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Design, synthesis and anti-microbial study of ethyl 2-(N-(substituted-phenyl) sulfamoyl) thiazole-4-carboxylate derivatives

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Abstract: A new series of novel ethyl 2-(N-(substituted-phenyl)sulfamoyl)thiazole-4-carboxylate derivatives (**4a-4l**) were designed and synthesized from commercially available ethyl 2-aminothiazole-4-carboxylate (**1**). The compounds were synthesized through two-step reactions involving sulfonation, and sulfonamide coupling. Both the steps were optimized for getting better yields and clean reaction profile. The synthetic compounds were characterized by analytical techniques like ^{1}H NMR, ^{13}C NMR, LCMS and IR. All the synthetic derivatives were evaluated for their antimicrobial activity (minimum inhibitory concentration) against a series of strains of *Bacillus subtillis*, *Staphylococcus aureus* and *Escherichia coli* for antibacterial activity and against the strains of *Candida albicans, Aspergillus flavus* and *Aspergillus niger* for antifungal activity. The compounds **4e**, **4f, 4k** and **4l** showed promising inhibitions for most of antimicrobial strains. The results of antimicrobial screening data revealed most of compounds showed moderate to promising microbial inhibitions. The compounds having electron withdrawing substituents shows promising antibacterial and antifungal activity against *bacillus subtillis* and *aspergillus niger* strains in the series. Furthermore, to gain insight into the mode of action of the synthesized compounds as antibacterial and antifungal activity, docking studies were performed for the synthesized compounds in order to evaluate their activity as antibacterial and antifungal agents. Virtual screening of the most promising compounds was performed against two PDB codes that were known PDB for antibacterial (1KZN) and antifungal activity (4BJK).

Keywords: Diazotization, Sulfonation, Sulfonamide coupling, antimicrobial and Molecular Docking.

Introduction:

The research on heterocyclic drug discoveries is a continuous process as there were many valid reasons for it like drug resistance, cost of drugs, treatment time, ineffectiveness of drugs,

emerging new strains and so many. Since early stages of life we mostly use drugs so there is occurrence of new strains of microorganisms which is having resistance to the available drug used. Therefore, there was constant need for the development of better and effective drugs. [1] The research on novel heterocycles rings has fascinates the medicinal science, various heterocycles bearing nitrogen and sulfur were important to construct and design for new compounds. Thiozole is a heterocyclic compound bearing nitrogen and sulfur atoms in aromatic ring. Thiazole has an important pharmacophore in medicinal chemistry and drug discoveries as its structure and its substituent's plays an important role in varied biological activities. [2, 3] Thiazole nuclei comprises delocalization of lone pair of electrons from the sulfur atoms provides the aromaticity to the nuclei. Thiazole nuclei have gained special importance in medicinal chemistry for their diversified activities like occurred due to azole nuclei found alone in scaffold or incorporation with other active scaffolds.

Thiazole and its derivatives showed diversified activities like antimicrobial, anti-tubercular, anti-viral, anticancer, anti-HIV, anti-diabetic, anti-convulsant, anti-oxidant, anti-inflammatory agents [4-10] The combination of thiazole with different heterocycles showed varied biological activities, the combination of thiazole-oxazole hybrid shows promising activity against tuberculosis, antibacterial and anti-proliferative. [11] The thiazole-sulfonamide derivatives show inhibitory activity towards carbonic anhydrase (hCA) I, II, IX, XII. [12-13] Thiazole nuclei have occupied an important place in the field of medicinal field for its diversified biological activities. The marketed drugs like Sulfathiazole, Fenetionle, Niridazole, Fentiazac, Combenadazole, Abufungin, Bleomycin, Tiazofurin, Febuxostat, Dasatinib, Meloxicam, Nitazoxanid etc. were used for antibacterial, anti-inflammatory, schistozomicidal, fungicidal etc. The substitution on different position of thiazole ring plays an important role in activity. Based on the literature search the 2, 4, 5-substituted thiazole plays a unique role in biological activities. The diversity in the biological response profile has attracted the attention of many researchers to explore this scaffold to its multiple potential against several activities with cheap way of synthesis to get different molecules.

Rational behind this work, drug discovery mainly focused on modification of existing drugs or some chemical modifications to the reported active scaffold with the hope to get promising activity. The diversified activities of thiazole nuclei found its applications in many marketed drugs as mentioned in figure **1**. Sulfathiazole were used for the treatment of antimicrobial drug up to very recently. Ritonavir is an antiretroviral drug mainly used along with other drugs for the treatment of HIV. Abafungin were used as a broad-spectrum antifungal drug, it directly impairs the fungal cell membrane, and it has antibiotic activity against gram-positive bacteria as well as sporicidal activity. Tiazofurin drug were used as inhibitor of the enzyme IMP dehydrogenase. It shows antiviral activity so it is potentially use for the treatment of emerging viral diseases. Cambendazole is a veterinary anti-parasitic drug used for the treatment of worm infections in horses. It inhibits the glucose uptake, fumarate reductase and phosphoenolpyruvate carboxy-kinase, which causes the paralysis of the parasites. Niridazoles were used for the treatment of schistosomiasis, and for the treatment of periodontitis. It rapidly concentrates in the parasite site and inhibits the process of oogenesis and spermatogenesis by inhibiting phosphofructokinase enzyme. Bleomycin is a drug, which is mostly used to treat cancers including testicular cancer, ovarian cancer, and hodgkins diseases. By considering the structure of available marketed drugs having thiazole we designed simple

sulfonamide coupling derivatives, the nuclei having sulfonamide linkage at second position of thiazole ring.

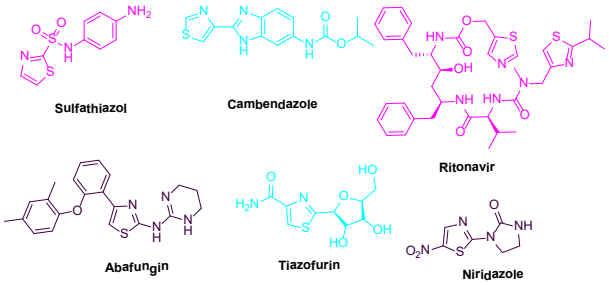


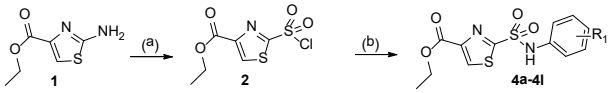
Figure. 1: Available Marketed drugs containing thiazole nuclei

Thiazole nuclei were identified as one of the important class of heterocyclic compounds because of its significant and versatile biological and pharmacological properties. From the available literature the diversified biological activities of thiazole and in continuation of our research on bioactive heterocyclic compound, as an antimicrobial and anticancer agent [14-15] we have synthesized a series of ethyl 2-(N-(substituted-phenyl)sulfamoyl)thiazole-4-carboxylate derivatives (4a-4l) depicted in below **scheme 1.**

Molecular docking is a calculated approach aiming to accurately predict the binding of complex and a small ligand. In this aspect, we did docking analysis to predict the docking set of the tested compounds in the binding pocket of bacterial proteins (DNA gyrase and DNA topoisomerase), and fungal protein (ergosterol) that are known targets for antibacterial and antifungal activity.

