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Synthesis of 2-imino 4-thiazolidinone derivatives and its antibacterial activity

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ABSTRACT

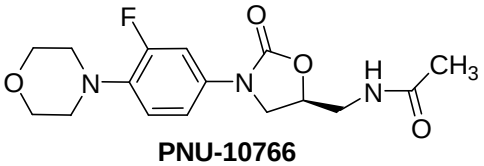
A series of novel (4-morpholinophenylimino)-thiazolidin- 4-one, (3-fluoro-4-yl-morpholin-4-yl-phenylimino) thiazolidin-4-one derivatives were synthesized and were tested for their antibacterial and antifungal activities. These compounds showed moderate in vitro activities against the microorganisms tested.

.

Keywords: 4-Morpholinophenylimino, 3-fluoro-4-yl-morpholin-4-yl-phenylimino thiazolidin-4-one, antibacterial, antifungal.

INTRODUCTION

4-Pheny-morpholine derivatives were reported to possess antimicrobial [1-2] and anti-inflammatory [3-5] activities. Linezolide (PNU-10766, commercially available antimicrobial drug) possess 4-(2-flourophenyl)morpholine moiety, Thiazolidin-4-one derivatives are known to exhibit diverse bioactivities such as anti-convulsant[6], anti-diarrheal[7], anti-platelet activating factor[8], anti-histaminic[9], anti-microbial [10], anti-diabetic [11], cycloxygenase inhibitory [12], Ca^{2+} channel blocker [13], PAF antagonist [14], cardio protective [15], anti-ischemic [16], anticancer [17], antiHIV [18], non-peptide thrombin receptor antagonist[19] and tumor necrosis factor-α antagonist activities. [20]. These observations led to the conception that 5-benzylidene derivatives of 2-(4-morpholinophenylimino) - thiazolidin- 4-one and 3-ethyl-2-(3-fluoro-4-morpholin-4-yl-phenylimino)-thiazolidin-4-one would possess potential antimicrobial properties.



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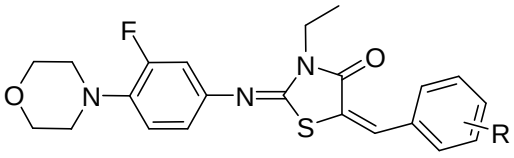

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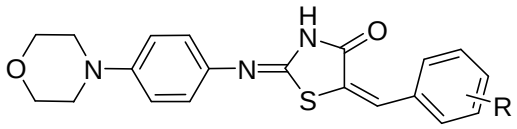


12

EXPERIMENTAL SECTION

Progress of reaction was monitored by silica gel-G coated TLC plates in Ethyl acetate: Hexane system (5:5). The spot was visualized by exposing dry plate in iodine vapours. Melting points were determined by the melting point determination apparatus (TEMPO) in open capillary tubes and are uncorrected. Infrared spectra were recorded on Schimadzu 8201 PC, FTIR spectrophotometer (ν_{max} in cm^{-1}) spectrophotomer in KBr phase. Proton NMR spectra were recorded on Bruker Advance II 400 & 200 NMR Ultra Shield Spectrometer using DMSO-d_6/$CDCl_3$ as a solvent and tetramethyl silane as internal standard. Chemical shift value is expressed in delta parts per million (ppm).

General Procedure for preparation 3-Ethyl-2-(3-fluoro-4-morpholin-4-yl-phenylimino) thiazolidin-4-one (5): To a solution of N-4-morpholinophenylimino N'-ethylthiourea (**2**) (1 mmol) and ethyl bromoacetate and disopropylethylamine (1.2 mmol), in ethanol and the resulting reaction mixture was refluxed at 80-90^{0}C for 3h. After completion of the reaction (TLC check), Ethanol was evaporated cold water was added to residue and extracted with Ethyl acetate (3 ×20 ml). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was recrystalised using absolute ethanol to get (**5**) 96%.

General Procedure for preparation (5E)-2-(3-fluoro-4-morpholinophenylimino)-5-benzylidene-3-ethylthiazolidin-4-one (6a-g):
A mixture iminothiazolidin-4-one (**5**) (1 mmol), aldehyde (1.1 mmol) and diisopropylethylamine (1.6 mmol) in absolute ethanol was refluxed at 90-95 ^{0}C. After completion of the reaction (TLC check), Ethanol was evaporated cold water was added to residue and extracted with Ethyl acetate (3 ×20 ml). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was recrystalised using absolute ethanol to get (**6**).

