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SYNTHESIS OF NOVEL 5-ARYLIDENE-3-ETHYL-2-(2, 4, 5-TRIFLUORO-PHENYLIMINO)-THIAZOLIDIN-4-ONE DERIVATIVES USING ULTRASONIC KNOEVENAGEL CONDITIONS AND EVALUATION OF ITS ANTIMICROBIAL ACTIVITY

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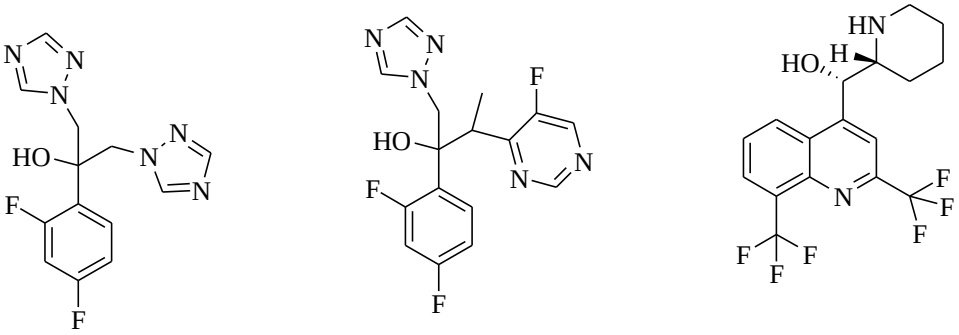
Abstract: A series of novel arylidene derivatives of 3-Ethyl-2-(2, 4, 5-trifluoro-phenylimino)-thiazolidin-4-one derivatives were synthesized using Knoevenagel reaction on the synthesized Iminothiazolidinone core, Knoevenagel reaction was carried out by using ultrasonic conditions and found a better method than conventional Knoevenagel reaction. All the synthesized arylidene derivatives were tested for their antibacterial activities. Compounds with trifluoromethyl group on benzilidine moiety are most active while all other compounds showed excellent antibacterial activity against tested microorganisms *Escherichia coli* and *Serratia marcescens*.

***Index Terms*:** 3-Ethyl-2-(2, 4, 5-trifluoro-phenylimino)-thiazolidin-4-one, Ultrasonic Waves, Knoevenagel Reaction, Antibacterial.

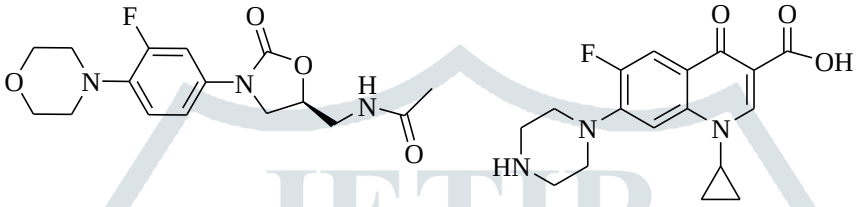
I. INTRODUCTION

During the last century cephalosporin's, macrolide, quinolones and fluoroquinolones, glycopeptides, macrolides and ketolides, and polymyxins are the available antibiotics for the treatment of infectious diseases but the Interagency Coordination Group on Antimicrobial Resistance (IACG) of the United Nations has recommended stopping the usage of these antibiotics [1]. Around 700 000 patients suffer due to infections every year in the world which have no available treatment [2]. Many scientists and the whole world fear that the world is going toward a "post-antibiotic era" where common infections, which were without difficulty cured and could become chronic or fatal. As a consequence, about 10 million deaths caused by infectious diseases due to the unavailability of treatment could be reached by 2050.[3]. As a consequence of these situations, there is an urgent need for the development of new small molecules which will be able to counteract the usual mechanisms underlying antibiotic resistance including enzymatic inactivation of antibiotics, alterations in cell penetrability, efflux pumps activity or biofilm formation. [4,5]. The MurB enzyme is an NADPH-dependent UDP-N-acetylenolpyruvylglucosamine reductase that plays an important part in the second step of bacterial peptidoglycan biosynthesis [6]. MurB looking as an interesting target for novel antibacterial drugs due to a] its inhibition leads to a bactericidal effect because it is fundamental for bacterial growth, b] there is no analogue in the eukaryotic cell therefore the selectivity should be easily obtainable, and 3] being present in both Gram-positive and Gram-negative pathogens its inhibition should result in a broad-spectrum antibacterial activity [7]. 4-thiazolidinone scaffold act as MurB inhibitor is reported by Andres and co-worker in 2000 [8,9]. The thiazolidinone nucleus is also known for specific in-vitro activity against Mycobacterium tuberculosis [10]. Thiazolidin-4-one derivatives are also exhibited diverse biological activities like anti-microbial [11], anti-diabetic [12], cyclooxygenase inhibitory [13], Ca^{2+} channel blocker [14], PAF antagonist [15], cardioprotective [16], anti-ischemic [17], anticancer [18], anti-HIV [19], non-peptide thrombin receptor antagonist [20] and tumour necrosis factor-α antagonist activities. [21]. Fluoro and trifluoro methylated compounds are of particular interest as the strong electron-withdrawing effect of F and CF_3 groups contribute to a number of biologically important molecular properties. Some of the most well-known fluorine-containing drugs with antibacterial activity are fluoroquinolones. The isosteric substitution of hydrogen by fluorine in organic compounds having fluorine atom in its structure may increase the lipophilicity and thus enhance the rate of cell penetration, which is a very important feature in drug delivery, both referring to prokaryotic, Gram-negative bacteria as well as eukaryotic cells. The C-F bond may give rise to a new potential for binding to the receptor.

