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Journal of Advanced Scientific Research

Available online through http://www.sciensage.info

ISSN
0976-9595
Research Article

RAPID AND GREENER MICROWAVE ASSISTED SYNTHESIS OF A SERIES OF (SUBSTITUTED-3-BENZYL-5-(3-PHENOXYBENZYLIDENE) THIAZOLIDINE-2,4-DIONE) DERIVATIVES

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ABSTRACT

A Novel series of thiazolidine-2, 4-dione compounds was synthesized under microwave irradiation and those compounds were evaluated for their biological property i.e. antimicrobial activity, against two Gram positive and two Gram negative bacterial strains additionally two fungal strains. Among the synthesized derivatives 9b, 9h and 9i were found to be the most effective antimicrobial compounds. All the prepared compounds were characterized for structural confirmation by IR, ^{1}HNMR, ^{13}CNMR and Mass spectroscopy.

Keywords: Thiazolidine, Benzyl chloride, Chalcones, Microwave assisted synthesis, Anti microbial activity.

1. INTRODUCTION

The literature on heterocyclic compounds is replete with examples of a large number of synthetic and naturally occurring systems, which are pharmaceutically active and quite a few there are essential to life processes [1]. The importance of heterocyclic compounds has been recognized in the field of medicinal chemistry.

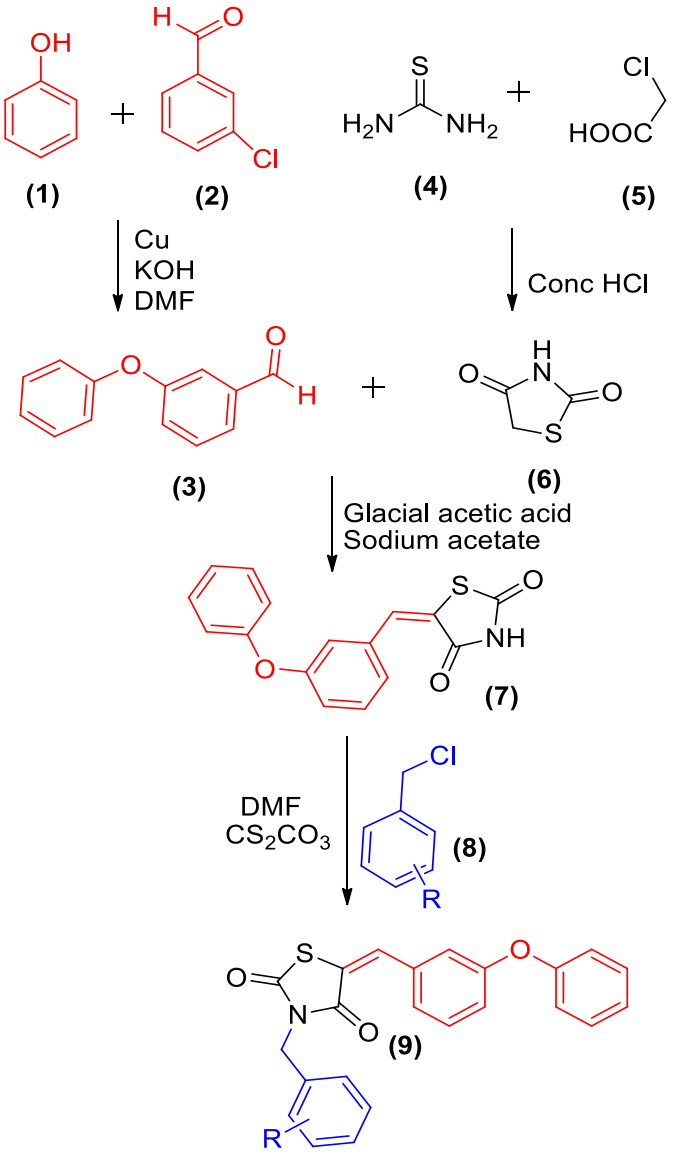
One of the most important heterocycles in medicinal chemistry is Thiazolidine-2,4-dione (TZD) having five-member ring containing sulphur, nitrogen and oxygen atoms [2] with wide applications including anti-microbial [3-7], antibacterial [8], anti-cancer [9-13], anti-inflammatory [14-17], antitubercular [18], antiarthritic [19], antiviral [20], antioxidant [21], anticonvulsant [22-23], anti-hyperglycemic [24] and anti malarial [25-26] etc. The expanding cases of microbial resistance pose a huge concern to the scientific community and have become a threat for human life globally. Moreover, invasive microbial infections induced by multi-drug-resistant microbes are hard to diagnose and treat. To overcome these difficulties, the development of new and safe antimicrobial agents with enhanced effectiveness is urgently required. One of the best ways to invent new antimicrobial agents is to generate hybrid molecules by combining two biological active heterocyclic compounds in a same molecular framework forms important structural feature in many synthetic drugs. In view of this, thiazolidinone derivatives have been treated as the most promising molecules to be studied as lead structures in the discovery of advanced medicinally potent agents.

