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FACILE GREEN SYNTHESIS AND ANTIMICROBIAL EVALUATION OF SOME NOVEL THIAZOLIDINONES WITH PYRIMIDINE MOIETY

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ABSTRACT

As a part of systematic investigation of synthesis and antimicrobial activity of 6-methyl-4-(Sub.)Phenyl-2-Oxo/Thioxo-1,2,3,4-Tetrahydropyrimidine-5-(2-Sub.Phenyl, 3-Amido)thiazolidine-4-ones (IVa-l) was achieved from corresponding Mannich Base (IIIa-l) by reaction with mercapto acetic acid and anhydrous zinc chloride for 2-3 minutes in Microwave irradiation. The synthesized compounds have been screened in vitro for their antimicrobial activity against *S. aureus* and *E.coli*. Some of the compounds displayed pronounced biological activity. The resulting products were characterized by IR, ^{1}H NMR and Mass spectroscopic method.

KEY WORDS: MW irradiation, Thiazolidine, Pyrimidine, Mannich bases, Antibacterial activity

INTRODUCTION

MW may be considered as efficient source of heating superior to conventional one, as it offers reduced chemical reaction time from hours to minutes, reduced side reactions and increased yields and it is ‘in situ’ mode of energy conversion. Thiazolidine has fascinated researchers worldwide as this heterocyclic ring system is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activities as it contains S-C=N, an easily metabolized biocidal unit. Thiazolidine-4-One derivatives exhibit [1]anti-HIV, [2]anti-viral, [3]anti-inflammatory, [4]anti-convulsant, [5]anti-diabetic, [6]anti-tubercular, [7]anti-histamine

activities. Similarly, Pyrimidine derivatives exhibit many biological activities viz. [8]anti-tumour, [9]anti-malerial, [10]anti-HIV, [11]anti-inflammatory,etc. As above cited molecules are active pharmacophores, linking together of them would cause a novel drug and may exhibit interesting biological activities. The biological and synthetic significance places this scaffold at a prestigious position in medicinal chemistry research .So we have developed an operationally simple, inexpensive, efficient and environmental benign protocol for synthesis of 6-methyl-4-(Sub.)Phenyl-2-Oxo/Thioxo-1,2,3,4-Tetrahydro pyrimidine -5(2-Sub.Phenyl-3-Amido) thiazolidine-4-one derivatives as per the given scheme.

MATERIALS AND METHODS

All chemicals were of synthetic grade (S.D. Fine Chem. Ltd. Mumbai, India). MP were determined by electro-thermal apparatus and are uncorrected. Products were recrystalized from methanol as a solvent. The purity of compounds was checked by the TLC on silica gel G plates and they were purified by column chromatography on silica gel (60-120 mesh). The microwave used for the synthesis is of LG-Little Chef MS-192 W. The compounds were characterized by IR, ^{1}H NMR and mass spectral analysis. IR spectra were recorded on Perkin-Elmer spectrum in the form of KBr Pellet. ^{1}H NMR was recorded in $CDCl_3$ and DMSO on Perkin-Elmer R-32 spectrum using TMS as internal standard. Mass spectra were recorded on EI-SHIMADZU GC-MS spectrometer. All the compounds were analyzed for C, H and N on Carlo-Erba elemental analyzer.

Experimental Section

Synthesis of Ethyl 6-methyl-2-oxo/thioxo -4-(substituted)phenyl-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (Ia-c)

Different substituted aldehydes (0.01 mole), Ethyl acetoacetate (0.01 mole) and Urea/ Thiourea (0.01 mole) were taken in a flask, added AR grade H_2SO_4 and placed in Micro-Oven for 2-3 min. gave solid. The reaction is monitored by TLC. Product was poured into ice cold water, filtered, washed and weighed.

Synthesis of 6-methyl-4-p-(substituted)phenyl -2-oxo/thioxo-1,2,3,4-tetrahydropyrimidine -5- carbohydrazide (IIa-c)

The compound (I; 0.01 mole) is dissolved in ethanol and added hydrazine hydrate (0.01 Mole) dropwise in flask and placed in Micro-Oven for 3-4 min. gave solid. The reaction is monitored by TLC. Then poured into ice cold water, filtered, washed and weighed.

