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Synthesis and biological evaluation of 2,4,5-trisubstituted thiazoles as antituberculosis agents effective against drug-resistant tuberculosis

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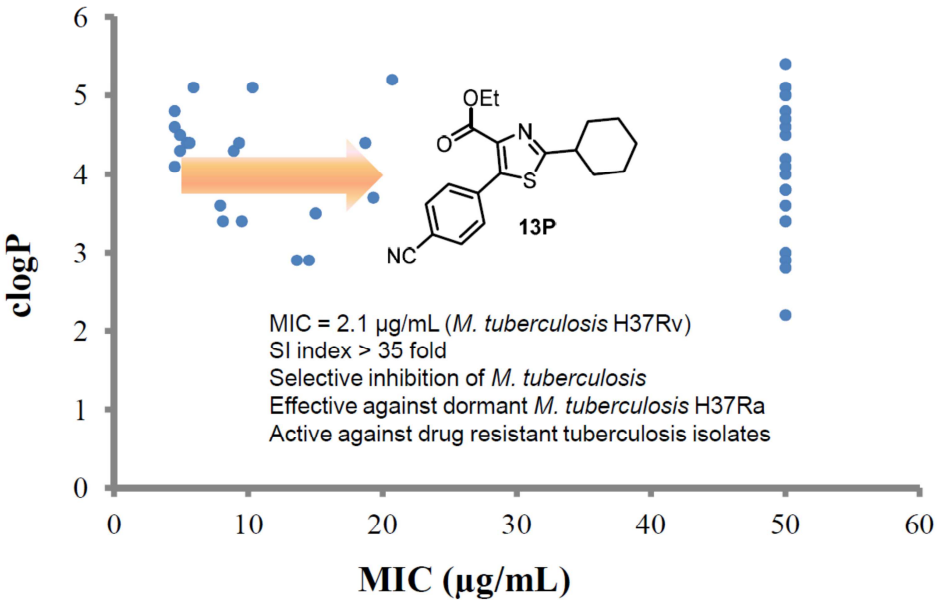

The synthesis and evaluation of trisubstituted thiazoles as antituberculosis agents active against drug-resistant tuberculosis are reported. The detail structure-activity-relationship study has identified a requirement of hydrophobic substituent at C2, ester functionality at C4, and various groups with hydrogen bond acceptor character at C5 of thiazole scaffold. This has led to the identification of **13h** and **13p** as lead compounds. These compounds inhibited the dormant *Mycobacterium tuberculosis* H37Ra strain and *M. tuberculosis* H37Rv selectively. Importantly, **13h** and **13p** were non-toxic to CHO cells. The **13p** showed activity against multidrug-resistant tuberculosis isolates.

Synthesis and biological evaluation of 2,4,5-trisubstituted thiazoles as antituberculosis agents effective against drug-resistant tuberculosis

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KEYWORDS: antituberculosis agents, thiazoles, tuberculosis, dormant tuberculosis, drug resistant tuberculosis

ABSTRACT: The dormant and resistant form of *Mycobacterium tuberculosis* presents a challenge in developing new anti-tubercular drugs. Herein, we report the synthesis and evaluation of trisubstituted thiazoles as antituberculosis agents. The SAR study has identified a requirement of hydrophobic substituent at C2, ester functionality at C4, and various groups with hydrogen bond acceptor character at C5 of thiazole scaffold. This has led to the identification of **13h** and **13p** as lead compounds. These compounds inhibited the dormant *Mycobacterium tuberculosis* H37Ra strain and *M. tuberculosis* H37Rv selectively. Importantly, **13h** and **13p** were non-toxic to CHO cells. The **13p** showed activity against multidrug-resistant tuberculosis isolates.

1. Introduction

Tuberculosis (TB) is one of the major cause of deaths resulting from infectious diseases. According to the WHO statistics, it was estimated that around 1.4 million deaths occurred due to TB in 2015 and around 0.4 million more deaths were associated with HIV co-infected TB patients.[1] Given the fact that emergence of multidrug-resistant TB (MDR-TB) and extremely drug-resistant TB (XDR-TB) is on rise, there is an urgent requirement for the development of new drugs. To develop drugs for TB is a complicated task as new drug needs to be efficacious and safe in combination with other known TB drugs. Taken together, it requires intense efforts to develop a new TB drug.

