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Microwave Initiated Synthesis of Pyrimidine Analogues and Study of their Antimicrobial Properties

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ABSTRACT

An efficient and convenient multi component reaction for the synthesis of 2-Imino-4,6-diaryldihydropyrimidines scaffolds have been accomplished from chalcones and guanidine hydrochloride in the presence of a catalytic amount of an alkali under solvent-free conditions using microwave irradiation. The synthesized pyrimidines have been characterized on the basis of their chemical properties and spectroscopic data. Operational simplicity, short reaction times, excellent yields and environmentally-benign conditions are the other advantages of this protocol. Using this method, we have synthesized some new pyrimidines with antimicrobial properties and high chemical yields in much short reaction times.

Keywords: Solvent- free, Antibacterial, Chalcones, Biological activity, Green Chemistry

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INTRODUCTION

Microwave assisted synthesis has been used as an alternative to accelerate the endothermic organic reactions since 1980. It is a major breakthrough in the methodology of synthetic organic chemistry. It has paved in an easy and convenient way in the organic synthesis and has been widely perceived in the scientific community. Conventional heating, long known to be inefficient and time-consuming, has been recognized to be creatively limiting as well. In this context, the microwave based synthesis can be effectively applied to most of the reaction, enabling faster reaction, improving yield, & cleaner chemistry. In addition, microwave synthesis creates completely new possibilities in performing chemical transformations. Microwave can transfer energy directly to the reactive species, so-called "molecular heating", they can promote transformation that are currently not possible using conventional heating. This is creating a new realm in the field of heterocyclic synthesis.

Heterocyclic molecules are of biological interest due to their potential physical and chemical properties[1] among these the pyrimidine moieties occupy a unique importance in pharmaceutical chemistry, as they are components of nucleic acids. Chalcones, Pyrimidine and its derivatives are known for their varied biological activities like antibacterial and antifungal[2,3]. Brugnatelli isolated "Alloxan", a pyrimidine derivative in 1818, and later this compound was found to possess antineoplastic properties[4]. Synthesis of pyrimidines from chalcones is one of the common route for the synthesis of pyrimidine moiety. Chalcones represent an essential group of natural as well as synthetic products and some of them possess wide range of pharmacological activity[5-20].

Available data suggest that heterocyclic compounds particularly five or six member ring compounds have occupied the first place among various classes of organic compounds for their diverse biological activities. These compounds possess one or the other chemotherapeutic or pharmacological activities and in the heterocyclic compounds, nitrogen containing heterocyclic compounds like pyrimidines possesses wide variety of activities[21].

Pyrimidine derivatives have played an important role in the medicinal chemistry. They are reported to possess a broad spectrum of biological activities such as antibacterial[22-24], anti-inflammatory[25-27]. Some of the other activities which are associated with these compounds are analgesic[28], anticancer[29], antiviral, antimalarial[30] and anti-tubercular activity[31-33]. The biological significance of the pyrimidines derivatives and its emergence as resistant to bacterial strains towards the existing antibacterial agents is one of the major reasons for the search and development of new molecules. Not many drugs with pyrimidines nucleus are available in current

antibacterial chemotherapy. In accordance with the availability of the earlier drugs having pyrimidine nucleus like trimethoprim and pyrimethamine for the chemotherapy of bacterial diseases, the present work is an approach to synthesize the molecules having pyrimidine nucleus with more potency and to investigate for their biological activities.

In this communication, we have reported the synthesis of said compounds by using microwave irradiation under solvent-free condition using chalcones, guanidine hydrochloride in the catalytic amount of alkali. The use of combinatorial approaches toward the synthesis of drug-like scaffolds is a powerful tool in helping to speed up drug discovery

MATERIALS AND METHOD

All the reagents used were of Merck and S.D. Fine make and were used as such. Melting points of the compounds were taken by open capillary method. Reactions were monitored by TLC on silica gel plates with eluent systems: 8:2(pet ether: ethyl acetate) and were purified by recrystallization using aqueous dioxane. The microwave reactions were performed in the CEM Focused Microwave™ Synthesis System. Infrared(IR) spectra were obtained from KBr disk using Shimadzu FT-IR-8400s spectrometer, Mass spectra were obtained on Accu TOF Mass Spectrometer (DART) and ^{1}H and ^{13}C NMR spectra were recorded on 400 and 100 MHz AVANCE II (Bruker) using DMSO-d6 using TMS as internal standard. Chemical shifts are reported in ppm.

