

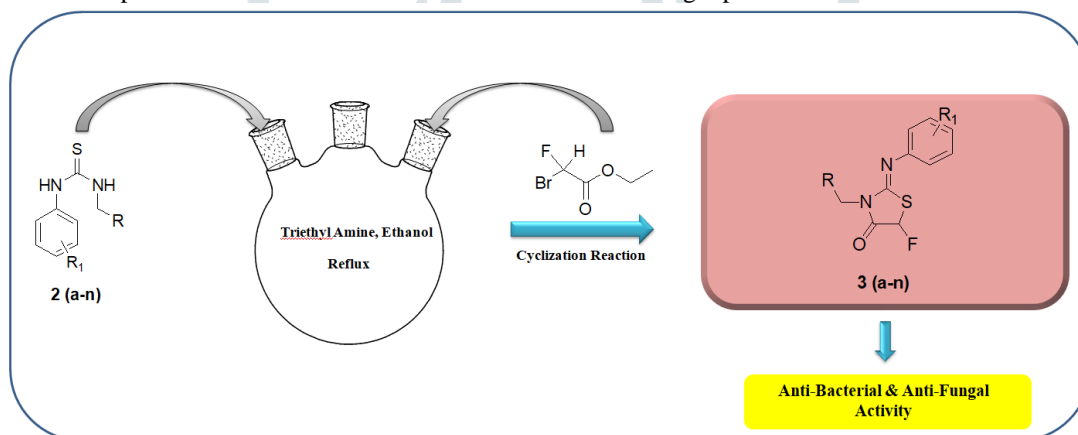


SYNTHESIS OF NOVEL FLUORINATED IMINOTHIAZOLIDINONE AND EVALUATION OF THEIR IN-VITRO ANTIMICROBIAL POTENTIALS

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Abstract : A series of novel 3-alkyl-5-fluoro-2-phenylimino-thiazolidin-4-one derivatives were synthesized by intramolecular cyclization of ethylbromofluoroacetate with substituted thiourea derivatives using normal base catalysed reaction on the synthesized iminothiazolidinone core. Synthesized fluorinated the compounds were characterized using ¹H, ¹⁹F, mass and IR spectroscopy. These compounds were tested for their antibacterial and antifungal potentials.



Index Terms: fluorine, alkylisothiocyanate, ethylbromofluoroacetate, antibacterial, antifungal activity.

I. INTRODUCTION

The first and foremost aims of organic and medicinal chemistry researcher is to plan, synthesis and making of molecules having beneficial medicinal properties for humans. Therefore, the development of innovative drug or lead compound having ability to a key to the difficult problem of resistant to current available drug is the need of the hour. Some of the small heterocyclic fragments act as highly functionalized scaffolds like 4-thiazolidinones and its derivatives. Fluorine(1) has identity as 'bio isostere' of the Hydrogen and hydroxyl moiety in medicinal chemistry. Fluorine(1) is more electronegative than hydrogen on Pauling's scale and it has the matching atomic radius that of hydrogen hence H-atom can be swapped by F-atom. Inset of fluorine atoms in a possible drug like molecules can have histronic effects on the characteristics of that molecule such as resulting in them more selective, enhancing their effectiveness, making them easier to inject, etc. Therefore, around a fifth of all commercial drugs today available have at least one fluorine substituent in its structure. Pfizer's lipid-lowering drug "Lipitor" has an aromatic fluorine substituent in it. Linezolid is known as antimicrobial drug of oxazolidinone class a possesses a fluorine atom in the 4-morpholino-phenyl imino ring.

Thiazolidinone(2-8) ring is called "wonder nucleus" for displaying innumerable biological actions. In today's scientific world interest is increased in synthesis and pharmacological evaluation(9-12) of imino-thiazolidinone containing molecules. Thiazolidinone ring also give rise many products which demonstrates many pharmacological effects, few of these compounds revealed activities(13-16) like anticonvulsant(17), antimicrobial(18-21), anticancer(22-27), anti-HIV(28), Ca²⁺ channel blocker(29), PAF antagonist(30), cardioprotective(31), antidiarrheal(32), antidiabetic(33,34), antihistaminic(35), anti-ischemic(36), cyclooxygenases inhibitory(37), anti-platelet activating factor(38), non-peptide thrombin receptor antagonist(39) and tumour necrosis factor- α antagonist activities(40). In this attempt, we made various Novel 3-alkyl-5-fluoro-2- phenylimino-thiazolidin-4-

one. having Fluorine substituent at 5th position of iminothiazolidinone ring on which in vitro anti-bacterial and antifungal activity is accomplished.