Result and Discussion

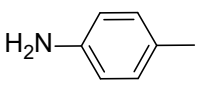
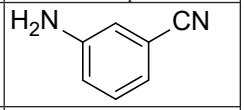
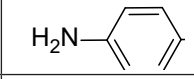
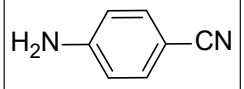
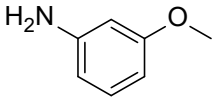
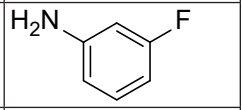
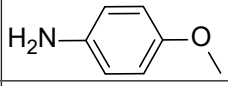
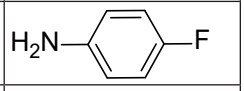
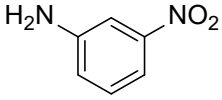
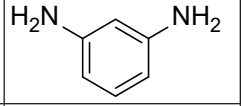
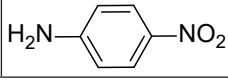
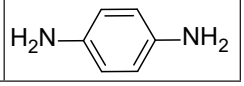
The synthesis of ethyl 2-(N-(substituted-phenyl) sulfamoyl)thiazole-4-carboxylate derivatives (**4a-4l**) were achieved starting from ethyl 2-aminothiazole-4-carboxylate (**1**). We have done sulfonation, and sulfonamide coupling reactions for the synthesis of target molecules. We converted the primary amine to sulfonyl chloride in one pot by using diazotization reaction. We have optimized both the reaction steps by considering yield, purity, economy, and safety etc. The reaction scheme for the synthesis of targets were depicted in below scheme **1** and substitution strategy for synthesis was shown in table **01**



Scheme 1: Synthesis of **ethyl 2-(N-(substituted-phenyl)sulfamoyl)thiazole-4-carboxylate derivatives** (**4a-4l**):

Reagents and conditions: (**a**): $NaNO_2$, HCl, $SOCl_2$, CuCl, H_2O, -10 °C-RT, 3 h; (**b**): Substituted aromatic aniline (**3a-3l**), pyridine, DCM, 0 °C-RT, 6 h.

Table 01: Substitution strategy:

Sr. No.	R_1	Sr. No.	R_1
3a=4a		3g=4g	
3b=4b		3h=4h	
3c=4c		3i=4i	
3d=4d		3j=4j	
3e=4e		3k=4k	
3f=4f		3l=4l	

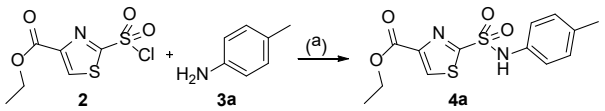
The conversion of primary amine to respected sulfonyl chloride were achieved by using sulfur dioxide, thionyl chloride etc. conditions. Previous literature shows, researcher had used

different diazotization conditions like the use of sodium nitrite, in water, hydrochloric acid, acetic acid, and acetonitrile as solvents along with the bubbling of sulfur dioxide gas in the reaction mixture and by using copper (II) chloride were used as a chlorinating agents. [16] Some researchers were used 1,2-dibenzyldisulfane as an sulfur source along with isoamyl nitrite or pentyl nitrite as an activator for amine, N-chlorosucinamide was used as an chlorinating source for the formation of product in acetonitrile and water as solvents. [17-20] These reactions conditions include some reactions were done at room temperature and some were done at heating condition, with variable reactions time and reactions were sluggish to undertake along with the less yields of obtained products. By taking the advantage of available literature, we have optimized the diazotization reaction for the clean reaction profile and good yields the details of the optimizations were depicted below.

The synthesis of intermediate **2** was achieved by using diazotization reaction for the formation of benzenediazonium ion in the presences of copper (I) chloride and hydrochloric acid and thionyl chloride to form desired compound with 85% yield. Temperature of reaction plays an important role in the yield of isolated product. The variation in the reaction temperature affects the yield of the intermediate **2**, the slight increase in temperature causes decreases in the reaction yield. As there are numerous side reactions if the variation temperature were observed, on TLC there are multiple spots if slight increase in temperature were seen. If temperature increases up to 0 °C them multiple spots were seen in TLC, as the TLC get worse in little higher temperature. The diazotization reaction were maintained at -20 °C through the course of progress of reaction.

In step **b** the compound **2** was reacted with different anilines (**3a-3l**), to obtained the desired compounds sulfonamides (**4a-4l**) with good yields. We used different bases like DIPEA, pyridine, triethyl amine and DMAP for sulfonamide coupling reactions for sulfonamide coupling we used some reported literature [21-22]. For optimization purpose, we have taken **3a** as model aniline and done some screening reactions for getting good yields and less reaction time. The details optimization conditions were mentioned in scheme **2** and table **02**.

Scheme 2: Synthesis of **ethyl 2-(N-(p-tolyl) sulfamoyl)thiazole-4-carboxylate** (**4a**):



Reagents and conditions: (**a**): base, solvent, temperature, time.

Table 02: Screening of base equivalents, solvents and time for synthesis of compound **(4a).**

Entry	Base	Solvent	Time (h)	Yield[a] (%)
1	TEA (4 eq.)	DCM	6	50
2	DIPEA (4 eq.)	DCM	8	40
3	DMAP (4 eq.)	DCM	12	35
4	Pyridine (4 eq.)	DCM	12	60
5	Pyridine (10 eq.)	DCM	6	90
6	DMAP (4 eq.)	THF	16	40
7	Pyridine (4 eq.)	THF	12	65
8	DIPEA (4 eq.)	THF	10	45
9	TEA (4 eq.)	THF	16	55
10	Pyridine (10 eq.)	THF	10	75

[a] Isolated yield, ethyl 2-(chlorosulfonyl)thiazole-4-carboxylate (1 eq.), substituted anilines (1.1 eq.)