Bedaquiline (**1**) has been approved for the treatment of MDR-TB and has shown efficacy in XDR-TB[2]; while Delamanid (**2**, figure 1) has been recommended in South Korea, Europe and Japan for the patients suffering from MDR-TB.[3] This has evoked optimism of the scientific community to develop drugs active against dormant and drug-resistant tuberculosis. Various heterocyclic and other agents with antituberculosis potential have been reported (figure 1).[4-5] These agents include adamantyl ureas[6], 1,4-azaindoles (**3**, MIC range= 0.78-3.12 µM)[7], azetidin-2-ones[8], benzimidazoles [9], benzothiazoles (**4**, MIC= 3.12µg/mL)[10], calanolides[11], pyridine containing diarylethers[12], hydrazides and hydrazones[13], quinoline-isoxazole hybrids (**5**, MIC= 0.2 µM)[14], nitrofurans[15], oxadiazoles[16], piperidones (**6**, MIC= 0.78 µg/mL)[17], pyrazoles (**7**, MIC= 0.35 µg/mL)[18], pyridines[19], pyrroles (**8**, MIC= 0.4 µg/mL)[20], pyrrolidines[21], spectinamides[22], sulfonamides[23], thiazoles[24], thiosemicarbazones[25] and triazoles[26]. The trisubstituted thiazoles effective against HIV-1 reverse transcriptase[27] and benzo[*d*]thiazole-2-carbanilides as antitubercular agents[28] have been reported. In 2014, Chatterji *et al.* reported diaryl thiazole containing pyridine (**9**, MIC= 0.12 µg/mL) with potent antimycobacterial activity.[29] From the SAR (structure-activity relationship) studies, it was clear that the thiazole containing substituents other than pyridine (**10**, MIC> 32 µg/mL) were inactive against *M. tuberculosis* H37Rv.[29] This was an important observation since pyridine might cause liver toxicity due to its potential to form reactive metabolites *in vivo*.[30-32] Hence, there is a need to develop thiazole inhibitors without pyridine substituents. Herein, we report on the development of thiazole-based

potential antituberculosis agents devoid of pyridine. In addition, these agents showed activity against dormant *M. tuberculosis* H37Ra and limited activity against drug resistant TB isolates.