II. RESULTS AND DISCUSSION:

2.1 Chemistry:

Chemistry

Reaction scheme was proposed by transforming substituted aniline compounds to its thiourea derivatives using thiocyanate synthon and then reacted with ethylbromofluoroacetate to construct fluorine containing iminithiazolidinone ring. designed synthetic scheme starts with a reaction of (4-Amino-phenyl)-fluoro-acetic acid methyl ester **1g** on reaction with alkyl isothiocyanate in absolute ethanol at 90°C furnishes Fluoro-[4-(3-methyl-thioureido)-phenyl]-acetic acid methyl ester **2g**. The synthesized thiourea intermediate Fluoro-[4-(3-methyl-thioureido)-phenyl]-acetic acid methyl ester **2g** was further treated with ethyl bromo fluoroacetate in absolute ethanol using triethylamine as a base at 90°C to obtain Fluoro-[4-(5-fluoro-3-methyl-4-oxo-thiazolidin-2-ylideneamino)-phenyl]-acetic acid methyl ester **3g** as a white sticky gum with 81%. Yield. Formation of desired compound was confirmed by using ¹H and ¹⁹F nmr spectroscopy. ¹H nmr shows Characteristic doublet between 6.72- 6.91 ppm with coupling constant of $J\{HF\} = 55.8$ Hz, and presence of peak at -157.9 ppm in ¹⁹F nmr confirms the formation of iminothiazolidinone ring with F atom at desired position. Mass spectroscopic data also supports the formation of desired compound.

In vitro antibacterial activity

Synthesized compounds [**3 a-n**] were tested to evaluate their antibacterial and anti fungal potential. From the activity data in **Table 1**, it was observed that all the novel fluorinated 3-Ethyl-2-(2,3,4-trifluoro-phenylimino)-thiazolidin-4-one compounds were evaluated and showed excellent results for antibacterial against *Escherichia coli* and *Serratia marcescens* and antifungal activity against *Aspergillus Niger* and *Rhizopus Ostoyae* fungi. Compounds **3e**, **3f**, **3g**, **3h**, **3k** and **3l** showed excellent results for both the activities among which compound **3g** and **3h** with fluorine functional group within ester group exhibited the best activity among all the tested compounds.

Table 1. Zone of Inhibition (mm) values of 3-alkyl-5-fluoro-2- phenylimino-thiazolidin-4-one(3a-n) based on antimicrobial activity study

Compound No.	Zone of Inhibition (mm)			
	Bacteria		Fungi	
	<i>Serratia marcescens</i> NCLM No.2602	<i>Escherichia coli</i> NCLM No.2809	<i>Aspergillus Niger</i> NCLM No.617	<i>Rhizopus Ostoyae</i> NCLM No.1299
3a	6.9	7.2	5.2	5.3
3b	7.7	8.9	6.5	6.3
3c	10.2	10.1	11.2	10.9
3d	7.8	7.9	8.6	8.6
3e	5.2	5.3	4.3	4.8
3f	5.8	5.6	5.6	5.7
3g	3.1	2.6	3.7	3.6
3h	2.4	2.1	3.8	4.1
3i	7.8	7.4	9.1	8.2
3j	8.7	8.6	7.8	9.3
3k	5.1	4.8	3.4	3.2
3l	6.1	6.4	3.3	3.1
3m	7.1	7.2	8.2	8.6
3n	9.4	9.8	9.3	9.1
Standard : Streptomycin for bacteria and Nystain for fungi	2.2	1.3	2.8	2.5

Compound No

*Serratia marcescens**Escherichia coli*

3k



3l



Figure 2: *In vitro* antimicrobial activity images of most active synthesized compounds 3k and 3l

III. CONCLUSION

The hypothesis designed for the introduction of fluorine in imino thiazolidinone ring by synthesizing 3-alkyl-5-fluoro-2-phenylimino-thiazolidin-4-one derivatives using ethyl bromo fluoro acetate yielded desired compounds in good yields. Synthesized compounds were confirmed using ^{19}F NMR which satisfied the gross structure. All the synthesized compounds exhibited excellent antimicrobial and anti fungal activity against used bacteria and fungi. Among tested compound **3e**, **3f**, **3g**, **3h**, **3k** and **3l** showed best antimicrobial and anti fungal activity among which compound **3g** and **3h** with fluorine functional group within ester group exhibited the excellent activity among all the tested compounds.