General procedure for synthesis of 2-(4-morpholin-4-yl-phenylimino) thiazolidin-4-one(11)
A solution of 2-chloro-N-(morpholinophenylimino acetamide (5 mmol) and ammonium thiocyanate(10 mmol) in 20 ml of absolute ethanol was refluxed for 3 h and allowed to stand overnight. The precipitate was filtered, washed with water and then recrystallised in absolute ethanol get regioisomer (**11**) 92%.

General Procedure for preparation (5E)-2-(4-morpholino phenyl imino)-5-benzylidene thiazolidin-4-one (12a-g):

A mixture iminothiazolidin-4-one (**11**) (1 mmol), aldehyde and sodium acetate (1.5 mmol) in glacial acetic acid was refluxed at 120-130 ^{0}C. After completion of the reaction (TLC check), cold water was added to reaction mixture, solid separated was filtered and the crude product was recrystalised using absolute ethanol to get (**12a-g**).

Spectroscopic data of representative compounds

3-Ethyl-2-(3-fluoro-4-morpholin-4-yl-phenylimino)thiazolidin-4-one **(5):** Reddish solid; ^{1}H NMR (DMSO-d_6, 200MHz): δ 1.16 (t, J = 6.9 Hz, 3H), 2.97 (t, J = 3.4 Hz, 4H), 3.72-3.79 (m, 6H), 4.02 (s, 2H), 6.70- 6.82 (m, 2H), 6.97-7.06 (m, 1H); MS (*m/z*): 324.5[M^+ +1]; IR (KBr): 1709, 1630.

2-(4-morpholin-4-yl-phenylimino) thiazolidin-4-one **(11):** White solid
^{1}H NMR (DMSO-d_6, 400MHz): δ 3.03-3.06 (t, J = 4.8 Hz, 4H), 3.71-3.73 (t, J = 4.8 Hz 4H), 4.07 (s, 2H), 6.90- 6.92 (d, 2H), 7.41-7.43 (d, 2H),10.19 (s, 1H exchangeable with D_2O); MS (*m/z*): 278.3[M^+ +1]; IR (KBr): 3158, 1730, 1568

(5E)-3-Ethyl-2-(3-fluoro-4-morpholinophenylimino)-5-(4-Hydroxybenzylidene)thiazolidin-4-one **(6a):** Yellow solid; mp: 123-125 ^{0}C; ^{1}H NMR ($CDCl_3$, 400MHz): δ 1.33-1.37 (t, J = 7.2 Hz, 3H), 3.16 (bs, 4H), 3.93 (bs, 4H), 4.03-4.08 (q, J =7.2 Hz 2H), 6.77-6.81 (d, 2H), 6.90-6.95(d, 2H), 7.20-7.25 (m, 2H), 7.26-7.37(d, 1H), 8.30(s, 1H); MS (*m/z)* 428.5 [M^+ +1]; IR (KBr): 3350, 2852, 2821, 1705, 1637, 1504, 1377, 1338, 1268, 1116, 1043, 923.

(5E)-3-Ethyl-2-(3-fluoro-4-morpholinophenylimino)-5-(4-methoxybenzylidene)thiazolidin-4-one **(6b):** Yellow solid; mp: 138-140 ^{0}C; ^{1}H NMR ($CDCl_3$, 400MHz): δ 1.34 (t, J = 7.0 Hz, 3H), 3.10-3.14 (m, 4H), 3.83 (s, 3H), 3.90-4.00 (m, 4H), 4.03 (q, J =7.0 Hz, 2H), 6.75-6.82 (m, 2H), 6.94(d, J = 8.8 Hz, 2H), 6.98-7.10 (m, 1H), 7.41(d, J = 8.8 Hz, 2H), 7.71(s, 1H); MS (*m/z)* 442.5 [M^+ +1]; IR (KBr): 2968, 2852, 2821, 1705, 1637, 1504, 1377, 1338, 1268, 1116, 1043, 923.

(5E)-3-Ethyl-2-(3-fluoro-4-morpholinophenylimino)-5-(4-hydroxy-3-methoxybenzylidene)thiazolidin-4-one **(6c):** Yellow solid; M.P.: 176-178 ^{0}C; ^{1}H NMR ($CDCl_3$, 200MHz): δ 1.34(t, J = 7.0 Hz, 3H), 1.59(bs, 1H, exchangeable with D_2O), 3.11 (t, J = 4.4 Hz, 4H), 3.83(s, 3H), 3.89(t, J=4.4 Hz, 4H), 4.03(q, J= 7.0 Hz, 2H), 6.74-6.82(m, 2H), 6.90-7.00(m, 3H), 7.41(d, J= 8.7 Hz, 1H), 7.70 (s, 1H); MS (*m/z)*: 458.5 [M^+ +1]; IR(KBr): 3541, 2969, 2854, 2824, 1710, 1639, 1509, 1380, 1339, 1270, 1115, 1043, 923.