Synthesis of 6-methyl-4-(substituted)phenyl-2-oxo/thioxo-1,2,3,4-tetrahydropyrimidine-5-Benzyli dene carbohydrazide(IIIa-l)

An equimolar solution of compound II(0.01 mole)in methanol and Benzaldehyde (0.01 mole) in presence of a catalytic amount of glacial acetic acid was placed in a Microwave oven for 3 min. The resulting crude product was purified by passing it through a chromatographic column packed with silica gel using chloroform and methanol (8:2 v/v) as eluent. The resulting purified product was recrystallized by chloroform to give compound (III).

6-methyl-4-(Sub.)Phenyl-2-Oxo/Thioxo-1,2,3,4-Tetrahydropyrimidine-5(2-Sub.Phenyl,3-Amido thiazolidine-4-one (IVa-l)

An equimolar mixture of compound III(0.01 mole) in methanol and Thioglycolic acid (0.01 mole) with a pinch of anhydrous zinc chloride was subjected in a Microwave oven for 3 min. The resulting crude product was purified by passing it through a chromatographic column packed with silica gel using chloroform and methanol(6:4 v/v) as eluent. The resulting purified product was recrystallized by ethanol to give compound (IVa -l).

Spectral Characterization and elemental analysis of synthesized compounds (IVa-l).

6-methyl-4-Phenyl-2-Oxo-1,2,3,4-Tetrahydropyrimidine-5-(2-p-methoxy-Phenyl,3-Amido) thiazolidine-4-one (IVa)

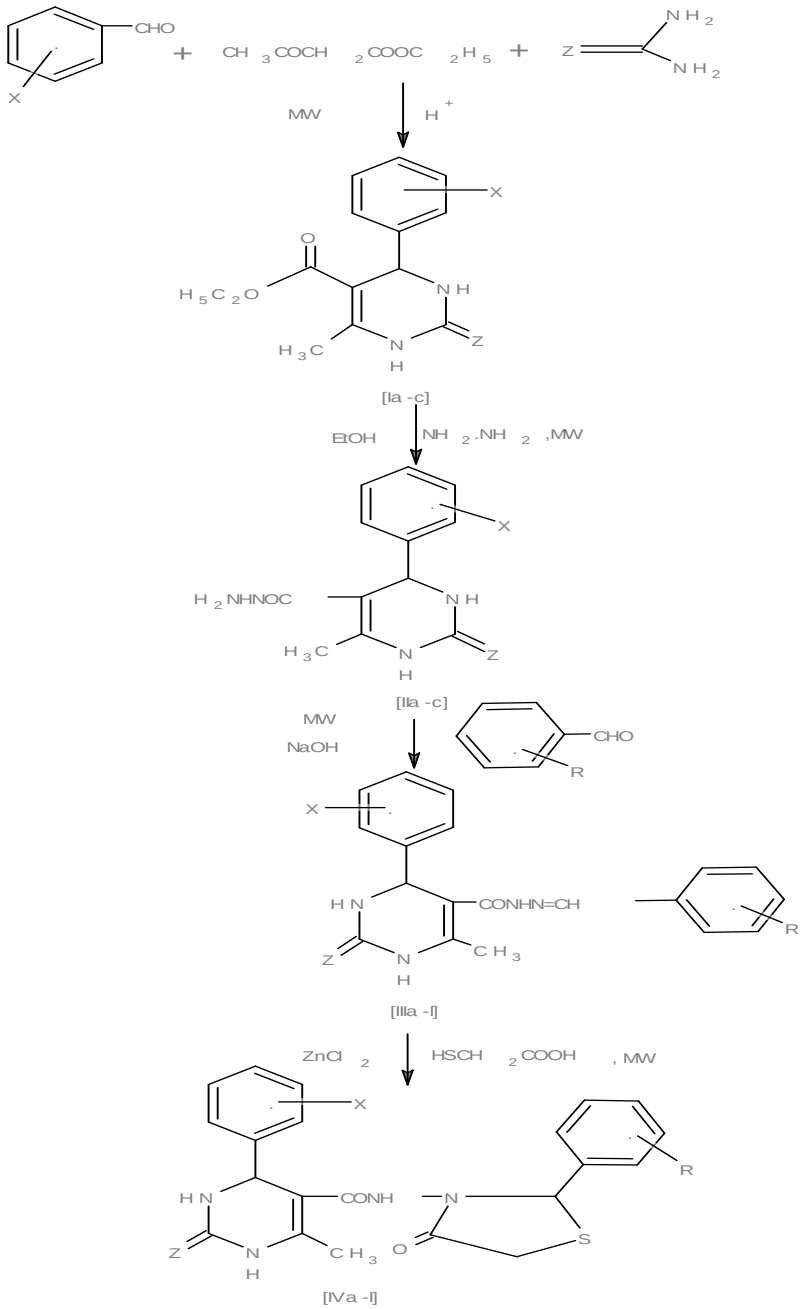
IR : 3334 (-NH), 3052(Ar-H), 1670(>C=O, amido), 1648(>C=C<) ,cm^{-1}