Fluorine substitution can also influence the pharmacokinetic and pharmacodynamic properties of the molecule [22]. Linezolid, the oxazolidinone class also possesses a Fluorine atom in its structure [23]. In continuation of our interest in thiazolidine-4-one derivatives, to achieve excellent antimicrobial activity, we reported that 5-benzylidene derivatives of 3-Ethyl-2-(2,4,5-trifluoro-phenylimino)-thiazolidin-4-one and 3-Ethyl-2-(2,3,4-trifluoro-phenylimino)-thiazolidin-4-one would possess potent antimicrobial properties.

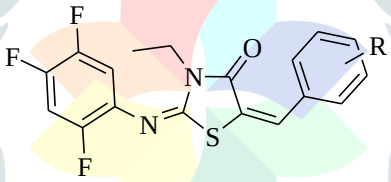


Fluconazole **Voriconazole** **Mefloquine**



Linezolide **Ciprofloxacin**

Fig.1 Fluorine containing Antibiotics



4a-p

Fig. 2 Synthesized Fluorinated Iminothiazolidinone

II. RESULTS AND DISCUSSION:

2.1 Chemistry:

The Designed synthetic route starts with a reaction of 2,4,5-Trifluoro-phenylamine **1** was reacted with ethylisothiocynate and in ethanol at 80ºC to afford the 1-Ethyl-3-(2,4,5-trifluoro-phenyl)-thiourea 2 The formation of the product was confirmed by the mass spectroscopy it shows m/z at 232.1 for [M^+ +1] the 1-Ethyl-3-(2,4,5-trifluoro-phenyl)-thiourea **2** was treated with ethyl bromoacetate in presence of piperidine as the base in refluxing ethanol gave the key intermediate 3-Ethyl-2-(2,4,5-trifluoro-phenylimino)-thiazolidin-4-one **3** with 82 % yield.

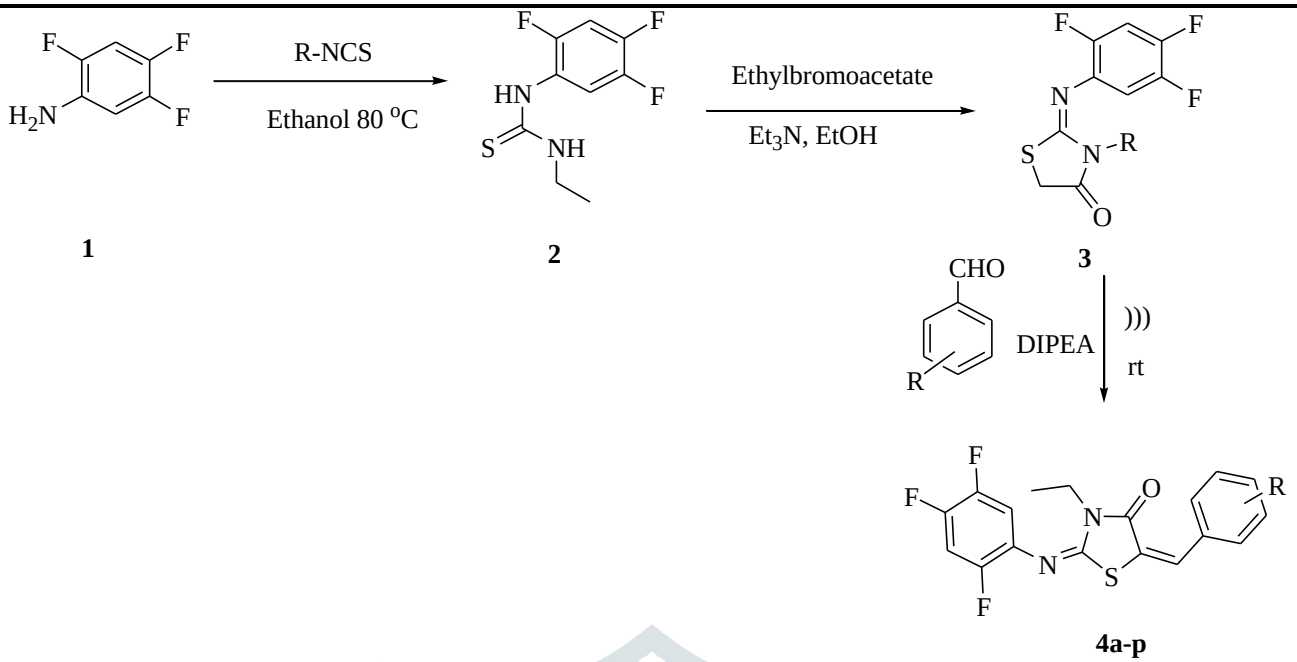


Fig. 3 Scheme

The formation of compound **3** was confirmed using ^{1}H NMR, the spectrum of compound **3** exhibited a triplet at 1.34 ppm with a Coupling constant of 7.12 Hz for 3 protons corresponding to methyl protons of N-ethyl group and its coupling partner at 3.91ppm with coupling constant 7.12 Hz for 2 protons N-ethyl group. A sign of iminothiazolidinone ring formation was established by observing singlet at 3.83 ppm with the integration of two protons for the methylene group attached to the S-atom of the iminothiazolidinone ring. The protons of 2,4,5-trifluoro-phenyl exhibited doublet of triplet due to 1H{19F} coupling at 6.80-6.92 and 6.98 to 7.05 ppm each integrating for one proton with a $^{1}H\{^{19}F\}$ coupling constant of 10.0, 8.0, & 4Hz. The mass spectrum exhibited a peak at m/z = 275.2 (M^{+} +1) in accordance with the molecular formula $C_{11}H_9F_3N_2OS$. IR spectrum of compound **3** showed strong absorption bands at 1634 cm-1 (C=O) and 1731 cm-1 (C=N) confirming the presence of C=O and C=N functional groups respectively.