IV. EXPERIMENTAL

Materials

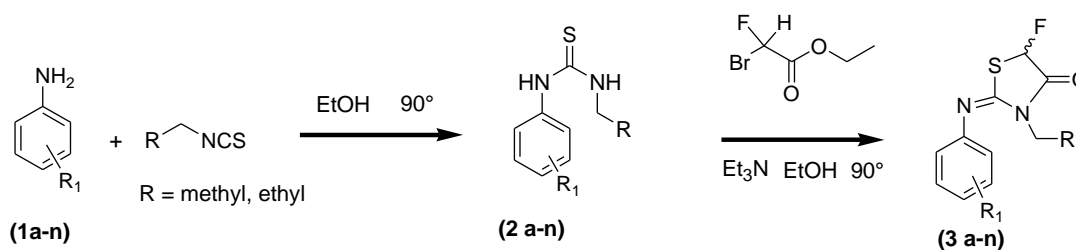
All compounds used during synthesis such as ethyl isothiocyanate, methylisothiocyanate, ethyl bromo fluoro acetate, Ethyl acetate, HCl, hexane, DMSO, and sodium sulphate have been procured from Sigma Aldrich Pvt. Ltd. Ethyl alcohol was supplied by Changshu Hongcheng Fine Chemical Co. Ltd., Jiangsu Province, China. Precoated silica gel 60F₂₅₄ TLC plates were procured from Merck India. Nutrient broth for antibacterial activity was purchased from HiMedia Laboratories Pvt. Ltd. The cultures for antibacterial stains *Escherichia coli* and *Serratia marcescens* and antifungal stains *Aspergillus Niger* and *Rhizopus Ostoyae* fungi. Compounds have been obtained from the National chemical laboratory Pune.

Methods

General procedure for Synthesis disubstituted thiourea derivatives [2 a-n]

To a solution of 4-aminophenylacetic acid methyl ester [**1a-n**] (6g, 0.041 mol) in absolute ethanol and alkyl isothiocyanate (4.05g, 0.046 mol) was added. The reaction mixture was heated at 90-100°C for 4 hours. After completion of the reaction (monitored using TLC) ethanol was evaporated completely. Ethyl acetate (50 mL) and 0.1N HCl (100mL) were added to the residue and stirred for 5 min. Organic layer was separated and washed with distilled water (2 x 50mL). The organic layer was dried over sodium sulphate and evaporated to get desired product [**2a-n**] as an off-white solid in 87% yield. The crude compound was used for further reaction.

General procedure for Synthesis of thiazolidin-4-one derivatives [3a-n]: In absolute ethanol the reagents 1-alkyl-3-phenylthiourea [**2a-n**] (0.25g, 0.0010 mole), ethyl bromo acetate (0.225g, 0.0013 mole), and triethylamine (0.21g, 0.0015 mole) was added and reaction mixture was heated at 80-90°C for 6 hours. After completion of the reaction the TLC was checked using the system of 4:1 hexane: ethyl acetate (v/v). The reaction mixture was cooled to room temperature and ethanol was removed under reduced pressure. The residue was treated with 30 mL distilled water, stirred for 15 min and extracted with ethyl acetate (3 x 20mL). The separated organic layer was evaporated under reduced pressure to get a gummy liq. This product was then recrystallized using absolute ethanol to obtain white gummy liquid product [**3 a-n**] figure 1 in 76% yield.^{18,19}