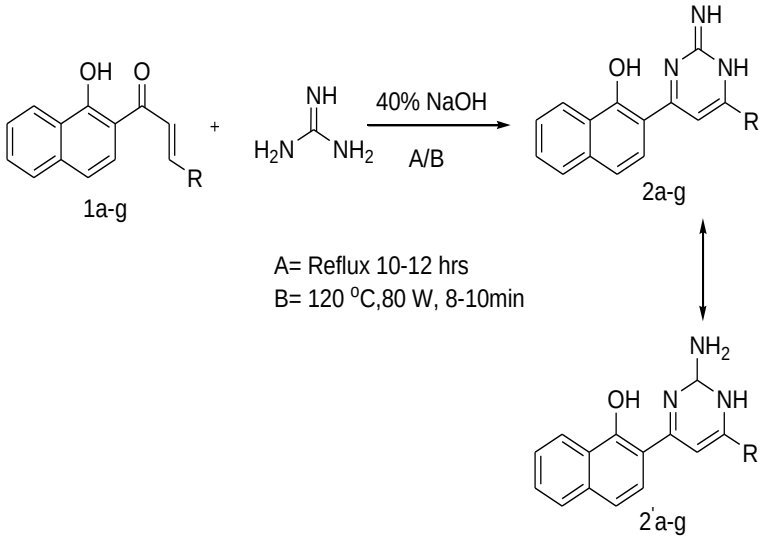
General Procedure for the preparation of dihydropyrimidines

Procedure A (under refluxing condition):

A mixture of Chalcone (1a-f) (10mmol), guanidine hydrochloride (10mmol) and 40%Sodium hydroxide (3ml) in 1, 4-dioxane (30ml) was refluxed for 18-20hr. After the completion of reaction (followed by TLC), reaction mixture was poured into cold water, filtered, washed, dried and recrystallized using aqueous dioxane.

Procedure B (under microwave-assisted solvent-free conditions):

Substituted Chalcone 1 (10mmol), guanidine hydrochloride (10mmol) and sodium hydroxide (40mmol) were mixed together. The mixture was taken in conical flask and mixture was irradiated under microwave oven for the 8-10 min. Reaction was monitored by TLC and after completion of reaction, the reaction mixture was cooled to room temperature and then poured into cold water and the formed precipitate was filtered and washed with dil. HCl to get the titled compounds 2, which were recrystallized from aqueous dioxane.



Scheme 1 General method for the synthesis of dihydropyrimidine

RESULTS AND DISCUSSION

In the present work a series of substituted 2-(2-imino -2, 3-dihydropyrimidin-4-yl) naphthalen-1-ol have been prepared by chalcones using microwave irradiation and conventional method. The synthetic strategy adopted follows the given sequence: Chalcones, guanidine hydrochloride and a small quantity of 40% NaOH were blended together and the mixture was put into a conical flask. The reactants were heated to 120˚C at 80W for 8-10 min in scientific microwave oven. The structures of synthesized compounds were confirmed on the basis of physico-chemical analysis and the data has been incorporated in **Table 1**.