Knoevenagel condensation of 3-Ethyl-2-(2,4,5-trifluoro-phenylimino)-thiazolidin-4-one 3 with aryl aldehydes in presence of Diisopropylethylamine as a base in absolute ethanol under ultrasonic conditions yielded (5-benzilidine 3-Ethyl-2-(2,4,5-trifluoro-phenylimino)-thiazolidin-4-one (4a-p). Spectral data of representative compound (4k) (2E,5E)-5-(2,3,4trimethoxy-benzilidine)- 3-ethyl-2-(2,4,5 trifluoro-phenylimino)–thiazolidin-4-ones showed strong IR absorption bands at 2942cm-1 (C=C), 1713cm-1 (C=O) and at 1589 cm-1 (C=N) confirms the presence of C=C, C=O and C=N functional groups respectively. In the 1H NMR spectrum, the absence of the signal of methylene protons of thiazolidin-4-one ring of starting compound 3 at 3.83 ppm together with the resonance of the methine proton as a singlet at 8.0 ppm confirms the formation of the proposed structure 4k. The protons of 2,4,5-trifluoro-phenyl exhibited doublet of triplet due to $^{1}H\{^{19}F\}$ coupling at 6.80-6.92 and 6.98 to 7.05 each integrating for one proton with a 1H{19F} coupling constant of 10.0, 8.0,4Hz. The mass spectrum exhibited a peak at m/z = 452.5 (M^{+} +1) in accordance with the molecular formula $C_{21}H_{19}F_3N_2O_4S$

Formation of imine and benzilidine bond is also studied by HMBC spectrum of compound 4a HMBC spectrum of compound 4a shows the correlation between NCH_2 protons at 4.00 ppm with Benzilidine carbon at 166 ppm which is 4 bond away. NCH_2 also shows 2 bonds away correlation with C=N carbon at 154.7 ppm of thiazolidinone rings but no interaction with the trifluorobenzene ring is observed.

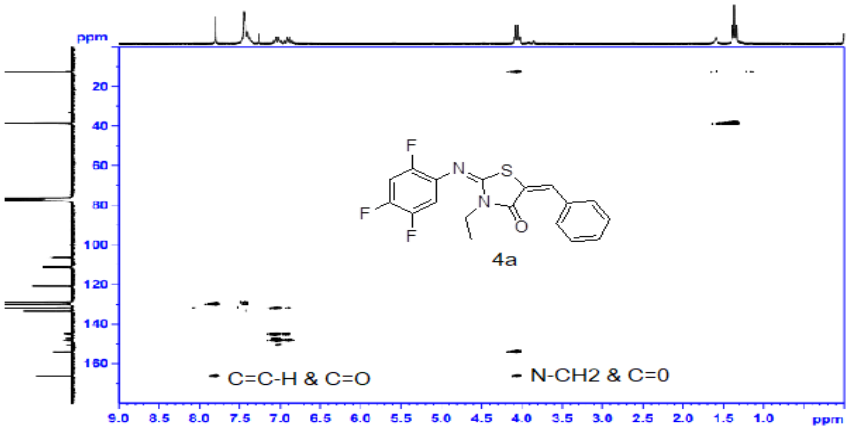


Fig-4 2D HMBC spectrum of compound 4a

Stereochemistry was confirmed by running a 2D NOESY NMR experiment of compound 4a, it shows no interaction of N-CH_2-CH_3 protons with benzilidine proton. Benzilidine proton at 7.79 shows co-relation with Benzene ring of benzilidine moiety, which means that benzilidine bond formation at thiazolidinone ring is trans to S atom of thiazolidinone ring. We also observed that there is no interaction of N-CH_2-CH_3 protons of ethyl ring with trifluorophenyl ring and benzilidine protons confirming that both

the phenyl rings are in the opposite direction of C=C and C=N bonds. It resulted in that the stereochemistry at C=N and C=C is E, E.

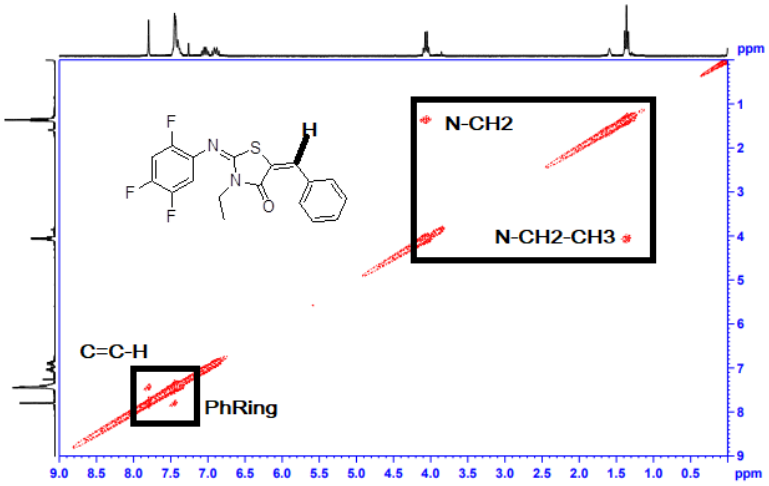


Fig-5 2D NOESY spectrum of compound 4a

Knoevenagel condensation with different substituted aryl aldehydes in presence of Disopropylethlamine as a base in absolute ethanol by sonicating at 300C afforded (2E, 5E)-2-(2, 4, 5-trifluorophenylimino)-5-arylidene-3-ethylthiazolidin-4-one (4a-p) in excellent yields. The reaction yield of the Knoevenagel reactions by using ultrasonic conditions are better than normal knoevenagel reactions at 90^0C(Table-1). All the compounds formed in 80-90% yields which is better than the conventional method using excess ethanol as solvent and under heating, during heating of reactions reaction yield decreases due to formation of impurities also the reaction time is more as compared to sonication. Sonication was done at room temperature using 'Leelasonic -250'sonicator of power 250 watt