NMR: δ 2.3 (3H,t,-CH_3); 3.20(2H,s,-CH_2-S) , 3.68(1H,s,Ar-CH); 4.3(3H,s,-OCH_3); 5.5(1H,s,-CH); 6.6 (1H,s,NH); 7.1-7.4(9H,m,Ar-H); 7.84(1H,s,-NH); 8.4(1H,s,-NHCO); Anal. MF.$C_{22}H_{22}N_4O_4S$; Calculated: C,60.27; H,5.02; N,12.78. Found: C,60.37; H,5.14; N,12.62

6-methyl-4-Phenyl-2-Oxo-1,2,3,4-Tetrahydropyrimidine-5(2-Phenyl,3-Amido thiazolidine-4-one (IVb)

IR : 3332 (-NH), 3048(Ar-H), 1668(>C=O amido), 1650(>C=C<) ,cm^{-1}

NMR δ 2.3(3H,t,-CH_3); 3.24(2H,s,-CH_2-S) , 3.82(1H,s,Ar-CH); 5.48(1H,s,-CH); 6.6(1H,s,NH); 7.1-7.4(10H,m,Ar-H); 7.78(1H,s,-NH); 8.4(1H,s,-NHCO); Anal. MF.$C_{21}H_{20}N_4O_3S$; Calculated: C,61.76; H,4.90; N,13.72. Found: C,61.80; H,5.00; N,13.8



SCHEME

6-methyl-4-Phenyl-2-Oxo-1,2,3,4-Tetrahydropyrimidine-5(2-p-hydroxy-Phenyl,3-Amido thiazolidine-4-one (IVc)

IR: 3432(-OH) , 3330(-NH), 3049(Ar-H), 1668(>C=O amido), 1652(>C=C<) ,cm^{-1}

NMR: δ 2.3(3H,t,-CH_3); 3.22(2H,s,-CH_2-S) , 3.72(1H,s,Ar-CH); 5.4(1H,s,-CH); 5.9(1H,s,Ar-OH), 6.6(1H,s,NH); 7.2-7.5(9H,m,Ar-H); 7.8(1H,s,-NH); 8.40(1H,s,-NHCO); Anal. MF.$C_{21}H_{20}N_4O_4S$; Calculated: C,59.43; H,4.72; N,13.20. Found: C,59.32; H,4.60; N,13.08

6-methyl-4-Phenyl-2-Oxo-1,2,3,4-Tetrahydropyrimidine-5(2-o-chloro-Phenyl,3-Amido thiazolidine-4-one (IVd)

IR: 3336 (-NH), 3054(Ar-H), 1670(>C=O amido), 1652(>C=C<) ,840(-C-Cl); cm^{-1}

NMR: δ 2.3(3H,t,-CH_3); 3.24(2H,s,-CH_2-S), 3.73(1H,s,Ar-CH); 5.42(1H,s,-CH); 6.58(1H,s,NH); 7.2-7.5(9H,m,Ar-H); 7.78(1H,s,-NH); 8.44(1H,s,-NHCO); Mass;m/z 442(M+),444(M++)Anal. MF.$C_{21}H_{19}N_4O_3SCl$; Calculated: C,56.95; H,4.29; N,12.65. Found: C56.79; H,4.38; N,12.43

6-methyl-4-Phenyl-2-Oxo-1,2,3,4-Tetrahydropyrimidine-5(2--(p-chloro-Phenyl,3-Amido thiazolidine-4-one (IVe)

IR : 3332(-NH), 3050(Ar-H), 1672(>C=O amido), 1652(>C=C<) ,836(-C-Cl); cm^{-1}

NMR: δ 2.32(3H,t,-CH_3); 3.20(2H,s,-CH_2-S), 3.68(1H,s,Ar-CH); 5.4(1H,s,-CH);6.60(1H,s,NH); 7.2-7.5(9H,m,ArH); 7.8(1H,s,-NH); 8.4(1H,s,-NHCO); Mass;m/z :442(M+),444(M++). MF. $C_{21}H_{19}N_4O_3SCl$; Calculated. : C,56.95; H,4.29; N,12.65 Found: C, C56.76; H,4.35; N,12.13