Table 1. **Showing physico-chemical properties of synthesized compounds**

Comp.	R	Mol.wt	M.p,˚C	Elemental Analysis Calculated (Observed)				Reaction Time	
				C	H	N	O	Conventional (hrs)	MWI (min)
2a	C_6H_5-p-OCH_3	343.37	168	73.45 (72.29)	4.99 (4.75)	12.24 (12.10)	9.32 (9.30)	20	10
2b	C_6H_5 -m-NO_2	358.3	174	67.03 (65.98)	3.94 (2.75)	15.63 (15.39)	13.39 (13.11)	18	8
2c	C_6H_5-p-Cl	347.37	122	69.07 (67.95)	4.06 (4.10)	12.08 (11.50)	4.60 (4.21)	19	8
2d	C_6H_5-o-Cl	347.37	128	69.07 (68.05)	4.06 (3.80)	12.08 (11.98)	4.60 (4.57)	20	7
2e	C_8H_7	339.38	130	77.86 (77.73)	5.05 (4.87)	12.38 (12.27)	4.71 (3.88)	18	8
2f	$C_{11}H_7$	363.4	142	79.32 (79.25)	4.72 (3.85)	11.56 (11.29)	4.40 (4.29)	18	9
2g	$C_8H_{10}N$	356.42	>300	74.14 (73.25)	5.66 (5.52)	15.72 (15.35)	4.49 (4.25)	19	8

The use of microwave provides high accessibility in case of time and yield. The less time for completion of the reactions and high yield of the products found to be very convenient through microwave irradiation which is discussed in Figure 2. As shown in Figure the corresponding products were obtained with 88-98% yields. Different kinds of substituted aromatic aldehydes, bearing either electron-releasing or electron-withdrawing substituent were all carried out smoothly in the reactions. The reaction time was very short, and the yield of product was quite high.

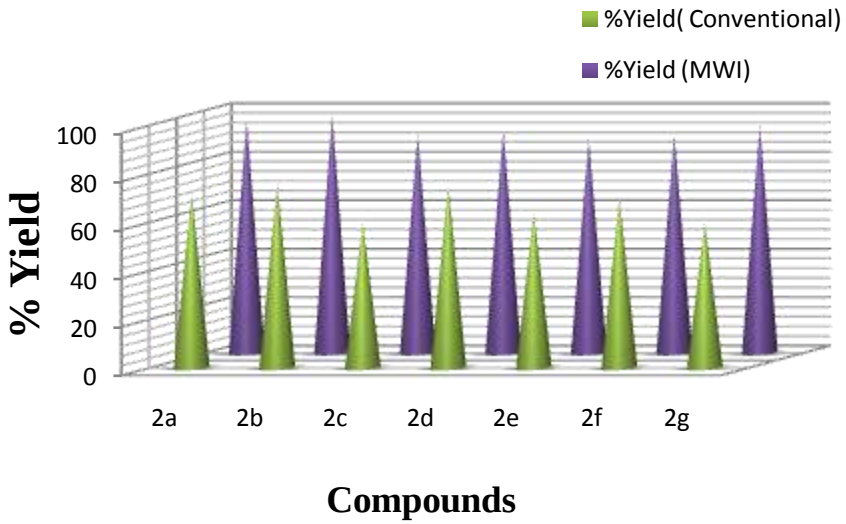


Figure. 1 Comparative study of the yield obtained in Conventional and Microwave methods

Spectral Study

2-(2-imino-6-(4-methoxyphenyl)-2, 3-dihydropyrimidin-4-yl) naphthalen-1-ol (**2a,** $C_{21}H_{17}N_3O_2$) Brown solid, M.p.: 168 ^oC; ^1H NMR (400 MHz, DMSO): δ = 15.7(1H,s,OH), 3.09(3H,s,OCH_3), 7.32-8.37(10H,m,Ar), 6.98(1H,s,NH), 6.94(1H,s,C=NH), 3.40(1H, s, CH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 55.0(CH_3), 100.8(CH), 110(CH), 113.6(CH), 117.4(C), 121.7(CH), 123.5(CH), 123.38(CH), 124.95(C), 125.6(C), 125.7(C), 126(CH), 126.9(CH), 127.7(CH), 128.5(CH), 129.4(CH), 135.1(C), 158.5(C), 163(C), 164.6(C), 164.9(C) ppm; IR (KBr); $\bar{\nu}$ = 3057, 1643, 1577, 1028 cm^{-1}; MS: m/z = 344.3 [M+1], 345 [M+2].