(5E)-3-Ethyl-2-(3-fluoro-4-morpholinophenylimino)-5-(24,6-trimethoxybenzylidene)thiazolidin-4-one **(6d):** Yellow solid; mp: 133- 135 ^{0}C; ^{1}H NMR ($CDCl_3$, 200MHz):: δ 1.34 (t, J = 7.0 Hz, 3H), 3.10(t, J = 4.6 Hz, 4H), 3.89 (s, 9H), 3.89 (t, J= 4.6 Hz, 4H), 4.02(q, J = 7.0 Hz, 4H), 6.07 (s, 2H), 6.72-6.94 (m, 3H), 7.98 (s, 1H); MS (*m/z)*: 502.5 [M^+ +1]; IR (KBr): 2954, 2902, 2853, 2820, 2360, 2333, 1655, 1640, 1620, 1550 ,1369, 1118, 915.

(5E)-5-((1H-indol-3-yl)methylene)-3-ethyl-2-(3-fluoro-4-morpholinophenylimino)thiazolidin-4-one **(6e):** Yellow solid; mp: 137-139 ^{0}C; ^{1}H NMR ($CDCl_3$, 400MHz): δ 1.36 (t, J = 7.0 Hz, 3H), 3.11(t, J =4.4 Hz, 4H), 3.90 (t, J = 4.4 Hz, 4H), 4.05(q, J = 7.0 Hz, 2H), 6.78-6.83(m, 2H), 6.96(t, J = 9.0 Hz, 1H), 7.28-7.32 (m, 2H), 7.42(d, J =7.6 Hz, 1H), 7.44(m, d, J =2.8 Hz, 1H), 7.85(d, J =7.6 Hz, 1H), 8.11(s, 1H), 8.62(bs, 1H, exchangeable with D_2O); MS (*m/z)*: 451.5 [M^+ +1]; IR (KBr): 3403, 3174, 2955, 2891, 2837, 2700, 2360, 2251, 1701, 1633, 1602, 1114, 923.

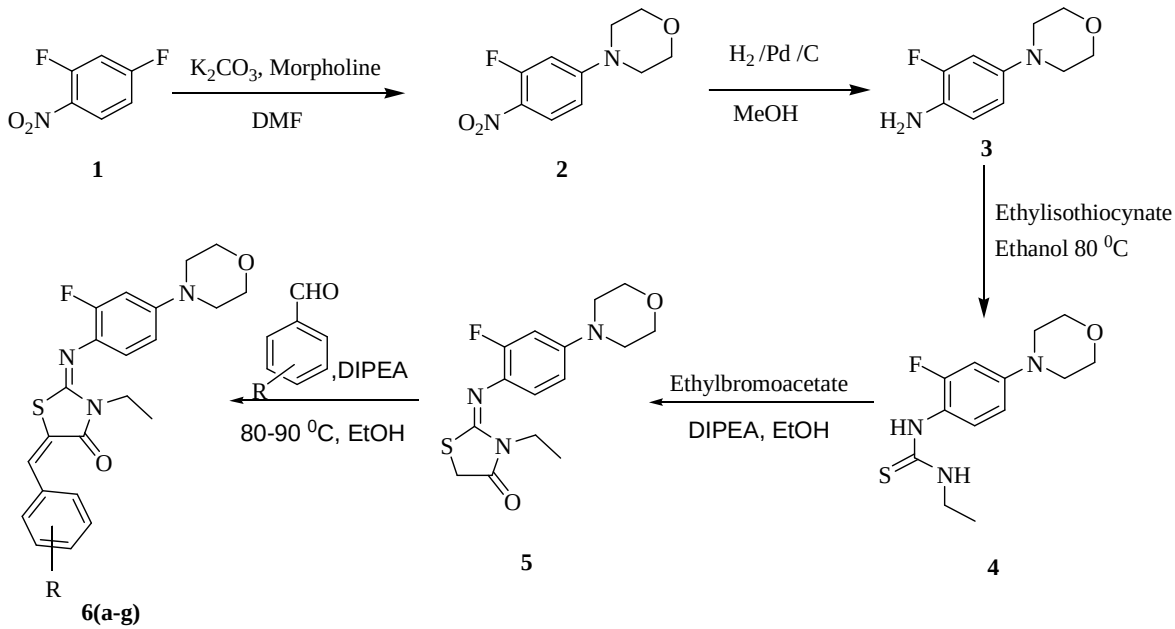
*(2E, 5E)-5-(4-hydroxybenzylidene)-2-(4-morpholinophenylimino) thiazolidin-4-one(**12a**)*: Off white solid mp: 187-189 ^{0}C; ^{1}H NMR (DMSO-d_6, 400MHz): δ 3.11(t, 4H), 3.74(t, 4H), 6.85-6.99(m, 5H), 7.45-7.64(m, 4H), 10.16(bs, 1H, exchangeable with D_2O); MS (*m/z)*: 382.6 [M^+ +1]; IR (KBr): 3156, 1732, 1567, 1109, 930