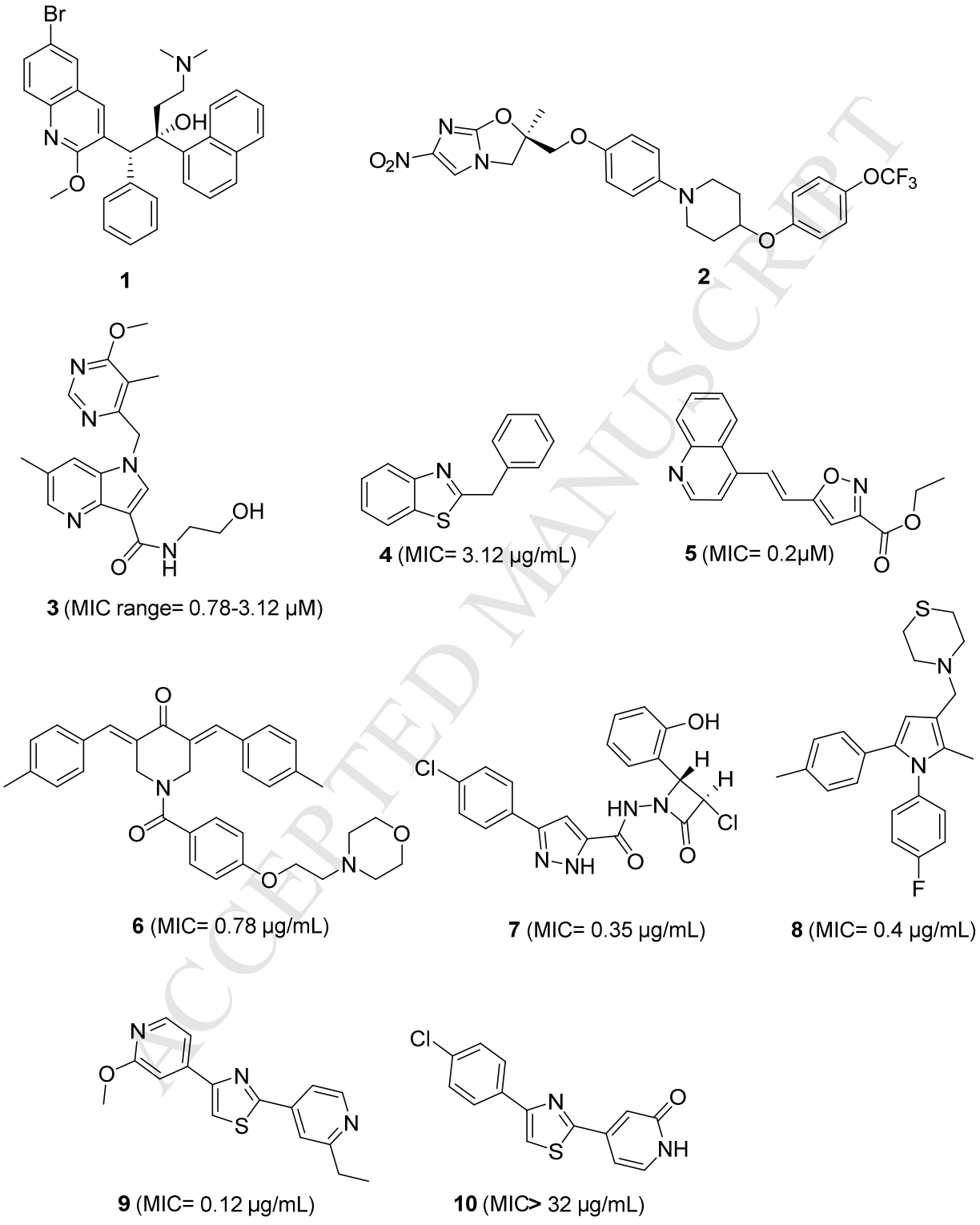
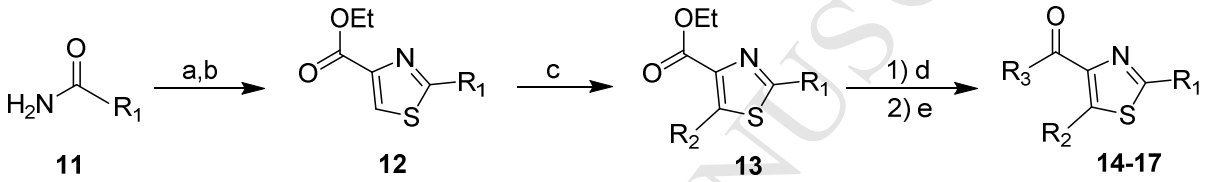


Figure 1: Structures of antituberculosis agents along with MIC value on *M. tuberculosis* H37Rv

2. Results and Discussion

2.1. Chemistry: We began our study by synthesizing thiazole derivatives as shown in figure 2. Thioamides were synthesized from respective amides (**11a**-**11c**). The condensation of ethyl bromopyruvate with thioamides resulted in 2,4-disubstituted thiazoles, **12a**-**12c**. The coupling of **12a**-**12c** with aryl bromides catalyzed by $PdCl_2(PPh_3)_2$ in the presence of potassium acetate furnished trisubstituted thiazole **13a**-**13r**. The esters **13a**-**13r** were hydrolyzed with sodium hydroxide and the obtained acids were used without purification to couple with amines affording 4-amido 2,5 disubstituted thiazole 1**4a**-1**4n**, 1**5a**-1**5f**, 1**6a**-1**6f**, and 1**7a**-1**7f** .



11 **12** **13** **14-17**

Figure 2: Synthesis of substituted thiazoles. a) P_2S_5, diethyl ether, RT, 2 h; b) ethyl bromopyruvate, EtOH, reflux, 30 min; c) R_2 substituted bromides, $PdCl_2(PPh_3)_2$, KOAc, DMA, 150 °C, 24 h; d) 2N NaOH, THF:MeOH (3:1); e) R_3 substituted amines, EDC.HCl, HOBt, Et_3N, DMF, 0°C to RT, overnight.