2-(2-imino-6-(3-nitrophenyl)-2, 3-dihydropyrimidin-4-yl) naphthalen-1-ol (**2b**, $C_{20}H_{14}N_4O_3$)

Orange solid, M.p.: 174 ^oC; ^1H NMR (400 MHz, DMSO): δ = 15.77(1H,s,OH), 7.51-8.12(10H,m,Ar), 7.04(1H,s,NH), 7.48(1H,s,C=NH), 2.52(1H,s,CH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 104.43(C), 117.6(C), 121(CH), 123(CH), 123.29(CH), 123.8(CH), 124(CH), 125(C), 126.59(CH), 126.7(CH), 127(CH), 130(CH), 130.12(CH), 135.25(C), 136.65(C), 150(C), 158.69(C), 163(C), 164.65(C), 168(C) ppm; IR spectrum (KBr) $\bar{\nu}$= 3057, 1643, 1577, 1533 cm^-

[1]; MS: m/z = 359.3[M+1], 360[M+2].

2-(6-(4-chlorophenyl)-2-imino-2, 3-dihydropyrimidin-4-yl) naphthalen-1-ol (**2c**, $C_{20}H_{14}ClN_3O$) Yellow solid, M.p.: 122 ^oC; ^{1}H-NMR(400 MHz DMSO-d_6): δ = 15.73(1H,s,OH), 7.51-8.12(10H,m,Ar), 7.60(1H,s,NH), 7.08(1H,s,C=NH), 1.22(1H,s,CH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 109(CH), 117.5(C), 118(CH), 123(CH), 123.07(CH), 124.97(C), 125.58(CH), 125.86(CH), 126.96(CH), 130.8(C), 135.75(C), 36.44(CH), 158(C), 160(C), 165(C), 164(C) ppm; δ = 109(CH), 117.5(C), 118(CH), 123(CH), 123.07(CH), 124.97(C), 125.58(CH), 125.86(CH), 126.96(CH), 127(CH), 128.64(CH), 128.97(CH), 131(C), 132.5(CH), 134(CH), 135.75(C), 158(C), 160(C), 164(C), 165(C) ppm; IR spectrum (KBr) $\bar{\nu}$ = 3057, 1690, 1577, 800 cm^{-1}; MS: m/z =348.3 [M+1] , 349[M+2] , 350[M+3].

2-(6-(2-chlorophenyl)-2-imino-2, 3-dihydropyrimidin-4-yl) naphthalen-1-ol (**2d**, $C_{20}H_{14}ClN_3O$)
Yellow solid, M.p.: 128 ^oC; ^{1}H-NMR(400 MHz DMSO-d_6): δ = 15.70(1H,s,OH), 7.56-8.15(10H,m,Ar), 7.30(1H,s,NH), 7.16(1H,s,C=NH), 7.60(1H,s,CH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 109(CH), 117.5(C), 118(CH), 123(CH), 123.07(CH), 124.97(C), 125.58(CH), 125.86(CH), 126.96(CH), 128.33(CH), 128.64(CH), 128.97(CH), 129.49(CH), 130.8(C), 135.75(C), 136.44(CH), 158(C), 160(C), 164(C), 165(C) ppm; IR spectrum (KBr) $\bar{\nu}$ = 3057, 1683, 1580, 785 cm^{-1}; MS: m/z = 348.3 [M+1], 349[M+2], 350[M+3].

(E)-2-(2-imino-6-styryl-2, 3-dihydropyrimidin-4-yl) naphthalen-1-ol (**2e**, $C_{22}H_{17}N_3O$)
Dark Brown solid, M.p.: 130 ^oC; ^{1}H-NMR(400 MHz DMSO-d_6): δ = 15.68(1H,s,OH), 7.14-8.10(11H,m,Ar), 7.30(1H,s,NH), 7.16(1H,s,C=NH), 5.6(1H,s,CH), 7.57(1H,d,=CH), 7.91(1H,d,=CH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 98.1(CH), 116(C), 117.8(C), 121.1(CH), 121.7(CH), 122.6(CH), 123.29(CH), 123.64(CH), 124.57(CH), 125(CH), 125.6(C), 126.6(CH),126.8(CH), 126.99(CH), 127.5(CH), 127.98(CH), 134.69(C), 138.22(C), 159.4(C), 163(C), 164.58(C), 169.98(C) ppm; IR spectrum (KBr) $\bar{\nu}$ = 3053, 1643, 1689 cm^{-1}; MS: m/z = 340[M+1], 341[M+2].