*(2E, 5E)-5-(4-methoxoxybenzylidene)-2-(4-morpholinophenylimino) thiazolidin-4-one(**12b**)*: Off white solid mp: 187-189 ^{0}C; ^{1}H NMR (DMSO-d_6, 400MHz): δ 3.16(t, 4H), 3.80(t, 4H), 3.86(s, 3H), 7.05-7.21(m, 5H), 7.61-7.82(m, 4H), 10.27(bs, 1H, exchangeable with D_2O); MS (*m/z)*: 396.6 [M^+ +1]; IR (KBr): 3161, 1738, 1570, 1119.

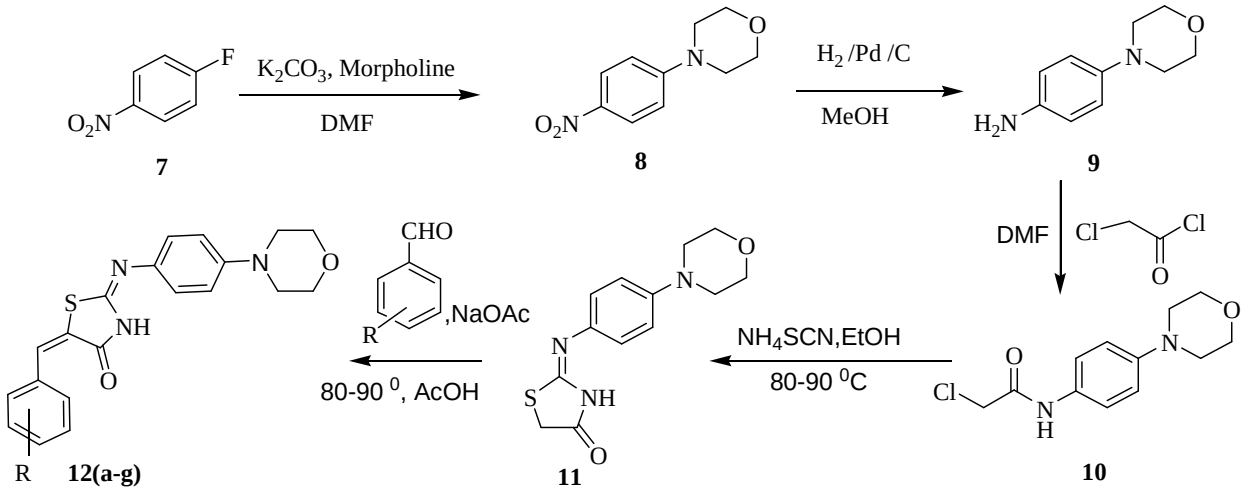
ANTIMICOBACTERIAL ACTIVITY

The synthesized compounds were evaluated for their *in vitro* antimicrobial activity against Gram-positive bacteria: *Staphylococous aureus* (NCLM- 2602), *Bacillus subtillis* (NCLM-2458), Gram negative *Escherichiacoli* (NCLM- 2809) and fungal strain *Aspergillus niger (*NCLM- 617), *Rhizopus otyzae* (NCLM- 1299).