In the present work we have synthesized a series of Thiazolidine derivatives which was identified by various spectroscopic techniques i.e. ^{1}HNMR, IR, ^{13}CNMR and MASS. Further synthesized compounds were evaluated against their antimicrobial activity including two gram positive, two gram negative, and two fungal strains.

2. MATERIAL AND METHODS

All the reagents and solvents used in the synthesis of final material were sourced from sigma aldrich, spectrochem, and lobachemie with maximum purity grade. Thin-layer chromatography was accomplished on 0.2-mm percolated plates of silica gel G60 F_{254} (Merck). Visualization was made with ultraviolet light (254 and 365nm) or with an iodine vapor. IR spectra were recorded on a FTIR-8400 spectrophotometer using DRS prob. ^{1}H (400 MHz), and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker AVANCE II spectrometer in $CDCl_3$ and DMSO. Chemical shifts are expressed in δ ppm downfield from TMS as an internal reference standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu) instrument. Solvents were evaporated with a

BUCHI rotary evaporator. Melting points were measured in open capillaries and are uncorrected.



Synthetic Scheme

2.1. Synthesis of (E)-5-(3-phenoxybenzylidene) thiazolidine-2,4-dione (7)

Phenol(1 mol) was taken in round bottom flask (RBF) with O-choloro benzaldehyde(1mol) in the presence of potassium hydroxide (1 mol) and Cu metal as catalyst, DMF was taken as a solvent and the reaction mixture was refluxed for 3 hours to get product (3). The product was obtained by pouring the mixture into ice cold water and purification of solid done by column chromatography. On other hand, for the Synthesis of Thiazolidine-2,4-dione (6), in a 250ml three-necked flask, a solution containing 56.4g (0.6M) of chloroacetic acid in 60ml of water and 45.6g (0.6M) of thiourea was dissolved in 60ml of water. The mixture was stirred for 15 min. till occurrence of white precipitates. To the contents of flask was now added slowly 60ml of conc. hydrochloric acid from dropping funnel to dissolve the precipitates, after which the reaction mixture was stirred and refluxed for 10-12hrs at 100-110°C. Upon cooling, the content of flask was solidified to a mass of clusters of white needles. The product (6) was filtered and washed with water to remove traces of hydrochloric acid, dried and re-crystallized from ethanol; yield 80%, m.p. (123-125°C). In the next step for Synthesis of (E)-5-(3-phenoxybenzylidene) thiazolidine-2,4-dione (7), a solution containing 0.01mole (0.143 g) of 3-phenoxybenzaldehyde and 0.01mole (0.25 g) of thiazolidine-2, 4-dione in 1.0 ml of hot acetic acid, 0.01mole (0.338 g) of sodium acetate was added and the mixture was refluxed for 1.5 hours. The product (7) was obtained by pouring the mixture into ice cold water and re-crystallizing the resulting solid from ethyl acetate.

2.2. General procedure for substituted-3-benzyl-5-(3-phenoxybenzylidene) thiazolidene-2,4-dion(9a-j).

In the RBF, a mixture of intermediate (E)-5-(3-phenoxybenzylidene) thiazolidine-2,4-dione(1 mol) and CS_2CO_3, as a base, were dissolved in solvent *i.e.* DMF, then substituted benzyl chloride (8) (2.5 mmol) was added drop wise with continuous stirring under microwave irradiation. The reaction was carried out for 3 hours at room temperature with continuous stirring and then heated for 4 hours at 70°C. When the mixture was cooled to room temperature, water (30 mL) was added and neutralized with aqueous hydrochloric acid. The resultant solid was filtered out and washed with water. Product was obtained as a solid to give respective derivatives.