2-(2-imino-6-(naphthalen-1-yl)-2, 3-dihydropyrimidin-4-yl) naphthalen-1-ol (**2f**, $C_{24}H_{17}N_3O$).
Green solid, M.p.: 142 ^oC; ^{1}H-NMR(400 MHz DMSO-d_6): δ = 15.67(1H,s,OH), 7.21-7.55(13H,m,Ar), 7.76(1H,s, NH), 9.05(1H,s,C=NH) 8.00(1H,s,CH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 29(CH_2), 39.15(CH_2), 39.36(CH_2), 39.99(CH), 99.79(CH), 116(C), 117.54(C), 121.59(CH), 122.6(CH), 123.29(CH), 123.64(CH), 124.57(CH), 125(CH), 125.6(C), 126.73(CH), 126.99(CH), 127.18(CH), 127.98(CH), 134.69(C), 147.22(C), 160.65(C), 162.66(C), 164.58(C), 165.71(C) ppm; IR Spectra = 3053, 1689, 1573 cm^{-1}. MS (m/z) = 364.4[M+1], 365.4[M+2].

2-(6-(4-(dimethylamino) phenyl)-2-imino-2, 3-dihydropyrimidin-4-yl) naphthalen-1-ol (**2g**, $C_{22}H_{20}N_4O$). Dark Brown solid, M.p.: 300 ^oC; ^1H-NMR [δppm] = 15.47(1H,s,OH), 7.21-7.25(13H,m,Ar), 7.26(1H,s,NH), 8.63(1H,s,C=NH), 8.00(1H,s,CH), 3.20(3H,s,NCH_3) ppm; ^{13}C NMR [δppm] = 40.3(CH_3), 4.03(CH_3), 104.2(CH),114.4(CH), 114.4(CH), 117.6(C), 121.1(CH), 121.7(CH), 122.6(CH), 122.7(CH), 126(C), 126.6(CH), 126.8(CH), 127.5(CH), 130.1(CH), 134.1(C), 151.9(C), 158.57(C), 163(C), 164(C), 164.6(C), 168.46(C) ppm; IR Spectra = 3053, 1643, 1579 cm^{-1}; MS: m/z = 357.4[M+1], 358.4[M+2].

IR spectrum of 2a in KBr exhibited bands at 3050 cm-1 and 1560-1440 cm-1 showing O-H, and (C=N) stretching in Aromatic ring respectively . IR data show one weak band at 3310 cm^{-1} instead of sharp NH_2 peak around 3650-3400cm^{-1} confirming the presence of secondary amines. The MS of 2a shows molecular ion peak at m/z 344.25 (M+1) peak. Similarly, the mass spectra of other pyrimidines shows peaks at m/z, 348.3, 364.4 and 359.3 (M+1) and fully supported by NMR spectra where only one singlet at 6.98 showing the formation of dihydroiminopyrimidine only and all other peaks of aromatic region and functional groups are found satisfactorily. However, the presence of substituted 2-(2-amino-2, 3-dihydropyrimidin-4-yl) naphthalen-1-ol (2'a-g) cannot be ruled out at all as in some of the IR Spectra and Mass Spectra the presence of NH_2 group and the existence of (2'a-g) is also found, but at very low concentration as found in mass and IR spectra.