The entries in table **02** indicate screening results different base, solvents time and obtained yields. Mostly we have used 4 equivalents of base in DCM and THF as solvents. In entries 1 and 9 we have used TEA as base to obtained 50% and 55% yield of **4a** respectably in DCM and THF as solvents. In slightly milder base we obtain

40% and 45% yields in both the solvents in entry 2 and 8. We got least yields when we used DMAP as base in both the solvents to obtain desired compound with 35% and 40% yields. In entries 4 and 7 we obtain 60% and 65% yields respectively in DCM and THF solvents. The excess of pyridine were used as base in entries 5 and 10 to obtain desired compound **4a** with 90% and 75% yields respectively. The reaction time was least from all other optimization reactions, and the isolation of product was done by acid-base work up to obtain desired product with good yields and good purity without tedious further purification. DCM is a favorable solvent for the sulfonamide coupling as it is easy to remove from the reaction mixture. We have used condition from entire 5 for the synthesis of remaining targets. The yields for the targets **4k** and **4l** were reduced, as there is formation of dimeric product, which is reducing the yield of reaction considerably. The detailed experimental details were provided in experimental section.

Biological Activity

All the synthesized compounds **(4a-4l)** screened for *in vitro* antimicrobial activity. The antibacterial activity was evaluated against two gram positive bacteria *Staphylococcus aureus* (NCIM-2901), *Bacillus subtilus* (NCIM-2063), gram negative bacteria, *Escherichia coli* (NCIM-2256), and three fungal stains *Candida albicans* (NCIM-3471), *Aspergillus flavus* (NCIM-539) and *Aspergillus niger* (NCIM-1196). For studying antimicrobial properties of compounds, Minimum Inhibitory Concentration (MIC, µg/mL), Minimum Bacterial Concentration (MBC) and Minimum Fungicidal Concentration (MFC) studied by modified macro-dilution technique. For bacterial strains MIC determination done by a serial of micro-dilution technique using 96-well micro-titer plate reader. Compounds (**4a-4l**) are prepared in saline (0.8% NaCl) solution containing 5% Dimethyl sulfoxide (DMSO) for dissolution. All microbial strains incubated with different concentration of each compound in a 96-well microliter plate for 20 h at 37 °C on Rotary shaker (160 rpm). After incubation, the lowest concentration value without growth defined as MICs. For Fungal strains agar dilution technique, on Potato Dextrose Agar (PDA) Medium used for MIC determination. The MBC and MFC of compounds determined by serial sub cultivation after inoculated for 72 h with tested compounds dissolved in saline containing 5% DMSO. The lowest concentration with no visible growth was defined as MBC/MFC indicating 99.5% killing of the original inoculums. All the experiments performed in triplicates and mean reading was taken as final reading. 5% DMSO was used as a negative control along with Ciprofloxacin as the standard antibacterial drugs and Fluconazole and Miconazole as the standard antifungal drugs. [23] The antimicrobial activity results given in table **03.**

Table 03 Antimicrobial activity data for compounds (4a-4l):

Compounds	MIC values[a] (µg/ml)					
	B. subtilis	*E. coli*	*S. aureus*	*C. Albicans*	*A. Flavus*	*A. Niger*
4a	40	55	70	50	40	50
4b	38	45	50	40	30	60
4c	45	65	55	75	80	100
4d	50	50	70	60	40	40
4e	**24**	**28**	32	**12.5**	30	**12.5**
4f	**26**	36	35	50	50	**12.5**
4g	30	40	35	25	25	25
4h	34	60	40	50	100	50
4i	40	60	55	90	75	50
4j	50	35	45	75	100	70
4k	**26**	31	32	**12.5**	30	**25**
4l	**26**	**28**	35	50	50	**25**
Ciprofloxacin	26	26	25	-	-	-
Fluconazole	-	-	-	40	25	25
Miconazole	-	-	-	12.5	12.5	12.5
[a]Values are the average of three readings.						

From the antimicrobial data, it was observed that all the newly synthesized compounds shows good to moderate level of antibacterial and antifungal activity. The antimicrobial activity data reveals that compounds **4e, 4f,**

4k and **4l** were found to be active and potent as antimicrobial agents among the series. The antimicrobial activity data reveals that among the compounds **4g**, and **4h** were moderately active for all the strains. The compounds **4a, 4b, 4c,** and **4d** are inactive for all the antimicrobial strains. The derivatives **4i** and **4j** are moderate activity for antimicrobial strains.

The effect of methyl and methoxy groups: The derivatives having methyl and methoxy group shows very less antimicrobial activity for all the strains. The electron donating groups shows less activity in the series.

The effect of cyano and halogen groups: The derivatives having cyano and flouro groups show moderate inhibitions for antimicrobial strains. For strains *B. subtilis* and *A. Niger* the derivatives shows good activity compared with the remaining antibacterial and antifungal strains in the series.

The effect of nitro and amino group: The derivative having nitro and amino groups as substitutions shows promising activity for all the antimicrobial strains. For strains *B. subtilis* and *A. Niger* the compounds shows very promising activity better than the standard.

The structure activity relationship can be drawn like when the sulfonamide were coupled with electron donating groups then the antimicrobial activity decreases. If the sulfonamide were coupled by electron withdrawing substituents like nitro, amino, and cyano group the antimicrobial activity of the compounds increases as compared with the standard drugs. The position of substitution doesn't affect the biological activity, weather the groups linked at *ortho*, *meta* or *para* positions in the series. In conclusion when the sulfonamide was substituted by more electron donating groups then the antimicrobial activity decreases among the series of derivatives.

Molecular docking study

Chemdraw program has been used to design the structures of all tested compounds. Using the Schrodinger software [24] the structures are optimized and energy minimized. Molecular docking was carried out using the optimized compounds. The molecular target's 3D structures were retrieved from Protein Data Bank (PDB) (www.rcsb.org): DNA gyrase and DNA topoisomerase (PDB: 1KZN, https://www.rcsb.org/structure/1KZN), and ergosterol (PDB: 4BJK, https://www.rcsb.org/structure/4BJK). The receptor preparation steps included removing water and ions, adding polar hydrogen, and assignment of charge were done. The active scaffold was delineated around the bound cocrystal ligands using grid boxes of perfect sizes.