2.3. Biological activity

In view of the biological importance of novel series of thiazolidine-2,4-dione derivatives, the synthesized compounds were screened against their antimicrobial activity. Activity was carried out at College of Computer, Science and Information Technology, Junagadh. The compounds were screened against two gram-negative bacteria, namely *Escherichiacoli* (MTCC (Microbial Type Culture Collection) No. 443), *Pseudomonas aeruginosa* (MTCC No. 1688), two gram-positive bacteria namely *Staphylococcus aureus* (MTCC No.

96) and Strptococcus pyogenus,(MTCC No. 442) and two anti fungal activity against Candida albicans, (MTCC No. 227), and Aspergillus niger (MTCC No. 282). The strains were inoculated in nutrient broth, and kept for 24 hours culture at 36°C. All the activities were carried out by comparision with Ampicilin and Griseofulvin as standard drugs in MIC. The MIC is defined as the minimum inhibitory concentration able to inhibit any visible bacterial growth. Antibacterial activity was determined by Broth dilution method [27] performed in 60 well micro plate, using 2,3,5-triphenyl tetrazolium chloride (TTC) as an indicator for bacterial growth, by dissolving 5 mg of sample in 1 mL DMF as a solvent.

3. RESULT AND DISCUSSION

The synthesis of substituted thiazolidin-4-ones **9a-j** was performed using a microwave irradiation and conventional procedure. All the reactions were performed in closed vessels and the microwave program was composed of appropriate ramping and holding steps. Identification of the optimum power was 350W.

3.1.Spectral data of the synthesized compounds

3.1.1. (E)-4-((2,4-dioxo-5-(3-phenoxybenzylidene)thiazolidin-3-yl)methyl)benzonitrile (9a)

White solid, **^{1}HNMR**(400MHz,$CDCl_3$)(δ ppm): 7.70 – 7.55 (m, 2H), 7.51 – 7.41 (m, 2H), 7.37 (d, J = 18.0 Hz, 2H), 7.23 (t, J = 0.8 Hz, 3H), 7.15 (s, 1H), 7.12 – 6.96 (m, 3H), 6.94 (s, 1H), 4.37 (s, 1H), 3.77 (s, 1H);**^{13}CNMR** (100 MHz,$CDCl_3$) (δ ppm): 176.06 (s), 163.81 (s), 156.43 (d, J = 0.8 Hz), 144.83 (s), 135.17 (s), 130.30 – 129.85 (m), 129.82 – 129.55 (m), 129.44 (s), 129.15 – 128.75 (m), 125.66 (s), 123.34 (s), 121.41 (s), 120.39 (s), 119.35 – 119.01 (m), 113.93 (s), 111.88 (s), 47.53 (s); **IR** (KBr, cm^{-1}): 3420, 3030, 1620, 1550, 1430, 1340, 1230, 850,730; **MS (m/z):** 412.

3.1.2. (E)-3-(4-nitrobenzyl)-5-(3-phenoxybenzylidene) thiazolidine-2,4-dione (9b)

White solid, **^{1}HNMR**(400MHz,$CDCl_3$)(δ ppm): δ 8.25 – 8.11 (m, 2H), 7.58 – 7.43 (m, 2H), 7.37 (d, J = 15.7 Hz, 2H), 7.23 (t, J = 0.8 Hz, 3H), 7.15 (s, 1H), 7.13 – 6.96 (m, 4H), 4.45 (s, 1H), 3.74 (s, 1H);**^{13}CNMR** (100 MHz,$CDCl_3$) (δ ppm): 176.06 (s), 163.81 (s), 156.43 (d, J = 0.8 Hz), 147.19 (s), 143.71 (s), 135.17 (s), 130.30 – 129.85 (m), 129.44 (s), 128.94 – 128.54 (m), 125.66 (s), 124.02 – 123.62 (m), 123.34 (s), 121.41 (s), 120.39 (s), 119.35 – 119.13 (m), 113.93 (s), 47.53 (s); **IR** (KBr, cm^{-1}): 3450, 3038,1750 1600, 1520, 1450, 850,750; **MS (m/z):**432.