The antimicrobial activity of the compuond was assayed by antimicrobial susceptibilty test [21]. 100 µl of 24h growth of each microorganism was spread on the surface of nutrient agar for bacteria (Mac Conkey's agar for *Escherichia coli*) and potato dextrose agar for fungi, in Petri plates. 50 µl compound at the concentration of 100 µg/ml in DMSO saturated on discs of 6mm diameter were kept on agar surface. The plates refrigerated for two hours to allow prediffusion of the compound from the discs in to the seeded agar layer and then incubated at 37 ^{0}C for 24h for bacteria and 28 ^{0}C for 48h for fungi. Zones of inhibition were measured in mm and size of the disc was subtracted from the zone size to measured final activity. DMSO saturated discs served as solvent control or negative control and Streptomycin saturated discs (30 µg) for bacteria and Nystatin (30 µg) for fungi as a reference or positive control. The MIC for the synthesized compound was given in table 2



Scheme-1 (5E)-2-(3-fluoro-4-morpholinophenylimino)-5-benzylidene-3-ethylthiazolidin-4-one



Scheme-2 Synthesis of (5E)-2-(4-morpholinophenylimino)-5-benzylidenethiazolidin-4-one

RESULTS AND DISCUSSION

Our synthetic strategy for thiazolidinone derivatives is illustrated in **Scheme 1**.and **Scheme-2 .**The synthesis starts with reaction of 2,4-difluoro-1-nitro-benzene (**1**) with with morpholine and potassium carbonate in dimethylformamide at 80^0C afforded 4-(3-Fluoro-4-nitro-phenyl)-morpholine (**2**) which on catalytic reduction by using H_2/Pd/C in methanol afforded 2-fluoro-4-morpholin-4-yl-phenylamine (**3**) [22]. The phenylamine (**3**) was futher treated with ethylisothiocynate in ethanol at 80^0C to afford the 1-ethyl-3-(2-fluoro-4-morpholin-4-yl-phenyl)-thiourea (**4**) [23]. 1-Ethyl-3-(2-fluoro-4-morpholin-4-yl-phenyl)-thiourea(**4**) was treated with ethylbromoacetate and disopropylethylamine in ethanol at 90^0C, the key intermediate 3-ethyl-2-(2-fluoro-4-morpholin-4-yl-phenylimino)-thiazolidin-4-one (**5**) was isolated with 94% yield. This key intermediate iminothiazolidin-4-one (**5**) on Knoevenagel condensation with different substituted aryl aldehydes in presence of disopropylethylamine as a base in absolute ethanol afforded the 5-Benzylidene-3-(3-fluoro-4-yl-morpholin-4-yl-phenylimino)-thiazolidin-4-one **6** (**a-g**) in excellent yields (**Table 1**).

Using the similar strategy the synthesis of (5E)-2-(4-morpholinophenylimino)-5-benzylidenethiazolidin-4-one was carried out the synthesis starts with reaction of 4-fluoro-1-nitro-benzene (**7**) morpholine and potassium carbonate in dimethylformamide at 80^0C afforded 4-(4-nitro-phenyl)-morpholine (**8**) which on catalytic reduction by using H_2/Pd/C in methanol afforded 4-morpholin-4-yl-phenylamine (**9**) [22]]. The phenylamine (**9**) was futher treated with Chloroacetyl chloride in DMF at R.T to afford the 2-chloro-N-(4-morpholinophenyl)acetamide (**10**) . 2-chloro-N-(4-morpholinophenyl)acetamide (**10**) was treated with Ammonium thiocynate in ethanol at 90^0C, afforded key intermediate (E)-2-(4-morpholinophenylimino)thiazolidin-4-one (**11**) was isolated with 91% yield. This key intermediate iminothiazolidin-4-one (**11**) on Knoevenagel condensation with different substituted aryl aldehydes in presence of sodium acetate as a base in glacial acetic acid afforded the (5E)-2-(4-morpholinophenylimino)-5-benzylidenethiazolidin-4-one **12** (**a-g**) in excellent yields

The newly synthesized compounds **6(a-g)** and **12(a-g)** were established on the basis of IR, ^{1}H NMR and MASS spectroscopy method. ^{1}H NMR spectrum of compound **5** shows a singlet at 4.02 ppm for two protons is characteristic value of C-5 protons of the iminothiazolidinone nucleus. The strong absorption bands at 1708cm^{-1} and at 1620 cm^{-1} confirms the presence of C=O and C=N functional groups respectively.