The molecular-docking study was used to predict the binding pockets of tested compounds against DNA-gyrase and DNA topoisomerase for antimicrobial activity and synthesis of ergosterol for antifungal activity which are important targets for the development of antibacterial and antifungal agents to gain perspective into the mechanism of action of the tested compounds. Based on their important roles in the formation of bacterial cells and fungal cell these targets have been selected respectively, so targeting these proteins provides perceived benefits in inhibiting bacteria and fungi. Using Schrodinger Maestro v11.3 to reflect the position and orientation of the ligand found in the crystal structure, the cocrystal ligand was redocked to assure accuracy of the docking parameters and methods.[25] The difference between the cocrystal ligands and the original cocrystal ligand in RMSD value was < 2Å which approved the accuracy of the docking steps and parameters. The docking results revealed that compound 4e, 4f, 4k and 4l has high docking score against bacterial and fungal target. Moreover, the antimicrobial

docking part consists, compound **4e** was able to form hydrophobic interactions with key amino acid residue CYS673, present in standard drug and with two other amino acids (TYR672, and THR670) as shows in Table 04 and Figure 02 & 03. Compound 4f formed hydrogen bond interactions with the key amino acid residues in the active site (hydrogen bond CYS673), hydrophobic interaction with TYR672. Compound 4k formed hydrogen bond interactions with the key amino acid residues in the active site (CYS673 and LYS623). Compound 4l also formed hydrogen bond interactions with the key amino acid residues in the active site (hydrogen bond CYS673), hydrophobic interaction with TYR670 and LYS602. The antifungal docking part consists, compound 4e was able to form hydrophobic interactions with key amino acid residue CYS674, present in standard drug and with two other amino acids (TYR670, and THR670) Table 05 and Figure 04 & 05. Compound 4f formed hydrophobic interactions with the key amino acid residues in the active site TYR675, and hydrogen bond interaction with LYS593. Compound 4k formed hydrogen bond interactions with the key amino acid residues in the active site (CYS670). Compound 4l formed hydrophobic interactions with the amino acid residues in the active site (CYS673 and TYR670).

Table 04: Docking interaction of antimicrobial compound.

Compound	Hydrophobic interactions	Hydrogen interactions	Dock score
4e	CYS673, TYR672, THR670		-8.567
4f	TYR672,	CYS673	-8.385
4k	------	CYS673, LYS623	-7.621
4l	TYR670, LYS602	CYS673	-7.390
Ciprofloxacin	TYR672, CYS674	CYS673	-8.604

Best docking poses of antimicrobial compound:

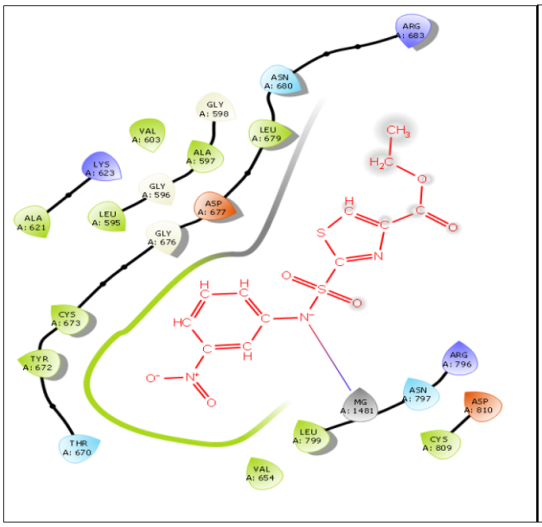


Figure 02 of Compound 4e

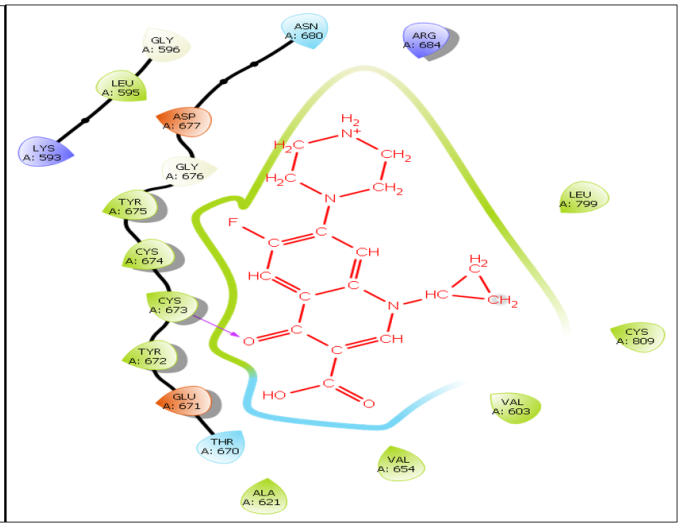


Figure 03 of Ciprofloxacin (std.)

***Figure 02 and Figure 03*:** The binding interaction of compound **4e** and Ciprofloxacin (std.) within the binding site in 2D.

Best docking poses of antifungal compound:

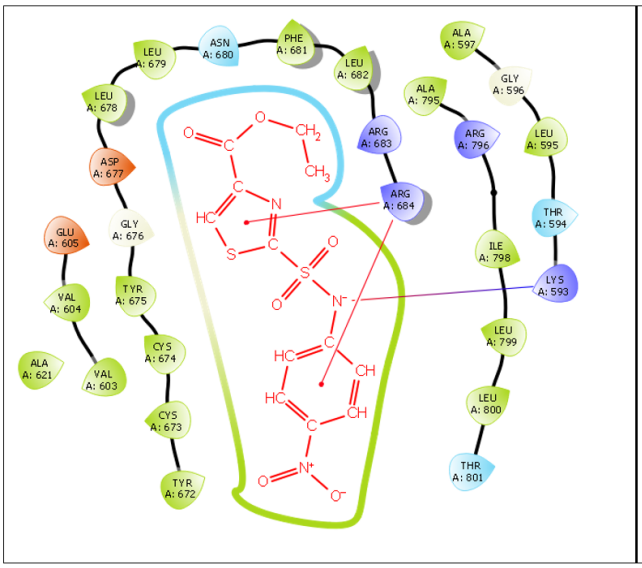


Figure 04 of Compound **4f**

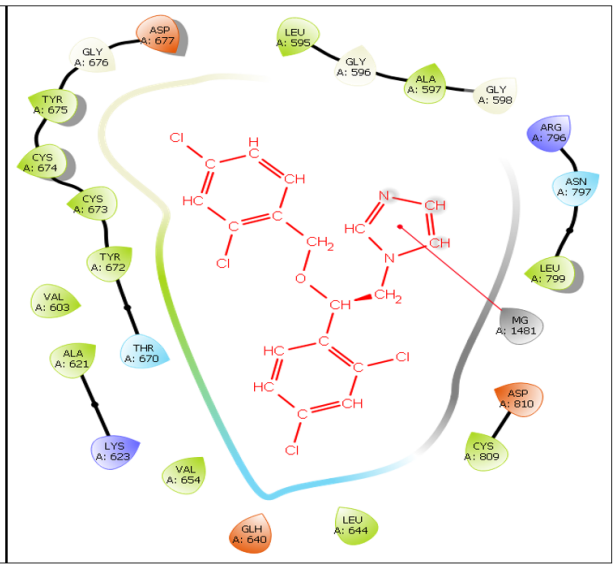


Figure 05 Miconazole (std.)