3.1.3. (E)-3-(4-chlorobenzyl)-5-(3-phenoxybenzylidene)thiazolidine-2,4-dione (9c)

White solid, **^{1}HNMR**(400MHz,$CDCl_3$)(δ ppm): 7.36 (d, J = 15.5 Hz, 2H), 7.32 – 7.22 (m, 4H), 7.22 – 7.20 (m, 1H), 7.20 – 7.13 (m, 3H), 7.12 – 6.97 (m, 3H), 6.95 (s, 1H), 4.37 (s, 1H), 3.65 (s, 1H). **^{13}CNMR** (100 MHz,$CDCl_3$) (δ ppm): 176.06 (s), 163.81 (s), 156.43 (d, J = 0.8 Hz), 135.09 (d, J = 20.5 Hz), 134.97 – 134.90 (m), 132.85 (s), 130.30 – 129.85 (m), 129.44 (s), 129.14 – 128.74 (m), 125.66 (s), 123.34 (s), 121.41 (s), 120.39 (s), 119.35 – 119.13 (m), 113.93 (s), 47.53 (s); **IR** (KBr, cm^{-1}): 3410, 3040, 1600, 1520, 1450, 850,710,680; **MS (m/z):**421.

3.1.4. (E)-3-(4-bromobenzyl)-5-(3-phenoxybenzylidene) thiazolidine-2,4-dione (9d)

brown solid, **^{1}HNMR**(400MHz,$CDCl_3$)(δ ppm): 7.54 – 7.40 (m, 2H), 7.40 – 7.20 (m, 5H), 7.17 – 7.06 (m, 3H), 7.06 – 6.95 (m, 3H), 6.93 (s, 1H), 4.32 (s, 1H), 3.73 (s, 1H); **^{13}CNMR** (100 MHz,$CDCl_3$) (δ ppm): 176.06 (s), 163.81 (s), 156.43 (d, J = 0.8 Hz), 135.17 (s), 134.25 (s), 132.05 – 131.65 (m), 130.30 – 129.85 (m), 129.44 (s), 125.66 (s), 123.34 (s), 122.69 (s), 121.41 (s), 120.39 (s), 119.35 – 119.13 (m), 113.93 (s), 47.53 (s); **IR** (KBr, cm^{-1}): 3450, 3038, 1600, 1510, 1450, 830,710,620; **MS (m/z):**466.

3.1.5. (E)-3-benzyl-5-(3-phenoxybenzylidene)thiazo -lidine-2,4-dione (9e)

White solid, **^{1}HNMR**(400MHz,$CDCl_3$)(δ ppm): 7.6-7.5(m,2H), 7.4-7.3(m,3H), 7.2(m, 2H),7.1(m,2H), 7.0(s,1H), 6.9(m,3H), 6.8(s,1H), 3.7(s, 2H) **^{13}CNMR** (100 MHz,$CDCl_3$) (δ ppm): 175(s), 163(s), 155(d), 144(s), 135(s), 130(s), 128(s), 125(s), 123(s), 121(s),119(m),113(s), 111(s), 47(s), **IR** (KBr, cm^{-1}): 3410, 3040, 1600, 1520, 1450, 850, 710, 680; **MS (m/z):**387.

3.1.6. (E)-3-(2-chlorobenzyl)-5-(3-phenoxybenzylidene) thiazolidine-2,4-dione (9f)

yellow solid, **^{1}HNMR**(400MHz,$CDCl_3$)(δ ppm): 7.6-7.4(m 2H), 7.3-7.1(m, 3H), 7.0(m,3H), 6.9(s,1H), 6.8(m,3H), 6.7(s,1H), 6.5(s,1H), 3.9(s, 2H);**^{13}CNMR** (100 MHz,$CDCl_3$) (δ ppm):177(s), 165(s), 157(s), 146(s), 137(s), 130(s), 127(s), 125(s), 121(s), 118(m),

111(s), 46(s) **IR** (KBr, cm^{-1}): 3420, 3022,1600, 1520, 1450, 850, 750; **MS (m/z):** 421.