6-methyl-4-Phenyl-2-Oxo-1,2,3,4-Tetrahydropyrimidine-5(2-o-nitro-Phenyl,3-Amido thiazolidine-4-one (IVf)

IR : 3336(-NH), 3049(Ar-H), 1670(>C=O amido), 1652(>C=C<) ,1348(N=O); cm^{-1}

NMR :δ 2.34(3H,t,-CH_3); 3.22(2H,s,-CH_2-S) , 3.76(1H,s,Ar-CH); 5.4(1H,s,-CH); 6.58(1H,s,NH); 7.1-7.3(9H,m,ArH); 7.8(1H,s,-NH); 8.4(1H,s,-NHCO); Anal. MF.$C_{21}H_{19}N_5O_5S$; Calculated: C55.63; H,4.19; N,15.45. Found: C,55.78; H,4.12; N,15.32

6-methyl-4-Phenyl-2-Oxo-1,2,3,4-Tetrahydropyrimidine-5(2-m-nitro-)Phenyl,3-Amido thiazolidine-4-one (IVg)

IR : 3332(-NH), 3048(Ar-H), 1672(>C=O amido), 1650(>C=C<) ,1352(N=O); cm^{-1}

NMR: δ 2.32(3H,t,-CH_3); 3.25(2H,s,-CH_2-S) , 3.8(1H,s,Ar-CH); 5.4(1H,s,-CH); 6.6(1H,s,NH); 7.1-7.3(9H,m,ArH); 7.8(1H,s,-NH); 8.4(1H,s,-NHCO); Anal. MF.$C_{21}H_{19}N_5O_5S$;; Calculated: : C55.63; H,4.19; N,15.45. Found: C,55.72; H,4.22; N,15.52

6-methyl-4-Phenyl-2-Oxo-1,2,3,4-Tetrahydropyrimidine-5(2-p-nitro)-Phenyl,3-Amido thiazolidine-4-one (IVh)

IR ; 3330(-NH), 3052(Ar-H), 1670(>C=O amido), 1648(>C=C<) ,1348(N=O); cm^{-1}

NMR: δ 2.34(3H,t,-CH_3); 3.2(2H,s,-CH_2-S) , 3.7(1H,s,Ar-CH); 5.42(1H,s,-CH); 6.62(1H,s,NH); 7.1-7.3(9H,m,ArH); 7.78(1H,s,-NH); 8.42(1H,s,-NHCO); Anal.

MF.$C_{21}H_{19}N_5O_5S$. Calculated: C55.63; H,4.19; N,15.45. Found: C, 55.5 2; H, 4.30; N, 15.58 .

6-methyl-4-(-p-chloro-)Phenyl-2-Thioxo-1,2,3,4-Tetrahydropyrimidine-5(2-Phenyl,3-Amido)thiazolidine-4-one (IVi)

IR: 3334(-NH), 3052(Ar-H), 1650(>C=C<) , 1249(C=S),842(-C-Cl); cm^{-1}

NMR: δ 2.36(3H,t,-CH_3); 3.22(2H,s,-CH_2-S) , 3.721H,s,Ar-CH); 5.54(1H,s,-CH); 6.64(1H,s,NH); 7.2-7.5(9H,m,ArH); 7.8(1H,s,-NH); 8.4(1H,s,-NHCO); Mass;m/z 458(M+),460(M++)Anal. MF.$C_{21}H_{19}N_4O_2S_2Cl$; Calculated: C,54.96; H,4.14; N,12.21. Found: C,54.84; H,4.25; N,12.36

6-methyl-4-(o-hydroxy)Phenyl-2-Oxo-1,2,3,4-Tetrahydropyrimidine-5(2-p-chloro-phenyl, 3-Amido)thiazolidine-4-one (IV j)

IR :3440(-OH), 3336(-NH), 3048(Ar-H), 1668(>C=O amido), 1648(>C=C<) ,836(-C-Cl); cm^{-1}

NMR: δ 2.3(3H,t,-CH_3); 3.28(2H,s,-CH_2-S) , 3.68(1H,s,Ar-CH); 5.4(1H,s,-CH); 6.62(1H,s,NH); 7.1-7.4(8H,m,ArH); 7.82(1H,s,-NH); 8.42(1H,s,-NHCO); Mass;m/z 458(M+),460(M++)Anal. MF.$C_{21}H_{19}N_4O_4SCl$; Calculated: C,54.96; H,4.14; N,12.21. Found: C,54.84; H,4.22; N,12.32