***Figure 04 and Figure 05*:** The binding interaction of compound **4f** and Miconazole (std.) within the binding site in 2D.

Table 05: Docking interaction of antifungal compound.

Compound	Hydrophobic interactions	Hydrogen interactions	Dock score
4e	CYS674, TYR670, THR670		-7.067
4f	TYR675	LYS593	-7.905
4k	------	CYS670	-6.601
4l	TYR670, CYS673	------	-7.201
Miconazole	TYR672, CYS674, THR670	----	-7.837

Computational Study and ADME Properties:

A computational study of synthesized ethyl 2-(N-(substituted-phenyl)sulfamoyl)thiazole-4-carboxylate derivatives (4a-4l) was performed for prediction of ADME properties and the value obtained was presented in the Table **06**. It shows that the synthesized compound exhibited a good % ABS (% absorption) and it was calculated by formula: % ABS = 109-(0.345×TPSA) [26-27] ranging from 63.73 to 79.54%. however, the molecule likely to be developed as an orally active drug candidate should not violet the more than or equal to these four criteria [28]: miLog P (octanol-water partition coefficient) ≤ 5, molecular weight ≤ 500, number of hydrogen bond acceptors ≤ 10 and number of hydrogen bond donors ≤ 5 and synthesized compounds were covered all five Lipinski's rule i.e. there was no violation of Lipinski's rule, values were calculated by using Molinspiration online property [29] calculation, the molecule having higher score in drug likeness model score [30] having high probability that it will be an active molecule. All the tested compounds followed the criteria for orally active drug and therefore, these compounds may have a good potential for eventual development as oral agents.

Conclusions:

In the present communication we have designed and synthesized ethyl 2-(N-(substituted-phenyl)sulfamoyl)thiazole-4-carboxylate derivatives (**4a-4l**) from

Table 06: Pharmacokinetic parameters important for good oral bioavailability.

Comp	% ABS	TPSA (A2)	n-ROTB	MV (A3)	MW	mi LogP	n-ON	n-OHNH	Lipinski violation	Drug likeness model score
Rule	-	-	-	-	< 500	≤ 5	< 10	< 5	≤ 1	-
4a	79.54	85.37	6	263.73	326.04	2.82	6	1	0	-0.38
4b	79.54	85.37	6	263.73	326.04	2.79	6	1	0	-0.53
4c	76.36	94.60	7	272.72	342.40	2.40	7	1	0	-0.38
4d	76.36	94.60	7	272.72	342.40	2.42	7	1	0	-0.17
4e	63.73	131.19	7	270.51	357.01	2.30	9	1	0	-0.87
4f	63.73	131.19	7	270.51	357.01	2.33	9	1	0	-0.69
4g	71.33	109.16	6	264.03	337.02	2.10	7	1	0	-0.53
4h	71.33	109.16	6	264.03	337.02	2.12	7	1	0	-0.45
4i	79.54	85.37	6	252.10	330.01	2.51	6	1	0	-0.46
4j	79.54	85.37	6	252.10	330.01	2.53	6	1	0	-0.08
4k	70.57	111.39	6	258.46	327.39	1.42	7	3	0	-0.15
4l	70.57	111.39	6	258.46	327.39	1.45	7	3	0	-0.31

commercially available ethyl 2-aminothiazole-4-carboxylate. These derivatives were synthesized through a series of reactions and final derivatives were characterized by spectral data. The compounds **4a-4l** were tested for their antimicrobial activity against antibacterial and antifungal strains. The compounds **4e**, **4f**, **4k** and **4l** bearing nitro and amino substituents shows promising activity against *bacillus subtillis* and *aspergillus niger* strains in the series. Remaining compounds shows moderate activity. The derivatives bearing electron withdrawing groups showed promising activity compared to electron donating groups. Docking studies for these four new compounds were performed to gain insight the mode of action. Virtual screening of the most liable compounds was performed against different PDB that are known targets for some antimicrobial and antifungal agents. Computational study of all the synthesized compounds were followed the Lipinski's rule and also follow the criteria for orally active drug and therefore, these compounds may have a good potential as oral agents.

Experimental Details:

Material and methods:

All chemicals, unless otherwise specified, were purchased from commercial sources and were used without further purification. The major chemicals purchased from Sigma Aldrich and Avra labs. The development of reactions were monitored by thin layer chromatography (TLC) analysis on Merck pre-coated silica gel 60 F254 aluminum sheets, visualized by UV light. All reactions carried out under inert atmosphere. Melting points recorded on Casia-Siamia (VMP-AM) melting point apparatus and all were uncorrected. The purity of intermediate was assessed by TLC, NMR, and LCMS. The purities of final compounds were checked by NMR, LCMS and HPLC and all structures were consistent with proposed structures characterization. The ^{1}H NMR spectra were recorded on a 400 MHz Varian NMR spectrometer. The ^{13}C recorded on a 100 MHz Varian NMR spectrometer. The chemical shifts were reported as NMR spectra δppm units. The following abbreviations are used; singlet (s),

doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). Mass spectra were taken with Micromass-QUATTRO-II of produced by WATERS Corporation.

Experimental procedure for synthesis of ethyl 2-(N-(substituted-phenyl)sulfamoyl) thiazole-4-carboxylate derivatives (4a-4l):

Step a: Synthesis of ethyl 2-(chlorosulfonyl) thiazole-4-carboxylate (2):

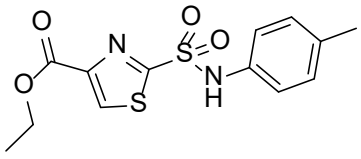
In round bottom flask **a** take a solution of ethyl 2-aminothiazole-4-carboxylate (**1**; 17.2 g, 0.1 mol) was dissolved in concentrated HCl (100 mL) and acetonitrile (50 mL) cooled reaction mixture to -20 °C. In round bottom flask **b,** take a solution of sodium nitrite (10.4 g, 0.15 mol) was dissolved in cold water (50 mL). Transfer the solution of round bottom flask **b** to round bottom flask **a** drop-wise by maintaining the temperature -20 °C. The content of reaction was stirred at same temperature for 2h. In round bottom flask **c,** thionyl chloride (36.3 mL, 0.5 mol) was added drop-wise in water (50 mL) and acetonitrile (50 mL) at -20 °C. Stirred the content of flask **c** for 30 min at same temperature, then added copper (I) chloride (1.7 g) portion wise in the flask at -20 °C, stirred the content for further 30 min. The content of round bottom flask **a,** was added to round bottom flask **c** at -20 °C drop-wise. Stirred it for 3h at same temperature and further at room temperature for 3h. Brown precipitate was formed in reaction mixture. Poured the content in cold water (200 mL) and stirred for 30 min. Filtered the precipitate washed the residue with cold water (150 mL), cold hexane (125 mL) cold diethyl ether (150 mL) and dried under reduced pressure to obtain ethyl 2-(chlorosulfonyl)thiazole-4-carboxylate (**2**; 21.7 g, 85%) as an brown solid.