Table-1 Knoevenagel condensation with different substituted aryl aldehydes using a sonicator

No.	Aldehyde	Comp	Ultrasonic		Conventional		Molecular Formula
			Yield(%)	Time(min)	Yield(%)	Time(hr)	
1	Benzaldehyde	**4a**	82	30	67	8	$C_{18}H_{13}F_3N_2OS$
2	4-Fluoro benzaldehyde	**4b**	85	30	70	9	$C_{18}H_{12}F_4N_2OS$
3	3-Bromo 4-fluoro, benzaldehyde	**4c**	88	30	73	9	$C_{18}H_{11}BrF_4N_2OS$
4	2,3 dichloro benzaldehyde	**4d**	90	30	75	6	$C_{18}H_{11}Cl_2F_3N_2OS$
5	2-Trifluoromethyl benzaldehyde	**4e**	86	40	76	10	$C_{19}H_{12}F_6N_2OS$
6	3-Trifluoromethyl benzaldehyde	**4f**	82	40	69	10	$C_{19}H_{12}F_6N_2OS$
7	4-Trifluoromethyl benzaldehyde	**4g**	82	40	71	10	$C_{19}H_{12}F_6N_2OS$
8	4-Dimethylamino benzaldehyde	**4h**	80	20	66	5	$C_{20}H_{18}F_3N_3OS$
9	4-Fluoro -3-Phenoxybenzaldehyde	**4i**	85	40	72	9	$C_{24}H_{16}F_4N_2O_2S$
10	2,3-Dimethoxy benzaldehyde	**4j**	78	20	72	4	$C_{20}H_{18}F_3N_3OS$
11	2,3,4-trimethoxy benzaldehyde	**4k**	74	20	71	4	$C_{21}H_{19}F_3N_2O_4S$
12	2,4,6-trimethoxy benzaldehyde	**4l**	80	20	70	4	$C_{21}H_{19}F_3N_2O_4S$
13	4-Hydroxy -3-Methoxy-benzaldehyde	**4m**	81	25	63	8	$C_{19}H_{15}F_3N_2O_3S$
14	Furfuraldehyde	**4n**	79	40	65	8	$C_{16}H_{11}F_3N_2O_2S$
15	Pyrol-2-carboxaldehyde	**4o**	85	20	63	4	$C_{16}H_{12}F_3N_3OS$
16	4-Methoxy	**4p**	89	20	76	4	$C_{19}H_{15}F_3N_2O_2S$

2.2 Invitro antibacterial activity:

All the novel benzilidine derivatives of 3-Ethyl-2-(2,4,5-trifluoro-phenylimino)-thiazolidin-4-one (**4a-p)** compounds were evaluated for antibacterial activity. All these compounds were found to exhibit excellent antibacterial against *Escherichia coli* and *Serratia marcescens* Compounds **4e,4f,4g, and 4k,** showed excellent activity against Escherichia *coli*, from all the tested Compounds. Compound **4f** with trifluoromethyl moiety at the meta position of benzaldehyde showed the best activity among all the synthesized derivatives. Compound **4f** showed excellent activity against *S. marcescens*

- These results are the average results of four experiments.
- These compounds were used at a concentration of 50.100,250 ng/mL.
- Ampicillin was used as standard at a concentration of 50.100,250 ng/mL.

. **Table2** Antimicrobial activity of (2E, 5E)-2-(2, 4, 5-trifluorophenylimino)-5-arylidene-3-ethylthiazolidin-4-one

Compound no.	Escherichia *coli* *NCLM No.2602*	*Serratia marcescens* *NCLM No.2919*
4a	6.7	6.4
4b	8.3	7.9
4c	5.0	5.5
4d	7.2	7.7
4e	9.0	8.0
4f	11	10.7
4g	8.19	8.0
4h	7.2	7.2
4i	7.4	7.8
4j	5.9	6.0
4k	10.1	8.7
4l	7.7	6.4
4m	3.2	3.1
4n	3.2	2.4
4o	2.5	2.5
4p	7.3	6.2
Standard (Ampicillin)	1.3	2. 2

III. CONCLUSION

In summary, we have synthesized a novel of (2Z 5Z)-2-(2, 4, 5-trifluorophenylimino)-5-arylidene-3-ethylthiazolidin-4-one derivatives by conventional knoevenagel reaction and by using sonication wave method knoevenagel reaction with aromatic aldehydes, by using sonication method got the excellent yields and reduce the time dramatically than the normal conventional method with a fluorinated imino-thiazolidinone ring system. Compounds having CF_3 trifluoromethyl group on benzilidine moiety showed excellent activity against tested gram-positive bacterial strains. MIC of all tested compounds shows excellent activity than the standard ampicillin drug.