Scheme 1: Synthesis of Fluorinated Iminothiazolidinone

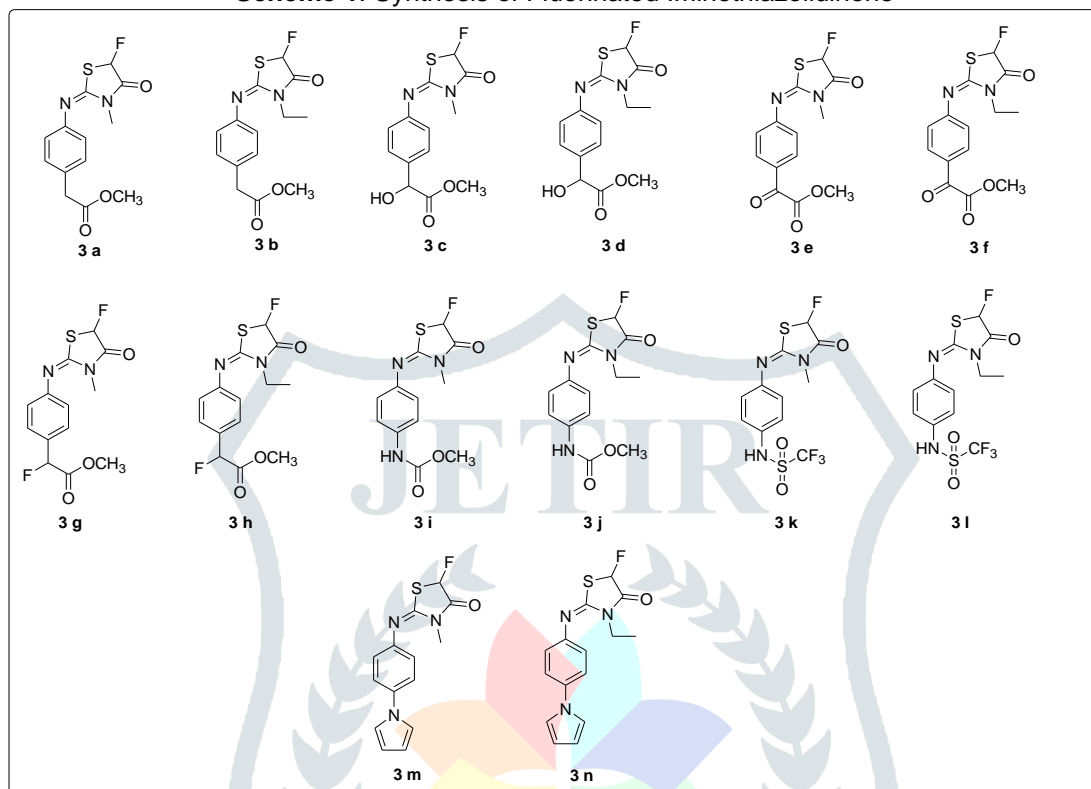


Figure 1. Synthesized Compounds (3a-n)

The synthesized compounds were characterised based on IR, NMR and mass spectrometry methods. Infrared spectra were recorded on Agilent spectrophotometer in a zirconium plate. ^1H , ^{19}F , and ^{13}C NMR spectra were recorded on Bruker Advance III 300 NMR Ultra Shield Spectrometer using CDCl_3 as solvent and tetramethyl silane as internal standard. The chemical shift value is expressed in delta parts per million (ppm). Melting points were determined using the Buchi-M565 melting point apparatus in open capillary tubes.

In-vitro antibacterial activity

Antibacterial activity of the synthesized compounds was carried out by antimicrobial susceptibility test to study the effect of these final synthesized iminothiazolidinone moieties [3 a-n] on bacterial growth. The bacteria's used for antibacterial activity are *Escherichia coli* and *Serratia marcescens* and for antifungal activity were *Aspergillus Niger* and *Rhizopus Ostoyae*. 100 μl of 24-hour growth of each microorganism was spread on the surface of nutrient agar for bacteria (Mac Conkey's agar for *E. coli*) and potato dextrose agar for *Aspergillus Niger* and *Rhizopus Ostoyae*, in Petri plates. (Composition of media is given below). 50 μl compounds at the concentration of 100 μg /ml in DMSO saturated on discs of 6mm diameter were kept on agar surface. The plates were refrigerated for 2 hours to allow pre-diffusion of the compounds from the discs into the seeded agar layer and then incubated at 37 $^\circ\text{C}$ for 24 hours for bacteria and 28 $^\circ\text{C}$ for 48 hour for fungi. Zones of inhibition were measured in millimetre and size of the disc was subtracted from the zone size to measure final activity. DMSO saturated disc served as solvent control or negative control and Streptomycin saturated discs (30 μg) for bacteria and Nystatin (30 μg) for fungi as reference or positive control. The various derivatives of iminothiazolidinone were tested for their potential to inhibit growth of different bacterial and fungal species at doses of 100 μg /ml in DMSO as a solvent, against bacterial and fungal cultures. All the compounds were found to have antimicrobial activities against different species of bacteria and fungi in our studies.