Antibacterial assay

In sequel to our continuous search for newer antibacterial agents, compounds with pyrimidine nucleus has been synthesized and evaluated for different bacterial strains. The invitro antimicrobial activity has been carried out at 24 hr incubation period at 25°C against three bacterial species by disc–diffusion method. The compounds 2(a-g) have been tested for their antimicrobial activity against S. aureus, P. vulgaris, and Klebsheilla. The compounds were tested at a concentration of 0.01 mg/ 1ml in DMSO against all organisms. The zone of inhibition has been compared with the standard drug after 24hr of incubation period at 25°C for antibacterial activities. The compounds, 2b (m-NO_2), 2d (o-Cl), 2e (p-CH=CH) and 2f (Naphthalene) has shown very good antimicrobial properties against P.vulgaris. Also compound 2a (p-MeO), 2b (m-NO_2), 2d (o-Cl) and 2f (Naphthalene) shows high zone of inhibition against s.aureus and similar results were obtained in case with Klebsheilla with compounds 2c (p-Cl), 2d (o-Cl) and 2g (N-(CH_3)$_2$). In brief, the compound 2b (m-NO_2), 2d (o-Cl) and 2f (Naphthalene) shows a very good zone of inhibition as compared with standard drug (i.e., Streptomycin). Results are incorporated in Figure 1.

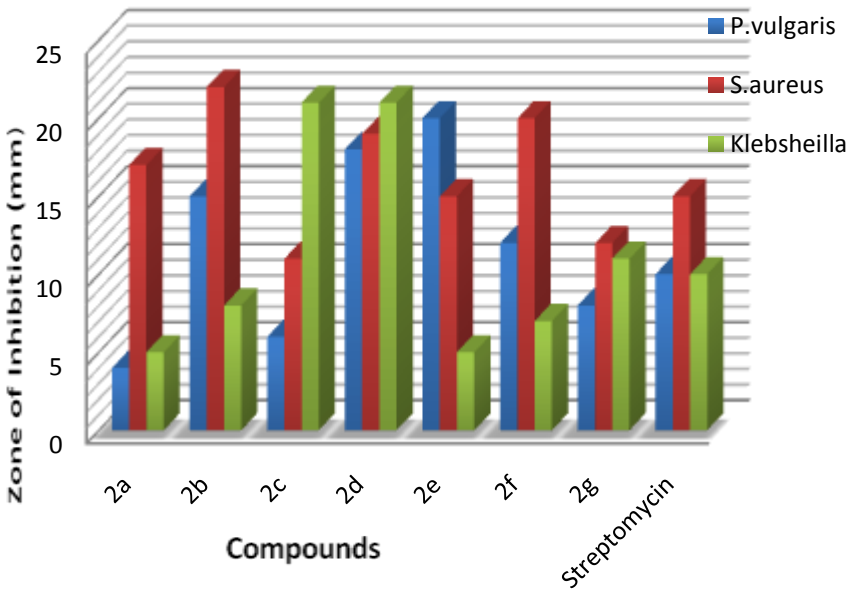


Figure 1: Evaluation of Antimicrobial Activity of compounds 2(a-g).

DMSO is used as control, Streptomycin is used as standard drug and all the zone of inhibition are calculated in mm.

CONCLUSION

The present work shows the development of a new rapid and simple multi-component cyclocondesation protocol for the synthesis of biologically active 2-imine-4,6-diarylpyrimidine. Furthermore, use of microwave avoids using organic solvent, this method contributes to the promotion of an economical and environmentally friendly experimental procedure. The final molecules (2a-g) have shown good antibacterial activity. Especially compound 2c, 2d and 2e have shown good activity against all the bacterial species (i.e. p.vulgaris, s. aureus and Klebsheilla). These molecules have shown higher activity than standard drug (Streptomycin) and might be useful as antibacterial drugs in the future.