3.1.7. (E)-3-(2-bromobenzyl)-5-(3-phenoxybenzylidene) thiazolidine-2,4-dione (9g)

brown solid, **^{1}HNMR**(400MHz,$CDCl_3$)(δ ppm): 7.4(m,2H), 7.1(m,3H), 7.0(m,3H), 6.8(s, 1H), 6.7(m,3H), 6.7(s,1H), 6.6(s, 1H), 3.9(s,2H);**^{13}CNMR** (100 MHz,$CDCl_3$) (δ ppm): 180(s), 176(s), 161(s), 156(s), 151(s), 138(s), 136(s), 129(s), 116(s), 44(s); **IR** (KBr, cm^{-1}): 3450, 3030,1600, 15601520, 1450, 850,750 **MS (m/z):** 466.

3.1.8. (E)-3-(2-nitrobenzyl)-5-(3-phenoxybenzyli dene) thiazolidine-2,4-dione (9h)

White solid, **^{1}HNMR**(400MHz,$CDCl_3$)(δ ppm): 7.7(m,2H), 7.4(m,3H), 7.3(m,3H), 7.1(s,1H), 7.0(m,3H) 6.8(s,1H), 6.7(s,1H), 4.0(s,2H);**^{13}CNMR** (100 MHz,$CDCl_3$) (δ ppm):179(s), 171(s), 163(s), 156(s), 139(s), 137(s), 135(s), 117(s), 49(s); **IR** (KBr, cm^{-1}): 3430, 3080, 1750 1600,1560 1520, 1450, 850,750; **MS (m/z):** 432.

3.1.9. (E)-2-((2,4-dioxo-5-(3-phenoxybenzylidene) thiazolidin-3-yl)methyl) benzonitrile (9i)

White solid, **^{1}HNMR**(400MHz,$CDCl_3$)(δ ppm):7.4 (m,2H), 7.2(m,3H), 7.1(m,3H), 7.0(s,1H), 6.90(m,3H), 6.7(s,1H), 6.6(s,1H), 3.8(s,2H);**^{13}CNMR** (100 MHz,$CDCl_3$) (δ ppm): 179(s), 171(s), 163(s), 156(s), 139(s), 137(s), 136(s), 117(s), 49(s) **IR** (KBr, cm^{-1}): 3410, 3050, 1630, 1520,1500, 1430, 1350-1200, 850,720; **MS (m/z):** 412.

3.1.10. (E)-3-(3-chlorobenzyl)-5-(3-phenoxybenzyli -dene) thiazolidine-2,4-dione (9j)

yellow solid, **^{1}HNMR**(400MHz,$CDCl_3$)(δ ppm): 7.8(m,5H), 7.6(s, 1H), 7.4(m,3H), 7.2(s,1H), 7.0(m3H), 6.8(s,1H), 4.2(s,2H);**^{13}CNMR** (100 MHz,$CDCl_3$) (δ ppm):176(s), 163(s),157(s),143(s), 135, 136(s), 128(m), 125(s), 123(s), 121(s), 119(s), 46(s);**IR** (KBr, cm^{-1}): 3420, 3030, 1620, 1550, 1430, 1340, 1230, 850, 730; **MS (m/z):** 421.

Table 1: List of substitutions with yields and melting points

Sr. No.	Code	Substitution (R)	Molecular formula	Yield (%)	M.P.(°C)
1	9a	4-CN	$C_{24}H_{16}N_2O_3S$	78	172
2	9b	4-NO_2	$C_{23}H_{16}N_2O_5S$	83	177
3	9c	4-Cl	$C_{23}H_{16}NO_3SCl$	82	182
4	9d	4-Br	$C_{23}H_{16}NO_3SBr$	73	181
5	9e	H	$C_{23}H_{17}NO_3S$	76	183
6	9f	2-Cl	$C_{23}H_{16}NO_3SCl$	75	185
7	9g	2-Br	$C_{23}H_{16}NO_3SBr$	83	189
8	9h	2-NO_2	$C_{23}H_{16}N_2O_5S$	77	183
9	9i	4-CN	$C_{24}H_{16}N_2O_3S$	71	182
10	9j	3-Cl	$C_{23}H_{16}NO_3SCl$	73	189