V. Spectroscopic data of representative compounds

[4-(5-Fluoro-3-methyl-4-oxo-thiazolidin-2-ylideneamino)-phenyl]-acetic acid methyl ester (3a)

White sticky gum;

^1H NMR (CDCl_3 , 300MHz): δ 3.68 (s,2H), 3.79(s,3H),3.82(S,3H), 6.72- 6.91 (d, $^1J[\text{HF}] = 55.8$ Hz, 1H), 6.92-6.97 (d, 2H), 7.28-7.32 (d, 2H).

^{19}F NMR (CDCl_3 , 300MHz); -157.9 (Ring F)

MS (m/z): 297.1 [$\text{M}^+ + 1$]; $\text{C}_{13}\text{H}_{13}\text{FN}_2\text{O}_3\text{S}$

IR (ATR): 1733(C=O), 1629(C=N), 1495(C=C), 1366(C-NCH₂), 1256(C-N)

[4-(3-Ethyl-5-fluoro-4-oxo-thiazolidin-2-ylideneamino)-phenyl]-acetic acid methyl ester (3b)

White sticky gum;

δ 1.22-1.39 (m, J= 7.12Hz ,3H), 3.69 (s,2H), 3.81(s,3H), 3.85-3.96 (q,2H, J= 7.12Hz), 6.74- 6.95 (d, $^1J\{HF\}$ = 55.8 Hz, 1H), 6.97-7.05 (d, 2H), 7.29-7.33 (d, 2H).

^{19}F NMR (CDCl_3 , 300MHz); -157.8 (Ring F)

MS (m/z): 311.1 [$\text{M}^+ + 1$]. $\text{C}_{14}\text{H}_{15}\text{FN}_2\text{O}_3\text{S}$

IR (ATR): 1734(C=O), 1632(C=N), 1498(C=C), 1367(C-NCH₂), 1250(C-N)

[4-(5-Fluoro-3-methyl-4-oxo-thiazolidin-2-ylideneamino)-phenyl]-hydroxy-acetic acid methyl ester (3c)

White sticky gum

^1H NMR (CDCl_3 , 300MHz) δ 3.79(s,3H), 3.82(s,3H), 5.00(s,1H), 4.50 (s,1H) exchangeable with D₂O, 6.74- 6.93 (d, $^1J\{HF\}$ = 55.8 Hz, 1H), 6.94-6.99 (d, 2H), 7.30-7.34 (d, 2H)

^{19}F NMR (CDCl_3 , 300MHz); -157.9 (Ring F)

MS (m/z): 313.1 [$\text{M}^+ + 1$]. $\text{C}_{13}\text{H}_{13}\text{FN}_2\text{O}_4\text{S}$

IR (ATR): 3352(O-H), 1730(C=O), 1631(C=N), 1497(C=C), 1366(C-NCH₂), 1252(C-N), 1093(C-F), 694(C-S-C) cm^{-1} .

[4-(3-Ethyl-5-fluoro-4-oxo-thiazolidin-2-ylideneamino)-phenyl]-hydroxy-acetic acid methyl ester (3d)

White sticky gum

^1H NMR (CDCl_3 , 300MHz) δ 1.22- 1.39 (m, J= 7.12Hz ,3H), 3.79(s,3H), 3.85-3.96 (q,2H, J= 7.12Hz), 5.00(s,1H), 4.81 (s,1H) exchangeable with D₂O, 6.78- 6.97 (d, $^1J\{HF\}$ = 55.8 Hz, 1H), 6.97-7.02 (d, 2H), 7.30-7.34 (d, 2H)

^{19}F NMR (CDCl_3 , 300MHz); -159.1 (Ring F)

MS (m/z): 327.1 [$\text{M}^+ + 1$]. $\text{C}_{14}\text{H}_{15}\text{FN}_2\text{O}_4\text{S}$

IR (ATR): 3352(O-H), 1730(C=O), 1631(C=N), 1497(C=C), 1366(C-NCH₂), 1252(C-N), 1093(C-F), 905(trisubstituted Ph ring), 694(C-S-C) cm^{-1} .