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REFERENCES

1. A.Domling. The discovery of new isocyanide-based reactions (2000) Curr Opin. Chem. Bio. 2000; 4: 318-323.
2. Sharma. P, Rane. N, Gurram V.K. Synthesis and QSAR studies of pyrimido [4, 5-d] pyrimidine-2, 5-dione derivatives as potential antimicrobial agents. Bio.Org. Med. Chem.2004; 4(16): 4185-4190.
3. B.S., Mahalingaa. M, Karthikeyana M.S, Akberalib P.M., Shetty .N.S. 2047Synthesis of some novel pyrazolo[3,4-*d*]pyrimidine derivatives as potential antimicrobial agents. Bio. Org. Med.Chem.2006; 6: 2040-45.
4. Kim BJ, Zhang J, Tan S, Matteson DS, Prusoff WH, Cheng YC. Synthesis and properties of 1-(3'-dihydroxyboryl-2',3'-dideoxyribosyl)pyrimidines. Org. Biomol. Chem.,2012; 10: 9349-9358.
5. Ahmed Mutanabbi Abdula. Synthesis, characterization and antibacterial activity of (E)+chalcone derivatives (2013) Eur. J. Chem. 4:207-210.
6. Dwipen Kakati, Sarma R.K, Saikia.R, Nabin C. N.B, Sarma J. C. Rapid microwave assisted synthesis and antimicrobial bioevaluation of novel steroidal chalcones. Steroids.2013; 78:321–326.
7. Chuanfei Jin, Yong-Ju Liang, Hongwu He, Liwu Fu. Synthesis and antitumor activity of novel chalcone derivatives. Biomedicine & Pharma.2013;67: 215–217.
8. Mohamed Abdel-Aziz, So-Eun Park, Gamal El-Din A.A. Abuo-Rahma, Mohamed A. Sayed, Youngjoo Kwon. Novel *N*-4-piperazinyl-ciprofloxacin-chalcone hybrids: Synthesis, physicochemical properties, anticancer and topoisomerase I and II inhibitory activity. Eur.J. Med. Chem. 201369:427-438.
9. Modzelewska A, Pettit C, Achanta G, Davidson NE, Huang P, R. Khan. Anticancer activities of novel chalcone and bis-chalcone derivatives. Bioorg. Med. Chem. 2006;14:3491–3495.
10. Hong-Jia Zhang, Yong Qian, Di-Di Zhu, Xu-Guang Yang, Hai-Liang Zhu. Synthesis, molecular modeling and biological evaluation of chalcone thiosemicarbazide derivatives as novel anticancer agents. Eur. J. Med. Chem.2011 46:4702–4708.
11. Zhao LM, Jin HS, Sun LP, Piao HR, Quan ZS. Synthesis and evaluation of antiplatelet activity of trihydroxychalcone derivatives Bioorg. Med.Chem. Lett.2005; 15:5027-5029.
12. Chen Y. H, Wang W. H, Wang Y. H, Lin Z. Y, Wen C. C, Chern C. Y. Evaluation of the

Anti-Inflammatory Effect of Chalcone and Chalcone Analogues in a Zebrafish Model Molecules.2013;18:2052-2060.

