Tetrahydropyrimidine Derivatives" European Journal of Biomedical and Pharmaceutical sciences, 2(2), 155-162, 2015.

[9] Joshi KA, Ram HK one-pot microwave irradiation synthesis of 1,2,4-Triazolo [1,5-a] pyrimidinesActaChim. Pharm. Indica: 2(2), 101-105, 2012.

[10] Joshi KA, Ram HK and Nimavat K, A one-pot microwave irradiation synthesis of 1,2,4-triazolo[1,5-a]pyrimidinesJournal of Chemical and Pharmaceutical Research, 4(4):2133-2137, 2012.

[11] Joshi KA, and Nimavat K,, Synthesis, Characterization And Biological Screening Of novel N-(2-chloro-4-(trifluoromethyl) phenyl)-4-(substitutedphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5 carboxamide,Journal of Chemical and Pharmaceutical Research, 4(2), 1106-1110, 2012.

[12] Singh, P.; Negi, J. S.; Pant, G. J.; Rawat, M. S. M. and Budakoti, A.; "Synthesis and Characterization of a Novel 2-Pyrazoline" Molbank 2009, M614.

[13] Corradi, A.; Leonelli, C.; Rizzuti, A.; Rosa, R.; Veronesi, P.; Grandi, R.; Baldassari, S.and Villa, C.; "New Green Approaches to the Synthesis of Pyrazole Derivatives" Molecules 2007, 12(7), 1482-1495

[14] Seitaro, K.; "Preparation, optical resolution, and formulation of 1-(3-pyridylcarbonyl)-5-methyl-2-pyrazoline as cerebrovascular protective agent" Eur. Pat. Appl., 373512.

[15] Suzuki, Y.; Naoe, S.; Oishi, S.; Fujii, N. and Ohno H.; "Gold-Catalyzed ThreeComponent Annulation: Efficient Synthesis of Highly Functionalized Dihydropyrazoles from Alkynes, Hydrazines, and Aldehydes or Ketones" Org. Lett. 2012, 14 (1), 326–329.

[16] De, L.; Giacomelli, G.; Porcheddu, A.; Salaris, M. and Taddei, M.; "Cellulose Beads: a New Versatile Solid Support for Microwave- Assisted Synthesis. Preparation of Pyrazole and Isoxazole Libraries" J. Comb. Chem. 2003, 5(4), 465- 471.

[17] Morelli, C.; Saladino, A.; Speranza, G. and Manitto, P.; "Expeditious Solid-Phase Synthesis of Pyrazoledicarboxylic Acid Derivatives by Functionalization of Resin-Bound Cyanoformate" Eur. J. Org. Chem. 2005, (21), 4621-4627.

[18] Ren, X.; Li, H.; Wu, C. and Yang, H.; "Synthesis of a small library containing substituted pyrazoles" ARKIVOC 2005, XV, 59-67.

[19] Ahn, J.; Kim, H.; Jung, S.; Kang, S.; Kim, K.; Rhee, S.; Yong, D.; Cheon, H. and Kim, S.; " Synthesis and DP-IV inhibition of cyanopyrazoline derivatives as potent anti diabetic agents" Bio. Med. Chem. Lett. 2004, 14, 4461–4465.

[20] Koval, I.; Schuitema, A.; Driessen W. and Reedijk, J.; "Unprecedented copper (II)-assisted acetal formation of a formyl substituted bis pyrazole. The X-ray structures of copper [1, 2-bis-(3_-dimethoxymethylpyrazol-1_-yl) ethane] dichloride and dibromide "J. Chem. Soc. Dal. Transa. 2001, 3663–3667.

[21] 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.

[22] D.H. Isenberg, Essential Procedure for Clinical Microbiology, American Society forMicrobiology, Washington, 1998.

[23] Zgoda JR, Porter JR. A convenient microdilution method for screening natural productsagainst bacteria and fungi. *Pharm Biol*., 2001; 39: 221-225.