[4-(5-Fluoro-3-methyl-4-oxo-thiazolidin-2-ylideneamino)-phenyl]-oxo-acetic acid methyl ester (3e)

Off white sticky gum

^1H NMR (CDCl_3 , 300MHz): δ 3.79(s,3H), 3.82(s,3H), 6.74- 6.93 (d, $^1J\{HF\}$ = 55.8 Hz, 1H), 7.39-7.43 (d, 2H), 7.70-7.75 (d, 2H), 13.10(s,1H)

^{19}F NMR (CDCl_3 , 300MHz); -157.7 (Ring F).

MS (m/z): 311.1 [$\text{M}^+ + 1$]. $\text{C}_{13}\text{H}_{11}\text{FN}_2\text{O}_4\text{S}$

IR (ATR): 2983(C-H), 1715(C=O), 1637(C=N), 1609(C=C), 1508(C-C), 1373(N-CH₂), 1314(C-N), 1204(C-F), 878(p-substituted Ph ring), 828(C-S-C) cm^{-1} .

[4-(5-Fluoro-3-methyl-4-oxo-thiazolidin-2-ylideneamino)-phenyl]-oxo-acetic acid methyl ester (3f)

Off white sticky gum

^1H NMR (CDCl_3 , 300MHz): δ 1.35 (t, J= 7.08Hz ,3H), 3.79(s,3H), 3.82(s,3H), 4.02(q, J= 7.08Hz ,3H) 6.76- 6.95 (d, $^1J\{HF\}$ = 55.8 Hz, 1H), 7.40-7.47 (d, 2H), 7.78-7.84 (d, 2H), 13.12(s,1H)

^{19}F NMR (CDCl_3 , 300MHz); -157.7 (Ring F).

MS (m/z): 325.1 [$\text{M}^+ + 1$]. $\text{C}_{14}\text{H}_{13}\text{FN}_2\text{O}_4\text{S}$

IR (ATR): 2943(C-H), 1697(C=O), 1586(C=N), 1505(C=C), 1359(CNCH₂), 1333(N-CH₃), 1109(C-F), 809(p-substituted Ph ring), 711(C-S-C) cm^{-1} .

Fluoro-[4-(5-fluoro-3-methyl-4-oxo-thiazolidin-2-ylideneamino)-phenyl]-acetic acid methyl ester (3g)

Off white sticky gum

^1H NMR (CDCl_3 , 300MHz): 3.79(s,3H), 3.82(s,3H), 5.85-6.04(d, $^1J\{HF\}$ = 53.5 Hz, 1H), 6.74- 6.93 (d, $^1J\{HF\}$ = 53.5 Hz, 1H), 6.94-6.99 (d, 2H), 7.30-7.34 (d, 2H).

^{19}F NMR (CDCl_3 , 300MHz); -159.1 (Ring F), -162.4

MS (m/z): 315.1 [$\text{M}^+ + 1$]. $\text{C}_{13}\text{H}_{12}\text{F}_2\text{N}_2\text{O}_3\text{S}$

IR (ATR): 2988(C-H), 1709(C=O), 1630(C=N), 1495(C=C), 1367(C-NCH₂), 1337(C-N), 1093(C-CF₃), 843(O-substituted Ph ring), 812(C-S-C) cm^{-1} .

[4-(3-Ethyl-5-fluoro-4-oxo-thiazolidin-2-ylideneamino)-phenyl]-fluoro-acetic acid methyl ester (3h)

Off white sticky gum

^1H NMR (CDCl_3 , 300MHz): 1.22- 1.39 (t, J= 7.12Hz ,3H), 3.79(s,3H), 3.85-3.96 (q,2H, J= 7.12Hz), 5.88-6.08(d, $^1J\{HF\}$ = 56.4 Hz, 1H), 6.74- 6.93 (d, $^1J\{HF\}$ = 53.5 Hz, 1H), 6.94-6.99 (d, 2H), 7.30-7.34 (d, 2H).