Table-1

Comp No.	Aldehyde	Yield	Molecular Formula	Melting Point
6a	4-Hydroxy benzaldehyde	96	$C_{22}H_{22}FN_3O_3S$	123-125^{0}C
6b	4-Methoxy benzaldehyde	96	$C_{23}H_{24}FN_3O_3S$	138-140^{0}C
6c	4-Hydroxy, 3-methoxy benzaldehyde	92	$C_{23}H_{24}FN_3O_4S$	176-178^{0}C
6d	2,4,6-Trimethoxy benzaldehyde	95	$C_{25}H_{28}FN_3O_5S$	133-135^{0}C
6e	1H-Indol-3-carboxaldehyde	95	$C_{24}H_{23}FN_4O_2S$	137-139^{0}C
6f	4-Cyano benzaldehyde	92	$C_{23}H_{21}FN_4O_2S$	127-129^{0}C
6g	4-Nitro benzaldehyde	97	$C_{22}H_{21}FN_4O_4S$	201-203^{0}C
12a	4-Hydroxy benzaldehyde	92	$C_{20}H_{19}N_3O_3S$	164-168^{0}C
12b	4-Methoxy benzaldehyde	97	$C_{21}H_{21}N_3O_3S$	171-173^{0}C
12c	4-Hydroxy, 3-methoxy benzaldehyde	95	$C_{21}H_{21}N_3O_4S$	145-147^{0}C
12d	2,4,6-Trimethoxy benzaldehyde	96	$C_{23}H_{25}N_3O_5S$	178-180^{0}C
12e	1H-Indol-3-carboxaldehyde	95	$C_{22}H_{20}N_4O_2S$	179-181^{0}C
12f	4-Cyano benzaldehyde	94	$C_{21}H_{18}N_4O_2S$	153-156^{0}C
12g	4-Nitro benzaldehyde	95	$C_{20}H_{18}N_4O_4S$	193-196^{0}C

Table-2 Biologial Evaluation of synthesized compounds[a]

compound[b]	Zone Of Inhibition (mm)[3]				
	Bactria			Fungi	
	Staphylococous aureus NCLM- 2602	*Bacillus subtillis* NCLM- 2458	*Escherichia coli* NCLM- 2809	*Aspergillus niger* NCLM- 617	*Rhizopus otyzae* NCLM- 1299
6a	1	3	2	3	2
6b	3	2	3	3	1
6c	3	2	3	3	3
6d	5	8	5	4	4
6e	2	2	3	4	3
6f	3	2	2	2	1
6g	2	2	1	1	2
6h	3	2	2	2	1
12a	-	-	-	-	-
12b	-	-	1	1	1
12c	1	2	2	1	1
12d	2	1	1	1	1
12e	1	1	1	2	1
12f	2	1	2	1	2
12g	1	2	2	1	1
Standard Antibiotic[c]	10	8	9	8	9

a. These results are average results of four experiments.
b. These compounds were used at concentration of 100 µg/ml.
c. Streptomycin for bacteria and Nystain for fungi were used at concentration of 30 µg.

Similarly ^{1}H NMR of compound (**11**) showed a singlet at 4.07 ppm for two protons and singlet at 10.19 which is exchangeable with D_2O. confirms the formation of iminothiazolidinone ring with free NH group and The strong absorption bands at 1730cm^{-1} and at 1558 cm^{-1} and 3158 cm^{-1} confirms the presence of C=O and C=N and NH functional groups respectively. The Knoevenagel products 6**(a-g)** and **12(a-g)** shows disappearance of C-5 protons. The mass spectra of the iminothiazolidinone derivatives were showed molecular ion peak corresponding to their molecular formula.

The newly synthesized compounds were tested to evaluate their antibacterial and antifungal activity. Some of these compounds were found to exhibit moderate antibacterial and antifungal activity against different species of bacteria and fungi. From the activity data (**Table 2**) it was observed that among all the compounds tested, compound **6d** shows good activity against all the tested bacteria and fungi. Among all tested bacteria and fungi compound **6d** showed good activity against *staphylococococous aureus* (inhibition 5 mm, standard showed 10 mm) and *Bacillus subtillis* (inhibition 8 mm, standard showed 8 mm). Among the other compounds **6a, 6b,** shown moderate activity against *Escherichia coli* and *Aspergillus Niger* compounds **6c** and **6e** showed moderate activity against *Aspergillus Niger* and *Rhizopus Otyzae* fungi. Compounds **12(a-g)** does not showed good activity against all bacteria and fungi.

CONCLUSION

In summary, we have synthesized a new series of Iminothiazolidinone derivatives containing 4-morpholinophenylimino, 3-fluoro-4-yl-morpholin-4-yl-phenylimino ring systems. Further these compounds were evaluated for their antimicobacterial activity. Some of the compounds showed moderate activity against gram positive and gram negative bacterial strains and fungi. Compound 6d was most active among all the synthesized compounds.

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