IV. EXPERIMENTAL

4.1 Method

Progress of the reaction was monitored by silica gel-G coated TLC plates in the Ethyl acetate: Hexane system (5:5). The spot was visualized by exposing the dry plate to iodine vapors. Melting points were determined by the melting point determination apparatus (Buchi-M565) in open capillary tubes. Infrared spectra were recorded on an Agilent spectrophotometer (λmax in cm^{-1}). 1H, 19F NMR spectra were recorded on Bruker Advance III 300 NMR Ultra Shield Spectrometer using $CDCl_3$ as a solvent and tetramethyl silane as the internal standard. The chemical shift value is expressed in delta parts per million (ppm).

Antibacterial activity of the synthesized compounds was carried out by Broth dilution assay to study the effect of these synthesized iminothiazolidinone compounds on bacterial growth. The Gram-negative bacteria, *Escherichia coli* and *Serratia marcescens* were used for the experiment. Both the organisms were challenged with different concentrations of compounds ranging from 50ng/ml to 250ng/ml. Nutrient broth (peptic digest of animal tissue 20 g/L, potassium sulphate 10 g/L, magnesium chloride 1.4 g/L, pH 7.0 ± 0.2) was used as a growth medium. The culture of both the organisms were used to prepare inoculum, which was standardized to 0.5 McFarland turbidity standard and added 10% v/v to the media supplemented with the required concentration (µg/mL) of test compounds. The amount of compound and/or DMSO was kept constant at 0.2%v/v for all the experiments. Appropriate controls i.e., vehicle control (containing DMSO), abiotic control (containing compound and growth medium, but no inoculum), Positive control (DMSO and culture) and negative control (only growth medium) were included in the experiment [23,24]. Treated and untreated cultures were incubated at 37°C for 24 hours followed by measuring its optical density (OD) at 600nm. The growth profile of the cultures was compared with positive control.

4.2 synthesis of 3-ethyl-2-(2,4,5 trifluoro-phenylimino)–thiazolidin-4-ones (3): To a solution of (2,4,5 trifluoro-phenyl)-3-ethylthiourea (4) (0.25gm, 0.0010 mole) in absolute ethanol (25 ml) ethyl bromoacetate (0.225gm, 0.0013 mole) and Triethylamine (0.21gm, 0.0015) was added and reaction mixture was heated at 80-90 °C for 3 hour. After completion of the reaction (TLC check 4:1 Hexane: ethyl acetate) reaction mixture was cooled to room temperature and ethanol was removed under vacuum. Water (30 ml) was added to the residue, stirred for 15 min and extracted with ethyl acetate (20ml × 3). The organic layer separated and evaporated to get a sticky red solid. It was then recrystallized using absolute ethanol to give 2.25 gm (76%) of 3-ethyl-2-(2,4,5 trifluoro-phenylimino)–thiazolidin-4-ones (3)) as an off-white solid.

4.3 General procedure for preparation 5-arylidene 3-ethyl-2-(2, 4, 5trifluoro-phenylimino)–thiazolidin-4-ones (4a-p):

Normal Knoevenagel Reaction:

A mixture 3-ethyl-2-(2,4,5trifluoro-phenylimino)-thiazolidin-4-ones(**3**)(1mmol), aromatic aldehyde (1.15mmol) and diisopropylethylamine (1.6 mmol) in absolute ethanol (20ml) was refluxed at 90°C. After completion of the reaction (TLC check), ethanol was evaporated, and cold water was added to the residue and extracted with ethyl acetate (3× 20 ml). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was recrystallized using absolute ethanol to get the title compound in good yields **(4a-p)**.

Knoevenagel Reaction by ultrasonic wave:

A mixture 3-ethyl-2-(2,4,5trifluoro-phenylimino)-thiazolidin-4-ones (**3**) (1mmol), aromatic aldehyde (1.15mmol) and diisopropylethylamine (1.6 mmol) in absolute ethanol (4ml) was sealed in GC-HS tube. The tube was placed in a sonicator and

sonicated for 10-15 min at 30^0C till the solution become clear. Sealed tube kept as it is for 10 min at RT. Solid formed was filtered through Whatman filter paper to get the desired compound. The residue was washed with absolute ethanol to get the pure product in good yields **(4a-p)**.

V. Spectroscopic data of representative compounds

3-ethyl-2-(2, 4, 5 trifluoro-phenylimino)–thiazolidin-4-ones (**3**):
Off White solid; M.P: 132- 134 ºC. ^{1}H NMR ($CDCl_3$, 300MHz)*:* δ 1.29 (t, J= 7.0Hz, 3H), 3.86(s, 2H), 3.92 (q, J= 7.0Hz, 2H) 6.80-6.88 (d t, 1H), 6.95-7.04 (d t,1H).
IR (ATR): 158(C=N), 171.3(C=O)
^{19}F NMR ($CDCl_3$, 282MHz)*:* δ -126 (d, 1F), -138 (d, 1F), -141(dd, 1F).
MS (m/z): 275.2 [M^+ +1] ;($C_{11}H_9F_3N_2OS$)
IR (ATR): 1701(C=O), 1596(C=N), 1200(C-S) cm^{-1}.

(2E, 5E)-2-(2, 4, 5-trifluorophenylimino)-5-benzylidene-3-ethylthiazolidin-4-one (4a)
White solid; M.P: 132- 134 ºC. ^{1}H NMR ($CDCl_3$, 300MHz)*:* δ 1.23 (t, J= 7.1Hz ,3H), 4.05 (q, J= 7.1Hz,2H), 6.84-6.91 (m, 1H), 6.98-7.11(d t, 1H), 7.33-7.51 (m,5H), 7.8 (S,1H).
^{19}F NMR ($CDCl_3$, 282MHz)*:* δ -126 (d, 1F), -138 (t, 1F), -141(dd, 1F).
MS (m/z): 363.3 [M^+ +1]; $C_{18}H_{13}F_3N_2OS$
IR (ATR): 2942(C-H), 1709(C=O), 1630(C=N), 1588(C=C), 1509(C-C), 1372(C-N), 1326(C-O), cm^{-1}.