^{19}F NMR (CDCl_3 , 300MHz); -158.7 (Ring F), -161.9

MS (m/z): 329.1 [$\text{M}^+ + 1$]. $\text{C}_{14}\text{H}_{14}\text{F}_2\text{N}_2\text{O}_3\text{S}$

IR (ATR): 2949(C-H), 1715(C=O), 1638(C=N), 1607(C=C), 1510(C-C) 1368(C-NCH₂), 1333(C-N), 1106(C-F₃), 863(O-substituted Ph ring), 683 (C-S-C) cm^{-1} .

[4-(5-Fluoro-3-methyl-4-oxo-thiazolidin-2-ylideneamino)-phenyl]-carbamic acid methyl ester (3i)

Off white sticky gum

^1H NMR (CDCl_3 , 300MHz): 3.50(s,3H), 3.85(s,3H), 5.90-6.09(d, $^1J\{HF\}$ = 56.4 Hz, 1H), 7.00-7.05 (d, 2H), 7.30-7.34 (d, 2H), 7.81(bs, 1H).

^{19}F NMR (CDCl_3 , 300MHz); -158.7 (Ring F)

MS (m/z): 298.1 [$\text{M}^+ + 1$]. $\text{C}_{12}\text{H}_{12}\text{FN}_3\text{O}_3\text{S}$

IR (ATR): 2950(C-H), 1703(C=O), 1628(C=N), 1586(C=C), 1464(C-NCH₂), 1366(C-N), 1333(C-F), 1125(C-O), 868(m-disubstituted Ph-ring), 687(C-S-C) cm^{-1} .

[4-(3-Ethyl-5-fluoro-4-oxo-thiazolidin-2-ylideneamino)-phenyl]-carbamic acid methyl ester(3j)

^1H NMR (CDCl_3 , 300MHz): 1.22- 1.39 (t, J= 7.12Hz ,3H), 3.85-3.96 (q, 2H, J= 7.12Hz). 3.50(s, 3H), 5.91-6.10(d, $^1J\{HF\}$ = 56.4 Hz, 1H), 7.05-7.10 (d, 2H), 7.35-7.40 (d, 2H), 7.81(bs, 1H).

^{19}F NMR (CDCl_3 , 300MHz); -158.7 (Ring F)

MS (m/z): 311.07 [$\text{M}^+ + 1$]. $\text{C}_{13}\text{H}_{14}\text{FN}_3\text{O}_3\text{S}$

IR(ATR):2942(C-H),1713(C=O),1614(C=N),1589(C=C),1445(C-NCH₂), 1366(C-N), 1128(C-O), 1090(C-F),907(m-disubstituted Ph-ring), 782(C-S-C) cm^{-1} .

C,C,C-Trifluoro-N-[4-(5-fluoro-3-methyl-4-oxo-thiazolidin-2-ylideneamino)-phenyl]-methanesulfonamide (3k)

Yellow sticky solid

¹H NMR (CDCl₃, 300MHz): 3.82(s,3H), 5.96-6.15(d, ¹J{HF} = 56.4 Hz,1H), 7.25-7.30 (d, 2H), 7.50-7.55 (d, 2H), 7.81(bs, 1H).¹⁹F NMR (CDCl₃, 282MHz): -71.2(3F), 158.7 (Ring F)MS (m/z): 372.02 [M⁺ +1]; C₁₁H₉F₄N₃O₃S₂IR (ATR): 2942(C-H), 1713(C=O), 1614(C=N), 1589(C=C), 1445(NCH₂), 1366(C-N), 1128(C-O), 1090(C-F) cm⁻¹.**N-[4-(3-Ethyl-5-fluoro-4-oxo-thiazolidin-2-ylideneamino)-phenyl]-C,C,C-trifluoro-methanesulfonamide (3l)**