13. Sashidhara KV, Kumar M, Modukuri RK, Sonkar R, Bhatia G, Khanna AK, Rai S, Shukla R Synthesis and anti-inflammatory activity of novel biscoumarin–chalcone hybrids. Bioorg. & Med. Chem. Lett. 2011;21:4480–4484.
14. Tadigoppula N, Korthikunta V, Gupta S, Kancharla P, Khaliq T, Soni A, Srivastava RK, Srivastava K, Puri SK, Raju KS, Wahajuddin, Sijwali PS, Kumar V,Mohammad. Synthesis and Insight into the Structure–Activity Relationships of Chalcones as Antimalarial Agents J. Med. Chem. 2013;56:31-45.
15. K.L. Lahtchev, D.I. Batovska, St.P. Parushev, V.M. Ubiyvovk, A.A.Sibirny. Antifungal activity of chalcones: A mechanistic study using various yeast strains Eur. J. Med. Chem. 2008;43:2220–2228.
16. Liu M, Wilairat P, Croft SL, Tan ALC, Structure–activity relationships of antileishmanial and antimalarial chalcones . Bioorg. Med. Chem. 2003; 11:2729–2738.
17. Deshpande A. M., Narshinha P. A., Natu A. A., Eckman.J. Synthesis and screening of a combinatorial library of naphthalene substituted chalcones: inhibitors of leukotriene B41. Bioorg. Med. Chem. 1999; 7:1237–1240.
18. Bittencourt, HR, Santos, LS, Souza Filho. Allelopathic activity of synthetic chalcone, its precursors and of related cetones and aldehydes. Planta Daninha,Viscosa. 2007;25: 747
19. Subramanian M, Vanangamudi G, Thirunarayanan G. Hydroxyapatite catalyzed aldol condensation: Synthesis, spectral linearity, antimicrobial and insect antifeedant activities of some 2,5-dimethyl-3-furyl chalcones. Spectrochim. Acta, Part A Mol Biomol Spectrosc. 2013;110:116-123.
20. Thirunarayanan G, Surya S, Srinivasan S, Vanangamudi G, Sathiyendiran V. Synthesis and insect antifeedant activities of some substituted styryl 3,4-dichlorophenyl ketones. Spectrochim Acta A Mol Biomol Spectrosc. 2010;75:152-156.
21. Chauhan M, Kumar R. ; Medicinal attributes of pyrazolo[3,4-*d*]pyrimidines: A review. Bioorg Med Chem.2013; 21:5657-5668.
22. Ghodasara HB, Trivedi AR, Kataria VB, Patel BG, Shah VH. Synthesis and antimicrobial evaluation of novel substituted pyrimidine scaffold Med Chem Res .2013;22:6121-6128.
23. Shimoga Nagaraj Sriharsha, Sridharamurthy Satish, Sheena Shashikanth, Koteshwara Anandarao Raveesha. Design, synthesis and antibacterial activity of novel 1,3-

thiazolidine pyrimidine nucleoside analogues. Bioorg.Med. Chem 2006;14:7476-7481.

24. Oya Bozdağ-Dündar, Özen Özgen, Arzu Menteşe, Nurten Altanlar, OnurAtlı, Engin Kendi, Rahmiye Ertan. Synthesis and antimicrobial activity of some new thiazolyl thiazolidine-2,4-dione derivatives. Bioorg. Med. Chem.2007;15: 6012–6017.
25. Sondhia SM, Singha N, Johara M, Kumar A. Synthesis, anti-inflammatory and analgesic activities evaluation of some mono, bi and tricyclic pyrimidine derivatives Bioorg. Med. Chem.2005; 13:6158-6166.
26. Al-Ashmawy MI, El-Feky SA, El-Samii ZK, Osman NA. Synthesis and antiinflammatory activity of novel pyrimidine derivatives. Bollettino Chimico Farmaceutico. 1997;136:492-499.
27. Birsen Tozkoparan, Mevlüt Ertan, Pelin Kelicen, Rümeysa Demirdamar. Synthesis and anti-inflammatory activities of some thiazolo[3,2-a]pyrimidine derivatives.Il Farmaco 1999;54: 588–593.
28. Sondhi SM, Singh N, Johar M, Kumar A. Synthesis, anti-inflammatory and analgesic activities evaluation of some mono, bi and tricyclic pyrimidine derivatives. Bioorg. Med. Chem. Lett. 2005;13:6158-6166.
29. AM, El-Sayed WA, Alsharari MA, Al-1 Qalawi HRM, Germoush MO. Anticancer activities of some newly synthesized pyrazole and pyrimidine derivatives. Arch. Pharm. Res. 2013;36: 1055- 1065.
30. Singha K, Kaura H, Chibaleb K, Balzarinic J. Synthesis of 4-aminoquinoline–pyrimidine hybrids as potent antimalarials and their mode of action studies. Eur. J.Med.Chem.2013; 66:314-323.
31. Mohan S.B, Kumar R B.V, Dinda S.C, Naik D, Seenivasan S.P, Kumar V,Rana D.N., Brahmkshatriya P.S. Microwave-assisted synthesis, molecular docking and antitubercular activity of 1,2,3,4-tetrahydropyrimidine-5-carbonitrile derivatives. Bioorg. Med. Chem. Lett.2012; 22:7539–7542.