(2E,5E)-2-(2,4,5-trifluorophenylimino)-5-(4-fluorobenzylidene)-3-ethylthiazolidin-4-one (4b)
Yellow solid; M.P: 167- 169 ºC. ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.35 (t, J= 7.14Hz ,3H), 4.05 (q, J= 7.11Hz ,2H), 6.84-6.93 (d t, 1H), 6.99-7.06 (d t, 1H), 7.08-7.1 (dd, 8.7 Hz, 2H), 7.42-7.46 (d, J= 8.7 Hz 2H), 7.75 (S,1H).
^{19}F NMR ($CDCl_3$, 282MHz)*:* δ -126 (d, 1F), -138 (t, 1F), -141(dd, 1F).
MS (m/z): 381.3 [M^+ +1]. $C_{18}H_{12}F_4N_2OS$
IR (ATR): 2947(C-H), 1709(C=O), 1628(C=N), 1590(C=C), 1506(C-C), 1363 (N-CH_2), 1336(C-N), 1228(C-F), 859(p-substituted Ph ring), 819(C-S-C) cm^{-1}.

(2E,5E)-2-(2,4,5-trifluorophenylimino)-5-(3-bromo-4-fluorobenzylidene)-3-ethylthiazolidin-4-one (4c)
Yellow solid; M.P.: 171-173 ºC. ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.36 (t, J= 7.14Hz ,3H), 4.06 (q, J= 7.11Hz ,2H), 6.84-6.92 (dt, 1H), 7.00-7.09 (dt, 1H), 7.15-7.20(t, J= 8.31 Hz, 1H), 7.35-7.40 (m, 1H), 7.62-7.64 (dd, J=6.42 & 2.01 Hz, 1H), 7.67 (S,1H)
^{19}F NMR ($CDCl_3$, 282MHz)*:* δ -102 (s,1F), -126 (d, 1F), -138 (t, 1F), -141(dd, 1F).
MS (m/z): 460.3 [M^+ +1].$C_{18}H_{11}BrF_4N_2OS$
IR (ATR): 2987(C-H), 1710(C=O), 1631(C=N), 1497(C=C), 1366(C-NCH_2), 1252(C-N), 1093(C-F), 905(trisubstituted Ph ring), 694(C-S-C) cm^{-1}.

(2E, 5E)-5-(2, 3dichlorobenzylidene)-2-(2, 4, 5-trifluorophenylimino)-3-ethylthiazolidin-4-one (4d)
Yellow solid; M.P.: 171-173 ºC. ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.36 (t, J= 7.14Hz ,3H), 4.06 (q, J= 7.11Hz ,2H), 6.82-6.94 (d t, 1H), 6.98-7.07 (d t, 1H), 7.27-7.30 (dd, 1H), 7.35-7.38(d, J= 8.4 Hz, 1H), 7.48-7.48(d, J= 2.0 Hz, 1H), 8.00 (s,1H).
^{19}F NMR ($CDCl_3$, 282MHz)*:* δ -126 (d, 1F), -138 (t, 1F), -141(dd, 1F).
MS (m/z): 432.3 [M^+ +1].; $C_{18}H_{11}Cl_2F_3N_2OS$
IR (ATR): 2943(C-H), 1714(C=O), 1644(C=N), 1512(C=C), 1364(C-NCH_2),1332(C-N), 1103(C-F),878 (disubstituted Ph ring cm^{-1}.

(2E,5E)-2-(2,4,5-trifluorophenylimino)-5-(2-(trifluoromethyl) benzylidene)-3-ethylthiazolidin-4-one (4e)
Yellow solid; M.P.: 171-173 ºC. ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.36 (t, J= 7.14Hz ,3H), 4.06 (q, J= 7.11Hz ,2H), 6.80-6.89 (d t, 1H), 6.96-7.05 (d t, 1H), 7.44-7.49(t, J=8.4 Hz 1H), 7.53-7.62 (m, J= 8.7 Hz 2H), 7.73-7.75 (d, J=8.4 Hz 1H), 8.0 (S,1H)
^{19}F NMR ($CDCl_3$, 282MHz)*:* δ-61(s,3F) -126 (d, 1F), -138 (d, 1F), -141(dd, 1F).
MS (m/z): 431.3 [M^+ +1].$C_{19}H_{12}F_6N_2OS$
IR (ATR): 2988(C-H), 1709(C=O), 1630(C=N), 1495(C=C), 1367(C-NCH2), 1337(C-N), 1093(C-CF_3), 843(O-substituted Ph ring), 812(C-S-C) cm^{-1}.

(2E,5E)-2-(2,4,5-trifluorophenylimino)-5-(3-(trifluoromethyl) benzylidene)-3-ethylthiazolidin-4-one (4f)
Yellow solid; M.P.: 171-173 ºC. ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.36 (t, J= 7.14Hz ,3H), 4.06 (q, , J= 7.11Hz ,2H), 6.84-6.93 (d t, 1H), 7.00-7.09 (d t, 1H), 7.54-7.61m,3H), , 7.67 (s, 1H), 7.80 (S,1H)
^{19}F NMR ($CDCl_3$, 282MHz)*:* δ -61(s,3F), -126 (d, 1F), -138 (t, 1F), -141(dd, 1F).
MS (m/z): 431.3 [M^+ +1].$C_{19}H_{12}F_6N_2OS$
IR (ATR): 2949(C-H), 1715(C=O), 1638(C=N), 1607(C=C), 1510(C-C) 1368(C-NCH_2), 1333(C-N), 1106(C-F_3) ,863(O-substituted Ph ring) ,683 (C-S-C) cm^{-1}.