The structure of the synthesized thiazolidine-2, 4-dione derivatives (9a-j) were determined by ^{1}H & ^{13}C NMR and mass spectral analysis. IR spectrum of all the final thiazolidinedione derivatives showed characteristic peaks for -N-H stretching in the range of 3402-3415cm^{-1} and -C=O stretching in the range of 1705-1720 cm^{-1},-C=O stretching for cyclic amide in the range of 1660-1675 $cm^{-1}$and -C=C- in the range of 1560-1575cm^{-1} was shown in experimental data. ^{1}H NMR showed characteristic peak in the range of 10.91-10.95 δ ppm to confirm the presence of -NH proton of thiazolidinedione derivatives. This large deshielding effect on -NH proton was attributed to the presence of electron withdrawing carbonyl groups. Thiazolidine- 2,4-dione derivatives (9a-j) showed a characteristic peak of benzylidene proton (=CH) between 7.15-8.15 δ ppm. The molecular weights of synthesized compounds were confirmed by mass spectral analysis. The observed molecular weights of particular compounds were showing (M+1) molecular ion peak which was summarized in.

In the present study, synthesized compounds were screened for their anti-microbial activities against two gram negative and two gram positive bacterial strains and two fungal strains. All the activities were carried out using Ampicilin and Griseofulvin as standard drugs in MIC (Minimum-bacterial Inhibitory Concentration). All

the values were resolved by Broth dilution technique where DMSO was used as diluent. MIC values of the appraised compounds are recorded in (Table 2). Derivative 9b and 9h was exhibited moderate activity against *E. Coli.(MTCC 443)* 9d possess moderate activity against *P. Aeruginosa (MTCC 1688)*. Compound 9b and 9g posses moderate activity against *S. Aureus (MTCC 96)*. 9f and 9i showed moderate activity against *S.pyogenus (MTCC 442)* by comparing *ampicilin*. While 9c, 9e and 9j were found to posses moderate activity against *C.albicans (MTCC 227)*, 9h and 9i showed activity against *A.niger (MTCC-282)* by comparing *griseofulvin* as a standard drug.

Table 2: Anti microbial activity of synthesized thiazolidine-2,4-dione derivatives

Sr. No.	Code	MIC (µg/mL)					
		Antibacterial activity				Antifungal activity	
		E.coli	*P.aeruginosa*	*S.aureus*	*S.pyogenus*	*C.albicans*	*A.niger*
1	9a	500	500	250	200	500	>1000
2	9b	100	250	62.5	500	1000	500
3	9c	1000	1000	250	500	200	500
4	9d	250	62.5	1000	200	1000	1000
5	9e	1000	1000	250	250	200	>1000
6	9f	250	500	500	62.5	500	500
7	9g	500	500	100	500	500	500
8	9h	100	500	1000	500	>1000	100
9	9i	500	500	500	100	1000	100
10	9j	250	1000	250	500	200	500
Ampicilin		250	100	250	200	-	-
Griseofulvin		-	-	-	-	500	250

E. coli: Escherichia coli, P.aeruginosa: Pseudomonas aeruginosa, S.pyogenus: Strptococcus pyogenus, S. aureus: Staphpyococcus aureus, C.albicans: Candida.albicans, A.niger: Aspergillus niger

4. CONCLUSION

We have successfully synthesized a novel series of substituted thiazolidin-4-one by using microwave irradiation in good amount of yield. The reaction of (E)-5-(3-phenoxybenzylidene) thiazolidine-2,4-dione with various substituted benzyal chloride derivatives was afforded the -(3-phenoxybenzylidene) thiazolidine-2,4-dione derivatives in moderate yield in the presence of base. Sodium methoxide was found as an efficient base. The structure of the synthesized thiazolidine-2, 4-dione derivatives (9a-j) were determined by ^{1}H, ^{13}CNMR, IR and mass spectral analysis. All the derivatives were screened against their antimicrobial activity containing two gram positive and two gram negative bacterial strains and two fungal strains by broth dilution method which confirmed that 9b, 9h and 9i derivatives showed potent activity, while many of the derivatives showed moderate antimicrobial activity.

5. ACKNOWLEDGEMENT

The authors are very thankful to Department of Chemistry (DST-FIST Funded & UGC-SAP Sponsored), Saurashtra University, Rajkot for providing all the required practical research work facilities. We are thankful to the NFDD (National Facility for Drug Discovery) for ^{1}HNMR, ^{13}CNMR analysis of samples and also thankful to College of Computer, Science and Information Technology for evaluation of biological activities.