6-methyl-4-(o-hydroxy) Phenyl-2-Oxo-1,2,3,4-Tetrahydropyrimidine-5(2- o-chloro - Phenyl, 3-Amido)thiazolidine-4-one (IVk)

IR: 3436(-OH), 3330(-NH), 3049(Ar-H), 1670(>C=O amido), 1649(>C=C<) ,848(-C-Cl); cm^{-1}

NMR: δ 2.32(3H,t,-CH_3); 3.22(2H,s,-CH_2-S) , 3.6(1H,s,Ar-CH); 5.42(1H,s,-CH); 6.6(1H,s,NH); 7.1-7.4(8H,m,ArH); 7.8(1H,s,-NH); 8.4(1H,s,-NHCO); A Mass;m/z458(M+), 460(M++) Anal. MF $C_{21}H_{19}N_4O_4SCl$; Calculated : C,54.96; H,4.14; N,12.21 Found : C,54.88; H,4.28; N,12.36.

6-methyl-4-(o-hydroxy-)-Phenyl-2-Oxo-1,2,3,4-Tetrahydropyrimidine-5(2-m-nitro-Phenyl, 3-Amido)thiazolidine-4-one (IV- l)

IR :3440(-OH), 3336(-NH), 3054(Ar-H), 1664(>C=O amido),1654(>C=C<) ,1349(N=O); cm^{-1}

NMR: δ 2.3(3H,t,-CH_3); 3.25(2H,s,-CH_2-S) , 3.621H,s,Ar-CH); 5.4(1H,s,-CH); 6.56(1H,s,NH); 7.1-7.4(8H,m,ArH); 7.9(1H,s,-NH); 8.4(1H,s,-NHCO); Anal. MF.$C_{21}H_{19}N_5O_6S$; Calculated: C,53.96; H,4.06; N,14.98. Found: C,53.82; H,4.12; N,14.82.

Table No.-I : Physical data of synthesized compounds (Ia-IVl)

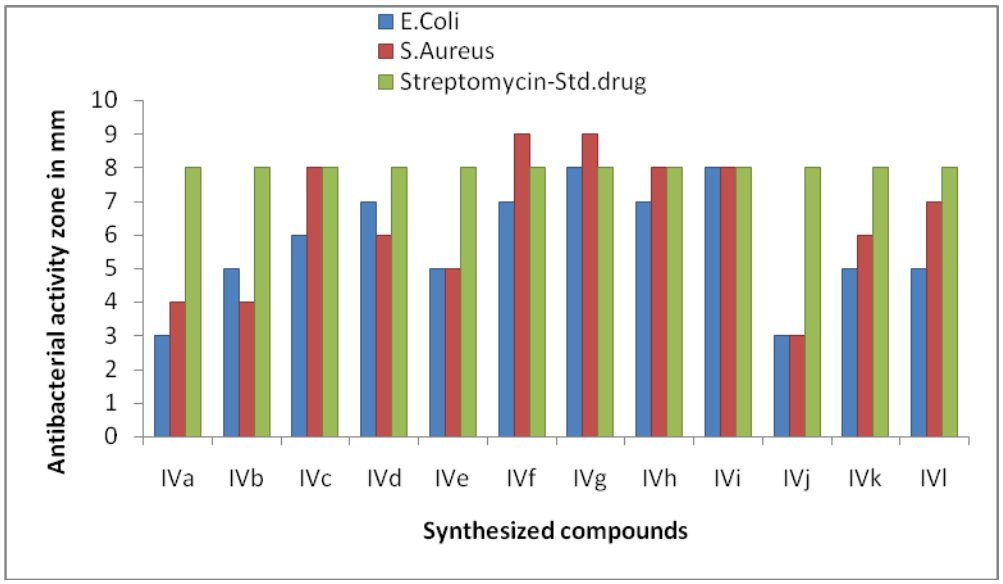
Compound No.	Z	R	R'	M.P. °C	Yield %	MW
Ia	O	-H	-	199	87	260
Ib	S	p-Cl	-	70	79	310.5
Ic	O	o-OH	-	172	80	276
IIa	O	-H	-	258	69	246
IIb	S	p-Cl	-	180	72	296.5
IIc	O	o-OH	-	197	68	262
IIIa	O	-H	p-OCH_3	193	71	364
IIIb	O	-H	-H	198	69	334
IIIc	O	-H	p-OH	244	74	350
IIId	O	-H	o-Cl	231	77	368.5
IIIe	O	-H	p-Cl	219	81	368.5
IIIf	O	-H	o-NO_2	234	68	379
IIIg	O	-H	m-NO_2	211	65	379
IIIh	O	-H	p-NO_2	205	69	379
IIIi	S	p-Cl	-H	160	83	384.5
IIIj	O	o-OH	p-Cl	178	79	384.5
IIIk	O	o-OH	o-Cl	162	72	384.5
IIIl	O	o-OH	m-NO_2	173	68	395
IVa	O	-H	p-OCH_3	182	83	438
IVb	O	-H	-H	178	79	408
IVc	O	-H	p-OH	252	80	424
IVd	O	-H	o-Cl	241	85	442.5
IVe	O	-H	p-Cl	238	76	442.5
IVf	O	-H	o-No_2	221	78	453
IVg	O	-H	m-NO_2	172	75	453
IVh	O	-H	p-NO_2	184	81	453
IVi	S	p-Cl	-H	178	84	458.5
IVj	O	o-OH	p-Cl	149	78	458.5
IVk	O	o-OH	o-Cl	173	81	458.5
IVl	O	o-OH	m-NO_2	182	77	467