(2E, 5E)-2-(2, 4, 5-trifluorophenylimino)-5-(4-(trifluoromethyl) benzylidene)-3-ethylthiazolidin-4-one (4g)
Yellow solid; M.P.: 175-177 ºC. ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.36 (t, J= 7.14Hz ,3H), 4.06 (q, J= 7.11Hz ,2H), 6.84-6.93 (d t, 1H), 7.00-7.09 (d t, 1H), 7.5.56 (d, 8.4 Hz, 2H), 7.66-7.69 (d, J= 8.7 Hz 2H), 7.79 (S,1H),
^{19}F NMR ($CDCl_3$, 282MHz)*:* δ -126 (d, 1F), -138 (t, 1F), -141(dd, 1F).
MS (m/z): 431.3 [M^+ +1].$C_{19}H_{12}F_6N_2OS$
IR (ATR): 2983(C-H), 1715(C=O), 1637(C=N), 1609(C=C), 1508(C-C), 1373(N-CH_2), 1314(C-N), 1204(C-F_3), 878(p-substituted Ph ring), 828(C-S-C) cm^{-1}.

(2E, 5E)-2-(2, 4, 5-trifluorophenylimino)-5-(4-(dimethylamino) benzylidene)-3-ethylthiazolidin-4-one (4h)
Yellow solid; M.P.: 171-173 ºC. ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.34 (t, J= 7.14Hz ,3H), 3.10 (s,6H) 4.02 (q, J= 7.11Hz ,2H), 6.66-6.69 (d, J=8.88Hz,2H), 6.86-6.95 (d t, 1H), 6.97-7.06 (d t, 1H), 7.32-7.35(t, J= 8.88 Hz, 1H), 7.70 (S,1H)
^{19}F NMR ($CDCl_3$, 282MHz)*:* δ -126 (d, 1F), -138 (t, 1F), -141(dd, 1F).
MS (m/z): 406.5 [M^+ +1]. $C_{20}H_{18}F_3N_3OS$
IR (ATR): 2943(C-H), 1697(C=O), 1586(C=N), 1505(C=C), 1359(CNCH2), 1333(N-CH_3), 1109(C-F), 809(p-substituted Ph ring), 711(C-S-C) cm^{-1}.

(2E,5E)-2-(2,4,5 trifluoro-phenylimino))-5-(4-fluoro-3-phenoxybenzilidine 3-ethylthiazolidin-4-one (4i)

Yellow solid; M.P: 167- 169 ºC. ^{1}H NMR ($CDCl_3$, 300MHz) : δ 1.32 (t, J= 7.14Hz ,3H), 4.02(q, , J= 7.11Hz ,2H), 6.79-6.99 (d t, 1H), 7.01-7.09 (m, 4H) , 7.12-7.14 (d, J= 8.7 Hz 1H), 7.15-7.19 (m,1H), 7.19-7.26 (d, J= 8.7 Hz 1H), 7.27-7.34 (m, 2H) 7.64 (S,1H).

^{19}F NMR ($CDCl_3$, 282MHz): δ -102 (s,1F), -126 (d, 1F), -138 (t, 1F), -141(dd, 1F).

MS (m/z): 473.1 [M^+ +1].; C24H16F4N2O2S

IR (ATR): 3056, (SP^2C-H) 2938(C-H), 1708(C=O), 1636 C=N), 1504(C=C), 1363(CNCH$_2$), 1203(C-F), 905(m-substituted Ph ring),874 (C-S-C) cm^{-1}.

(2E,5E)-5-(3,4-dimethoxybenzylidene)-2-(2,4,5-trifluorophenylimino)-3-ethylthiazolidin-4-one (4j)

Yellow solid; M.P.: 171-173 ºC. ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.34 (t, J= 7.14Hz ,3H), 3.83 (s,3H), 3.85 (s,3H) 4.02 (q, J= 7.11Hz ,2H), 6.44-6.45(d, J=2.1Hz,1H), 6.50-6.54 (d, d J=8.6 & 2.1 Hz,2H), 6.84-6.93 (d t, 1H), 6.97-7.06 (d t, 1H), 7.28-7.31(d, J= 8.6 Hz, 1H), 8.13 (S,1H)

^{19}F NMR ($CDCl_3$, 282MHz): δ -126 (d, 1F), -138 (t, 1F), -141(dd, 1F).

MS (m/z): 423.5 [M^+ +1]. $C_{20}H_{17}F_3N_2O_3S$

IR (ATR): 2950(C-H), 1703(C=O), 1628(C=N), 1586(C=C), 1464(C-NCH$_2$), 1366(C-N)), 1333(C-F), ,1125(C-O),868(m-disubstituted Ph-ring),687(C-S-C) cm^{-1}.

(2E, 5E)-5-(2, 3, 4-trimethoxybenzylidene)-2-(2, 4, 5-trifluorophenylimino)-3-ethylthiazolidin-4-one (4k)

Yellow solid; M.P.: 171-173 ºC. ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.35 (t, J= 7.14Hz ,3H), 3.86 (s,3H), 3.88 (s,3H), 3.92(s,3H), 4.04 (q, J= 7.11Hz ,2H), 6.70-6.73(d, J=8.82Hz,1H), 6.84-6.93 (d t, 1H), 6.97-7.06 (d t, 1H), 7.09-7.12(d, J= 8.6 Hz, 1H), 8.0 (S,1H).