Step b: General procedure for the synthesis of (4a-4l) :

To a stirred solution of ethyl 2-(chlorosulfonyl) thiazole-4-carboxylate (**2**; 1 eq.) in DCM (10 mL) was added pyridine (10 eq.) at 0 °C and stirred reaction mixture at same temperature for 15 min. Added **3a-3j** (1.2 eq.) drop/portion wise and stirred reaction mixture at room temperature for 6 h. Progress of reaction was monitored by TLC and LCMS. After completion, the reaction mixture was poured on cold 2N aqueous HCl (10 mL) and stirred reaction mixture for 30 min. The work up procedure was different for different derivatives, some compounds isolated by following work up procedure 1 and some compounds were isolated by following work up procedure 2.

[(1) Precipitation formed in some derivatives, which filtered. The obtained solid was washed with water (3×10 mL), cold diethyl ether (3×10 mL) and cold pentane (3×10 mL) to afford crude **4a-4l**; (2) Extracted it with DCM (2 × 20 mL) the organic layer was separated washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford crude **4a-4l**.] The crude obtained was purified by column chromatography (silica, 100-200 mesh, 25-70% EtOAc in hexane) to afford **4a-4l** as solids.

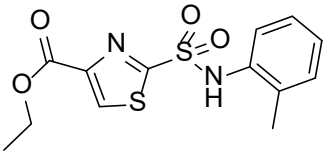
Synthesis of ethyl 2-(N-(p-tolyl)sulfamoyl) thiazole-4-carboxylate (4a):



To a stirred solution of ethyl 2-(chlorosulfonyl) thiazole-4-carboxylate (**2**; 0.5 g, 1.95 mmol) in DCM (5 mL) was added pyridine (1.57 mL, 19.5 mmol) at 0 °C and stirred reaction mixture at same temperature for 15 min. Added p-toluidine (**3a;** 0.23 g, 2.15 mmol) drop-wise and stirred the reaction mixture at room temperature for 6h. The progress of reaction was monitored by TLC and LCMS. After completion, the reaction

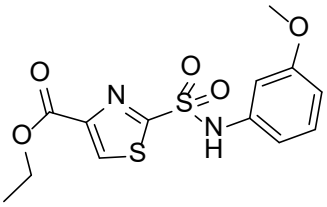
mixture was poured on cold 2N aqueous HCl (5 mL) and stirred reaction mixture for 10 min. Extracted it with DCM (2 × 10 mL) the organic layer was separated, washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo.* The obtained crude was purified by column chromatography (silica, 100-200 mesh, 30% EtOAc in hexane) to afford ethyl 2-(N-(p-tolyl)sulfamoyl)thiazole-4-carboxylate (**4a**; 0.57 g, 89.4%) as an yellow solid; m.p. 111-113 °C; IR (KBr, nmax, cm-1): 1167 (S=O symmetric), 1321 (S=O asymmetric), 1350 (Ar-C=C), 3370 (b, NH); ^{1}H NMR (400 MHz, $CDCl_3$, ppm)= δ 9.12 (brs, 1H), 8.12 (s, 1H), 7.90 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J*= 8.2 Hz, 2H), 4.46-4.41(q, *J* = 13.6, 7.6 Hz, 2H), 2.38 (s, 3H), 1.42 (t, *J* = 8.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MH_Z, ppm)= δ 169.2, 161.4, 147.6, 141.2, 130.2, 129.8, 126.4, 125.6, 60.4, 22.4, 14.8. LC-MS *m/z* (%): 327 (M+1); Anal. calc. for $C_{13}H_{14}N_2O_4S_2$: C, 47.84; H, 4.32; N, 8.58; S, 19.65; Found: C, 47.80; H, 4.40; N, 8.50; S, 19.72.

Synthesis of ethyl 2-(N-(o-tolyl)sulfamoyl) thiazole-4-carboxylate (4b):



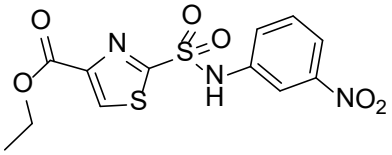
Yellow solid; Yield- 89.4 %; m.p. 122-123 °C; IR (KBr, nmax, cm-1): 1164 (S=O symmetric), 1320 (S=O asymmetric), 1360 (Ar-C=C), 3252 (b, NH); ^{1}H NMR (400 MHz, $CDCl_3$, ppm)= δ 9.10 (brs, 1H), 8.22 (s, 1H), 7.70-7.68 (m, 1H), 7.36-7.27 (m, 3H), 4.46-4.42 (q, *J* = 14.4, 7.2 Hz, 2H), 2.48 (s, 3H), 1.42 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MH_Z, ppm)= δ 168.1, 160.5, 146.7, 136.8, 132.6, 131.2, 129.8, 128.6, 126.8, 126.2, 60.2, 22.4, 14.2; LC-MS *m/z* (%): 327 (M+1); Anal. calc. for $C_{13}H_{14}N_2O_4S_2$: C, 47.84; H, 4.32; N, 8.58; S, 19.65; Found: C, 47.79; H, 4.44; N, 8.52; S, 19.61.

Synthesis of ethyl 2-(N-(3-methoxyphenyl) sulfamoyl)thiazole-4-carboxylate (4c):



Off white solid; Yield- 87 %; m.p. 137-138 °C; IR (KBr, nmax, cm-1): 1160 (S=O symmetric), 1322 (S=O asymmetric), 1356 (Ar-C=C), 3262 (b, NH); ^{1}H NMR (400 MHz, $CDCl_3$, ppm)= δ 9.22 (s, 1H), 8.12 (s, 1H), 7.58 (s, 1H), 7.57-7.54 (q, *J* = 8.8 Hz, 1H), 7.36-7.32 (q, 1H), 6.98-6.97 (t, *J* = 3.6 Hz 1H), 4.46-4.41 (q, *J* = 14.0, 6.8 Hz, 2H), 3.86 (s, 3H), 1.42 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MH_Z, ppm)= δ 168.7, 161.2, 160.1, 148.2, 133.7, 129.9, 127.4, 119.5, 118.6, 112.4, 60.4, 54.6, 14.6; LC-MS *m/z* (%): 343 (M+1); Anal. calc. for $C_{15}H_{12}N_4O_2S_2$: C, 45.60; H, 4.12; N, 8.18; S, 18.73; Found: C, 45.66; H, 4.04; N, 8.10; S, 18.60.