Table-II : Antimicrobial activity of Synthesized compounds(IVa-l):

Compound No.	E.Coli	S.Aureus
IVa	3	4
IVb	5	4
IVc	6	8
IVd	7	6
IVe	5	5
IVf	7	9
IVg	8	9
IVh	7	8
IVi	8	8

IVj	3	3
IVk	5	6
IVl	5	7
Streptomycin	8	8

The synthesized compounds (IVa-l) were screened for their in vitro antimicrobial activities by using disc diffusion method.They were screened for Gram positive bacteria, staphylococcus aureus and Gram negative bacteria viz. Escherichia coli by measuring the zone of inhibition at concentrations of 100 mg/ml. The standard used for comparison was streptomycin. Compounds IVg and IVh exhibited activities comparable to the standard against both Gram positive and Gram negative bacteria- indicating that electron withdrawing substituent (-NO_2) at meta and para position in phenyl ring of thiazolidine moiety enhances the property. Compounds IVd, IVf, IVi and IVl exhibited moderate while rest from the list showed poor activity.



RESULTS AND DISCUSSION

Knowing that Thiazolidine-4-One substituted with pyrimidine moiety enhances the antimicrobial activity, we synthesized totally new Thiazolidine-4-One derivatives from Synthesis of Ethyl 6-methyl-2-oxo/thioxo -4-phenyl-1,2,3,4-tetrahydro pyrimidine-5-carboxylate as a substrate by microwave irradiation (2-4 mins.), an environmentally benign synthetic root. The yield of all synthesized compounds were found to be in the range of 60-87%. The titled compounds were characterized by melting points and R_f values by using Ethyl acetate (20%) and n- hexane (80%) as a solvent system. The synthesized derivatives I (a-c), II (a-c), III (a-l) and IV (a-l) were established on the basis of elemental analysis, NMR

and Mass spectral analysis. The assigned structures were supported by spectral data. In H^1 NMR spectra of compounds showing triplet at 1.4 ppm due to $–CH_3$ and quartet at 3.4 ppm due to $–CH_2$ of ester group in I (a-c) were absent in II (a-c); instead a signal appeared at 4.3 ppm for them showing the presence of $–NO_2$ group which later on disappeared in the compounds III (a-l); while formation of IV (a-l) was confirmed by the appearance of singlet at 3.2 ppm (2H) due to the presence of $–CH_2$-S of thiazolidine. IR spectra also supported above fact. It showed the presence of ester group in I (a-c), its absence and appearance of $–NH_2$ band in II (a-c) which latter on disappeared in III (a-l). Mass spectra of thiazolidine- 4-One derivatives were useful and revealed molecular iron peaks corresponding to molecular formulae. Compounds containing Cl showed (M+ and M+2) peaks in 1:3 ratio as shown in the table. To put the result in a nutshell, some of the synthesized Thiazolidine-4-One derivatives exhibited biological activities comparable with those of the standard where as the activity exhibited by IVg against S. Aureus is more pronounced than that of a standard drug and that was the aim of the present study.

CONCLUSION

We have demonstrated microwave assisted eco-friendly, operationally simple and time efficient protocol for the synthesis of thiazolidine-4-one derivatives with pyrimidine moiety. Reaction procedures are very simple and yield of products are also excellent. All synthesized compounds were screened for antimicrobial activities and found to be moderate to excellent activity as compare to standard drug. A few exhibited activities comparable to those of a standard drug while one of them showed antibacterial activity more pronounced than that of the standard drug.

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