^{19}F NMR ($CDCl_3$, 282MHz): δ -126 (d, 1F), -138 (t, 1F), -141(dd, 1F).

MS (m/z): 453.1 [M^+ +1].; $C_{21}H_{19}F_3N_2O_4S$

IR (ATR): 2942(C-H), 1713(C=O), 1614(C=N), 1589(C=C), 1445(C-NCH$_2$), 1366(C-N), 1128(C-O), 1090(C-F),907(m-disubstituted Ph-ring) 782(C-S-C) cm^{-1}.

(2E, 5E)-5-(2, 4, 6-trimethoxybenzylidene)-2-(2, 4, 5-trifluorophenylimino)-3-ethylthiazolidin-4-one (4l)

Yellow solid; M.P.: 171-173 ºC. ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.35 (t, J= 7.14Hz ,3H), 3.86 (s,9H) ,4.04 (q, J= 7.11Hz ,2H), 6.66 (s,2H), 6.85-6.98 (d t, 1H), 7.01-7.13 (d t, 1H), 7.72 (s,1H).

^{19}F NMR ($CDCl_3$, 282MHz): δ -126 (d, 1F), -138 (t, 1F), -141(dd, 1F).

MS (m/z): 453.1 [M^+ +1].; $C_{21}H_{19}F_3N_2O_4S$

IR (ATR): 2942(C-H), 1713(C=O), 1614(C=N), 1589(C=C), 1445(NCH$_2$), 1366(C-N), 1128(C-O), 1090(C-F),907(m-disubstituted Ph-ring) 782(C-S-C) cm^{-1}.

(2E,5E)-2-(2,4,5 trifluoro-phenylimino))-5-(4-hydroxy-3-methoxybenzilidine 3-ethylthiazolidin-4-one(4m)

White solid; M.P: 132- 134 ºC. ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.35 (t, J= 7.14Hz ,3H), 3.88(s,3H) 4.06 (q, J= 7.11Hz ,2H), 4.08 (bs,1H) 6.85-6.94 (m, 3H), 6.98-7.07 (m, 2H), 7.72 (S,1H)

^{19}F NMR ($CDCl_3$, 282MHz): δ -126 (d, 1F), -138 (t, 1F), -141(dd, 1F).

MS (m/z): 409.5 [M^+ +1].; $C_{19}H_{15}F_3N_2O_3S$

IR (ATR): 3350 (OH), 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}.

(2E,5E)-2-(2,4,5 trifluoro-phenylimino)-3-ethyl-5-((furan-2-yl) methylene) thiazolidin-4-one (4n)

Yellow solid; M.P.: 171-173 ºC. ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.36 (t, J= 7.14Hz ,3H), 4.04 (q, J= 7.11Hz ,2H), 6.54-6.55 (dd, 1H), 6.73-6.74 (d, 1H), 6.88-6.96 (d t, 1H), 7.01-7.10 (d t, 1H), 7.56 (s,1H),7.61-7.62(d,1H).

^{19}F NMR ($CDCl_3$, 282MHz): δ -126 (d, 1F), -138 (t, 1F), -141(dd, 1F).

IR (ATR): 353.4 [M^+ +1].; $C_{16}H_{11}F_3N_2O_2S$

IR (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),878(disubstituted furan ring) cm^{-1}.

(2E, 5E)-5-((1H-pyrrol-2-yl) methylene)-2-(2, 4, 5-trifluorophenylimino)-3-ethylthiazolidin-4-one (4o)

Yellow solid; M.P.: 215-217 ºC. ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.35(t, J= 7.14Hz ,3H), 4.03(q, J= 7.11Hz ,2H), 6.38-6.39 (m,1H), 6.54 (bs,1H), 6.86-6.95 (dd, 1H), 6.99-7.08(m, 1H), 7.69 (s,1H), 8.89 (bs,1H, exchangeable with D2O)

^{19}F NMR ($CDCl_3$, 282MHz): δ -126 (d, 1F), -138 (t, 1F), -141(dd, 1F).

MS (m/z): 352.5 [M^+ +1].; $C_{16}H_{12}F_3N_3OS$

IR (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),962 (disubstituted phenyl ring) cm^{-1}.

(2E, 5E)-2-(2, 4, 5-trifluorophenylimino)-5-(4-methoxybenzylidene)-3-ethylthiazolidin-4-one (4p)

White solid; M.P: 132- 134 ºC. ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.35 (t, J= 7.14Hz ,3H), 3.83(s,3H) 4.05 (q, J= 7.11Hz ,2H), 6.85-6.97 (d t, 1H), 6.93-6.96 (d, 8.7 Hz 2H), 6.97-7.11 (d t, 1H), 7.39-7.42 (d, J= 8.7 Hz 2H), 7.75 (S,1H)

^{19}F NMR ($CDCl_3$, 282MHz): -126 (d, 1F), -138 (t, 1F), -141(dd, 1F).

MS (m/z): 393.3 [M^+ +1]. $C_{19}H_{15}F_3N_2O_2S$

IR (ATR): 2954(C-H), 1700(C=O), 1628(C=N), 1592(C=C), 1508(C-C), 1363(N-CH$_2$), 1253(C-O), 1026, 818(p-substituted Ph ring), 691(C-S-C) cm^{-1}.

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VI. CONFLICT OF INTEREST:

The authors declared that they had no conflicts of interest.

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