6. REFERENCES:

1. Mulay A, Ghodke M, Pratima NA. *Int. j. pharma. sci.,* 2009; **(1):**57-64.
2. Zhuang Q, Wang X, Gao Y, Shi F, Jiang B, Tu S. *ACS. Comb. Sci.,* 2011; **13:**84-88.
3. Madhukar A, Kumar P, Kumar M, Verma P. *Int. J. Chem. Tech. Res.,* 2009; **1(4):**1376-1380.
4. Omar K, Geronikaki A, Zoumpoulakis P, Camoutsis C. *J. Bioorg. Med. Chem.,* 2010; **18:**426-432.
5. Kumar M, Jain S, Deep A. *J. Pharma.,* 2011; **30(2):** 388-391.
6. Chawla P, Singh R, Saraf SK. *Med. Chem. Res.,* 2013; **21(8):**2064-2071.

7. Desai NC, Dodiya AM, Shihora PN. *Med. Chem. Res.,* 2012; **21(8):**1577-1586.
8. Saeed A, Abbasa N, Florke U. *Chem. Soc.*, 2007; **18(3):**559-565.
9. Chandrappa S, Nagegowda P, Karuna M, Rangappa KS. *Med. Chem. Res.,* 2010; **19:**236-249.
10. Deep A, Kumar P, Narasimhan B, Lim SM, Ramasamy K, Mishra RK, Mani V. *Acta. Pol. Pharm.,* 2016; **73(1):**93-106.
11. Havrylyuk D, Mosula L, Zimenkovsky B, Vasylenko O, Gzella A, Lesyk R. *Eur. J. Med. Chem.,* 2010; **45(11):**5012-5021.
12. Kumar P, Narasimhan B, Majeed AB. *Curr. Top. Med. Chem.,* 2015; **15(11):**990-1002.
13. Narasimhan B, Ramasamy K, Mani V, Mishra RK, Majeed AB. *Curr. Top. Med. Chem.,* 2013; **13(16):**2034-2046.
14. Unsal-Tan O, Ozadali K, Piskin K. *Eur. J. Med. Chem.* 2012; **57:**59-64.
15. Deep A, Jain S, Sharma PC. *Acta Pol. Pharm.,* 2010; **67(1):**63-67.
16. Kumar V, Sharma A, Sharma PC. *J. Enzyme Inhib. Med. Chem.,* 2011; **26(2):**198-203.
17. Deep A, Jain S, Sharma PC, Phogat P, Malhotra M. *Med. Chem. Res.,* 2012; **21:**1652-1659.
18. Patel RB, Desai PS, Desai KR, Chikhalia KH. *Indian J. Chem.,* 2006; **45B:**773-778.
19. Rawal RK, Katti SB, Kaushik-Basu N, Arora P, Pan Z. *Bioorg. Med. Chem. Let.,* 2008; **18(23):**6110-6114.
20. Kulabas N, Özsavcı D, Leyssen P, Neyts J, Küçükgüzel I. *J. Pharm.,* 2017; **21(2):** 371-384.
21. Ottana R, Maccari R, Giglio M, Del Corso A, Cappiello M, Mura U, *Eur. J. Med. Chem.,* 2011; **46(7):**2797-2806.
22. Agarwal A, Saxena KK, Srivastava VK, Kumar A. *Eur. J. Med. Chem.,* 2006; **41(10):**1223-1229.
23. Gursoy A, Terzioglu N. *Turk. J. Chem.,* 2005; **29:**247-254.
24. Kishore A, Nampurath GK, Rao MS, Valiathan M, Chamallamudi MR. *Chem. Biol. Interact.,* 2009; **177(3):**242-246.
25. Rojas Ruiz FA, Garcia-Sanchez RN, Martinez-Fernandez AR, Kouznetsov VV. *Med. Chem.,* 2011; **19(15):**4562-4573.
26. Pudhom K, Terauchi H, Inoue H, Kaiser M, Brun R, Ihara M, Takasu K. *Bioorg. Med. Chem.,* 2006; **14(24):**8550-3563.
27. Waisser K, Gergor J, Kubicova L, Kaustova K.Eur. *J. Med. Chem.,* 2000; **35:**733-741.