Yellow sticky solid

¹H NMR (CDCl₃, 300MHz): 1.22- 1.43 (t, J= 7.12Hz ,3H), 3.85-4.06(s,2H), 5.96-6.15(d, ¹J{HF} = 56.4 Hz,1H), 7.25-7.30 (d, 2H), 7.50-7.55 (d, 2H), 7.81(bs, 1H).¹⁹F NMR (CDCl₃, 300MHz); -158.7 (Ring F), -161.9MS (m/z): 386.01 [M⁺ +1]. C₁₂H₁₁F₄N₃O₃S₂IR (ATR): 2944(C-H), 1714(C=O), 1598(C=C), 1504 (C-O-C), 1363(C-N), 1127(C-O), 872 (disubstituted Ph ring), 730(C-S-C) cm⁻¹.**5-Fluoro-3-methyl-2-(4-pyrrol-1-yl-phenylimino)-thiazolidin-4-one (3m)**

Yellow sticky solid.

¹H NMR (CDCl₃, 300MHz): δ 3.82 (s, 3H), 5.80-5.99(d, 1J{HF} = 56.4 Hz,1H), 6.36 (t, J = 2Hz, 2H), 6.92- 6.94(d, J = 8.8 Hz, 2H) 7.07- 7.09 (d, J = 8.8 Hz, 2H), 7.40-7.43 (d, 2H).¹⁹F NMR (CDCl₃, 282MHz): δ -158.22(s, 1F).IR (ATR): 290.4 [M⁺ +1]; C₁₄H₁₂FN₃OSIR (KBr):3100(C=C-O), 2943(C-H), 1714(C=O), 1644(C=C), 1512(C-O-C), 1364(C-N),1332(C-C-F), 1103(C-O) cm⁻¹.**3-Ethyl-5-fluoro-2-(4-pyrrol-1-yl-phenylimino)-thiazolidin-4-one (3n)**

Yellow solid; M.P.: 105-107 °C.

¹H NMR (CDCl₃, 300MHz): δ 1.35(t, J= 7.14Hz ,3H), 4.03(q, J= 7.11Hz ,2H), 5.89-6.08(d, ¹J{HF} = 56.4 Hz,1H), 6.37 (t, J = 2Hz, 2H), 6.93- 6.95(d, J = 8.8 Hz, 2H) 7.06- 7.08 (d, J = 8.8 Hz, 2H), 7.40-7.43 (d, 2H).¹⁹F NMR (CDCl₃, 282MHz): δ -158.22(s, 1F).MS (m/z): 304.5 [M⁺ +1]; C₁₅H₁₄FN₃OSIR (ATR): 3742(C-C=N), 2978(C-H),1705(C=O), 1633(C=C), 1598(C-O-C), 1503(C-N), 1377(C-C-F),1200(C-O) cm⁻¹.**Analysis of spectral data**

Confirmation of final product formation was done by ¹H NMR, ¹⁹F NMR, IR, and Mass spectroscopy. The ¹H NMR spectrum of [4-(5-Fluoro-3-methyl-4-oxo-thiazolidin-2-ylideneamino)-phenyl]-oxo-acetic acid methyl ester (3g) displayed peaks 3.79(s,3H) due to the methyl protons of ester group, another singlet at 3.82ppm integrated for 3 protons is assigned for the N-methyl group of imino-thiazolidinone ring. A doublet appeared between 6.74- 6.93 ppm with ¹J{HF} coupling constant = 55.8 Hz for geminal proton attached to fluorine atom on geminal carbon of iminothiazolidinone ring. A similar doublet between 5.88-6.08 ppm with coupling constant d, ¹J{HF} = 56.4 Hz,1H) was assigned to geminal proton of fluoromethine proton attached to carbon adjacent to ester. Aromatic protons of benzene ring showed two doublets between 6.94-6.99 (d, 2H), 7.30-7.34 (d, 2H). ¹⁹F NMR spectrum shows two singlets at -157.7 and -169.8 ppm due to two C-F atoms of iminothiazolidinone ring and Fluoromethine fluorine attached to adjacent ester carbon. Infrared spectrum exhibited absorbance at 1715(C=O), 1637(C=N), 1609(C=C), 1508(C-C),1314(C-N), 1204(C-F).Mass spectrum exhibited MS (m/z): 311.1 [M⁺ +1] which confirms to molecular formula.

V. ACKNOWLEDGMENT

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VI. CONFLICT OF INTEREST:

The authors declared that they had no conflicts of interest.

VII. REFERENCES

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