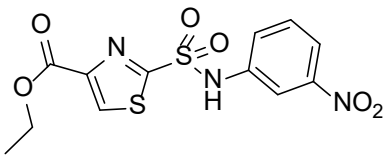
Synthesis of ethyl 2-(N-(4-methoxyphenyl) sulfamoyl)thiazole-4-carboxylate (4d):



Off white solid; Yield- 88.6 %; m.p. 112-114 °C; IR (KBr, nmax, cm-1): 1162 (S=O symmetric), 1320 (S=O asymmetric), 1366 (Ar-C=C), 3251 (b, NH); ^{1}H NMR (400 MHz, $CDCl_3$, ppm)= δ 9.16 (s, 1H), 8.10 (s, 1H), 7.96-7.93 (d, *J* = 6.8 Hz, 2H), 6.98-6.93 (d, *J* = 8.2 Hz 2H), 4.46-4.41 (q, *J* = 14.2, 7.0 Hz, 2H), 3.84 (s, 3H), 1.42 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MH_Z, ppm)= δ 168.4, 161.4, 160.2, 147.9, 129.6, 126.4, 125.2, 116.6, 112.4, 61.41, 54.4, 14.3; LC-MS *m/z* (%): 343 (M+1); Anal. calc. for $C_{15}H_{12}N_4O_2S_2$: C, 45.60; H, 4.12; N, 8.18; S, 18.73; Found: C, 45.69; H, 4.09; N, 8.22; S,

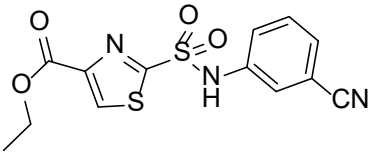
18.68.

Synthesis of ethyl 2-(N-(3-nitrophenyl) sulfamoyl)thiazole-4-carboxylate (4e):



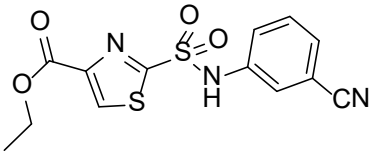
Brown Solid; Yield- 83.2%; m.p. 193-194 °C; IR (KBr, nmax, cm-1): 1167 (S=O symmetric), 1321 (S=O asymmetric), 1350 (Ar-C=C), 3251 (b, NH); ^{1}H NMR (400 MHz, $CDCl_3$, ppm)= δ 9.09 (s, 1H), 8.54 (s, 1H), 8.44 (s, 1H), 8.22-8.21 (d, *J* = 4.4 Hz, 1H), 7.79-7.74 (m, 2H), 4.48-4.44 (q, *J* = 13.6, 7.6 Hz, 2H), 1.46 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHZ, ppm)= δ 165.7, 161.3, 148.3, 147.8, 137.9, 129.4, 127.6, 126.1, 61.6, 14.8; LC-MS *m/z* (%): 358 (M+1); Anal. calc. for $C_{12}H_{11}N_3O_6S_2$: C, 40.33; H, 3.10; N, 11.76; S, 17.94; Found: C, 40.43; H, 3.21; N, 11.81; S, 18.04.

Synthesis of ethyl 2-(N-(4-nitrophenyl) sulfamoyl)thiazole-4-carboxylate (4f):



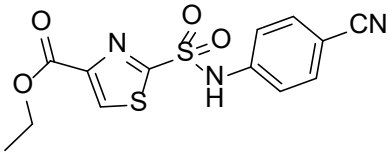
Brown Solid; Yield- 80.8%; m.p. 201-203 °C; IR (KBr, nmax, cm-1): 1162 (S=O symmetric), 1318 (S=O asymmetric), 1344 (Ar-C=C), 3231 (b, NH); ^{1}H NMR (400 MHz, $CDCl_3$, ppm)= δ 9.14 (brs, 1H), 8.33-8.31 (d, *J* = 8.2 Hz, 2H), 8.28 (s, 1H), 8.21-8.18 (d, *J* = 8.2 Hz, 2H), 4.49-4.44 (q, *J* = 13.6, 7.6 Hz, 2H), 1.43 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MH_Z, ppm)= δ 165.67, 161.3, 148.2, 147.9, 137.8, 129.1, 127.9, 126.1, 61.6, 14.4; LC-MS *m/z* (%): 358 (M+1); Anal. calc. for $C_{12}H_{11}N_3O_6S_2$: C, 40.33; H, 3.10; N, 11.76; S, 17.94; Found: C, 40.30; H, 3.01; N, 11.69; S, 17.88.

Synthesis of ethyl 2-(N-(3-cyanophenyl) sulfamoyl)thiazole-4-carboxylate (4g):



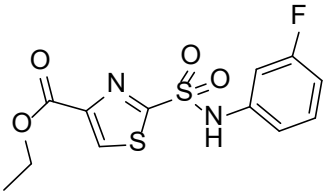
Off-White Solid; Yield- 83.4%; m.p. 149-151 °C; IR (KBr, nmax, cm-1): 1160 (S=O symmetric), 1320 (S=O asymmetric), 1360 (Ar-C=C), 3233 (b, NH); ^{1}H NMR (400 MHz, $CDCl_3$, ppm)= δ 9.12 (s, 1H), 8.20 (s, 1H), 8.19 (s, 1H), 7.92 (d, *J* = 2.4 Hz, 1H), 7.58 (d, *J* = 2.4 Hz, 1H), 7.34-7.30 (m, 1H), 4.48-4.43 (q, *J* = 13.6, 7.6 Hz, 2H), 1.43 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MH_Z, ppm)= δ 167.2, 161.8, 148.3, 135.2, 133.4, 130.2, 129.8, 127.6, 125.8, 122.9, 63.8, 14.4; LC-MS *m/z* (%): 338 (M+1); Anal. calc. for $C_{13}H_{11}N_3O_4S_2$: C, 46.28; H, 3.29; N, 12.46; S, 19.01; Found: C, 46.34; H, 3.22; N, 12.52; S, 18.97.

Synthesis of ethyl 2-(N-(4-cyanophenyl) sulfamoyl)thiazole-4-carboxylate (4h):



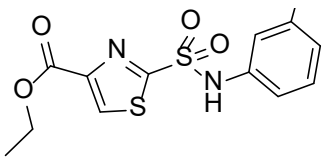
Off-White Solid; Yield- 82.6%; m.p. 144-145 °C; IR (KBr, nmax, cm-1): 1167 (S=O symmetric), 1321 (S=O asymmetric), 1350 (Ar-C=C), 3281 (b, NH); ^{1}H NMR (400 MHz, $CDCl_3$, ppm)= δ 9.12 (s, 1H), 8.20 (s, 1H), 8.12 (d, *J* = 8.4 Hz, 2H), 7.58-7.57 (d, *J* = 8.4 Hz, 2H), 4.48-4.43 (q, *J* = 13.6, 7.6 Hz, 2H), 1.43 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MH_Z, ppm)= δ 167.4, 161.2, 148.4, 135.2, 133.6, 130.2, 129.8, 127.6, 125.4, 122.9, 62.4, 14.4; LC-MS *m/z* (%): 338 (M+1); Anal. calc. for $C_{13}H_{11}N_3O_4S_2$: C, 46.28; H, 3.29; N, 12.46; S, 19.01; Found: C, 46.36; H, 3.20; N, 12.39; S, 18.91.

Synthesis of ethyl 2-(N-(3-fluorophenyl) sulfamoyl)thiazole-4-carboxylate (5i):



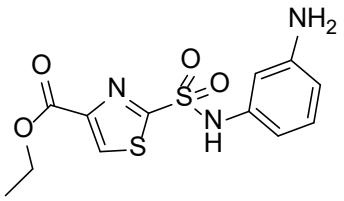
Yellow Solid; Yield- 85.7%; m.p. 116-117 °C; IR (KBr, nmax, cm-1): 1166 (S=O symmetric), 1326 (S=O asymmetric), 1360 (Ar-C=C), 3270 (b, NH); ^{1}H NMR (400 MHz, $CDCl_3$, ppm)= δ 9.13 (brs, 1H), 8.20 (s, 1H), 7.75-7.53 (d, *J* = 7.2 Hz, 2H), 7.44-7.41 (m, 1H), 7.17-7.13 (m, 1H), 4.47-4.43 (q, *J* = 13.6, 7.6 Hz, 2H), 1.43 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MH_Z, ppm)= δ 167.4, 164.4, 161.4, 161.2, 148.8, 134.8, 134.7, 130.7, 130.6, 127.6, 122.7, 122.3, 118.1, 117.8, 113.8, 113.7, 61.6, 14.4; LC-MS *m/z* (%): 331 (M+1); Anal. calc. for $C_{12}H_{11}FN_2O_4S_2$: C, 43.63; H, 3.36; N, 8.48; S, 19.41; Found: C, 43.70; H, 3.48; N, 8.41; S, 19.32.

Synthesis of ethyl 2-(N-(4-fluorophenyl) sulfamoyl)thiazole-4-carboxylate (4j):



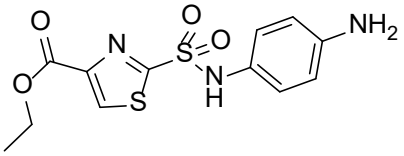
Yellow Solid; Yield- 88.9%; m.p. 104-105 °C; IR (KBr, nmax, cm-1): 1162 (S=O symmetric), 1318 (S=O asymmetric), 1363 (Ar-C=C), 3280 (b, NH); ^{1}H NMR (400 MHz, $CDCl_3$, ppm)= δ 9.10 (brs, 1H), 8.18 (s, 1H), 7.62-7.49 (d, *J* = 8.8 Hz, 2H), 7.44-7.41 (d, *J* = 8.4 Hz, 2H), 4.46-4.43 (q, *J* = 13.6, 7.6 Hz, 2H), 1.44 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MH_Z, ppm)= δ 166.7, 164.2, 161.4, 161.2, 148.8, 134.8, 134.7, 130.7, 130.6, 127.6, 122.7, 122.3, 118.1, 117.4, 113.8, 113.6, 63.6, 14.4; LC-MS *m/z* (%): 331 (M+1); Anal. calc. for $C_{12}H_{11}FN_2O_4S_2$: C, 43.63; H, 3.36; N, 8.48; S, 19.41; Found: C, 43.55; H, 3.44; N, 8.40; S, 19.28.

Synthesis of ethyl 2-(N-(3-aminophenyl) sulfamoyl)thiazole-4-carboxylate (4k):



Yellow Solid; Yield- 48.1%; m.p. 181-183 °C; IR (KBr, nmax, cm-1): 1166 (S=O symmetric), 1322 (S=O asymmetric), 1354 (Ar-C=C), 3248 (b, NH); ^{1}H NMR (400 MHz, $CDCl_3$, ppm)= δ 9.40 (brs, 1H), 8.30 (s, 1H), 7.61-7.54 (t, *J* = 6.8 Hz, 1H), 7.34-7.21 (dd, *J* = 8.4 Hz, 2H), 7.20 (s, 1H), 5.63 (s, 2H), 4.47-4.42 (q, *J* = 13.8, 7.2 Hz, 2H), 1.44 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MH_Z, ppm)= δ 162.2, 152.4, 148.8, 148.6, 136.4, 130.2, 124.5, 112.3, 111.3, 109.8, 62.4, 14.6; LC-MS *m/z* (%): 328 (M+1); Anal. calc. for $C_{12}H_{13}N_3O_4S_2$: C, 44.03; H, 4.00; N, 12.84; S, 19.59; Found: C, 43.97; H, 3.88; N, 12.89; S, 19.63.

Synthesis of ethyl 2-(N-(4-aminophenyl) sulfamoyl)thiazole-4-carboxylate (4l):



Yellow Solid; Yield- 44.6%; m.p. 176-177 °C; IR (KBr, nmax, cm-1): 1164 (S=O symmetric), 1326 (S=O asymmetric), 1354 (Ar-C=C), 3274 (b, NH); ^{1}H NMR (400 MHz, $CDCl_3$, ppm)= δ 9.38 (brs, 1H), 8.28 (s, 1H), 7.81-7.72 (d, *J* = 8.4 Hz, 2H), 7.44-7.28 (d, *J* = 8.4 Hz, 2H), 5.66 (s, 2H), 4.48-4.44 (q, *J* = 13.8, 7.2 Hz, 2H), 1.43 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MH_Z, ppm)= δ 162.4, 156.4, 146.2, 138.8, 128.6, 124.6, 116.4, 62.4, 14.6; LC-MS *m/z* (%): 328 (M+1); Anal. calc. for $C_{12}H_{13}N_3O_4S_2$: C, 44.03; H, 4.00; N, 12.84; S, 19.59; Found: C, 43.94; H, 3.91; N, 12.70; S, 19.48.

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Supporting information for this article is given via a link at the end of the document.

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