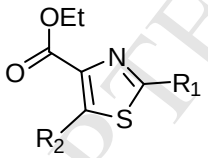
2.2. Biological activity

2.2.1. Antituberculosis activity

The compounds were screened for their inhibitory potential against *M. tuberculosis* H37Rv using MABA assay. The MIC (minimum inhibitory concentration) of these derivatives along with cLogP is shown in table 1. Rifampicin was used as positive control and demonstrated MIC of 0.2 µg/mL. In the trisubstituted thiazole series (**13a-13r**), the MIC varied from 1.8 to >32 µg/mL. Initially, compounds **13a-13h** (isopropyl as R_1 substituent) were prepared and screened against *M. tuberculosis* H37Rv. Importantly, compounds **13a**-**13h** (except **13b**) showed antitubercular activity. Compound **13h** showed MIC of 1.8 µg/mL with cLogP of 3.5. Next, we synthesized compounds with cyclohexyl as R_1 substituent (**13i-13p**) which led to the identification of **13p** as potent antitubercular agent with

MIC of 2.1 µg/mL. This Compound has cLogP of 4.2 and has comparable MIC to that of **13h**. In **13i-13p** subseries, except **13j**, all other compounds showed antitubercular activity in single digit. When **13a-13h** (isopropyl as R_1 substituent) compared with **13i-13p** (cyclohexyl as R_1 substituent), it clearly showed the preference for cyclohexyl over isopropyl as R_1 substituent. Further, compounds with methyl as R_1 substituent (**13q**, **13r**) were less potent as compared to their isopropyl and cyclohexyl counterparts (**13a**, **13h** and **13i**, **13p**). It is clear from the structure-activity relationship (SAR) study that cyclohexyl or isopropyl as R_1 substituent and benzonitrile as R_2 substituent are important for their antitubercular activity. From the subseries, **13h** and **13p** were identified as potent compounds. Important to note that the position of nitrile on R_2 substituent is crucial as 4-benzonitrile as R_2 is more active (**13h**, MIC= 1.8 µg/mL; **13p**, MIC= 2.1 µg/mL) than 3-benzonitrile or 2-benzonitrile as R_2 (**13f**, **13g** and **13n**, **13o**). Here, the R_2 substituent has hydrogen bond acceptor character which might be important for their activity.

Table 1: Antitubercular activity of thiazole derivatives along with inhibition of dormant *M. tuberculosis* H37Ra and cLogP values



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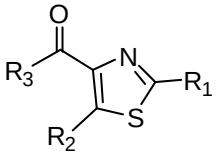
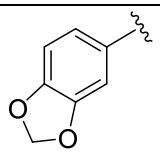
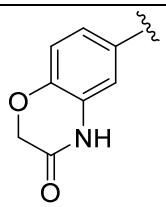
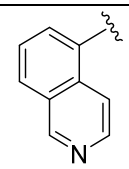
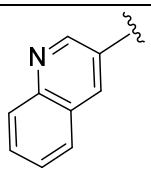
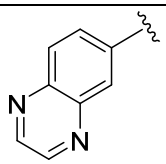
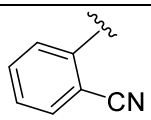
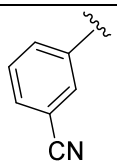
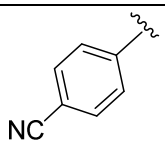
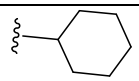
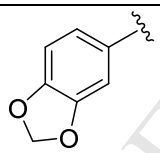
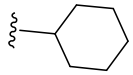
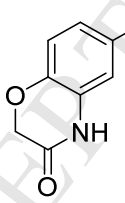
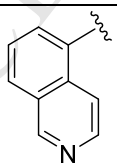
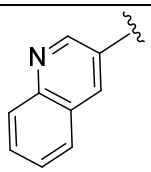
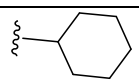
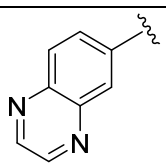
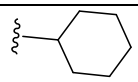
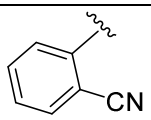
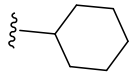
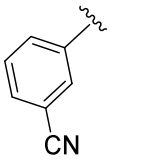
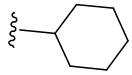
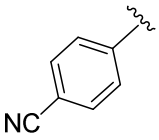
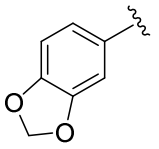
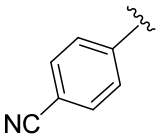
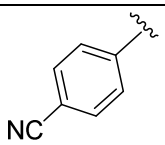
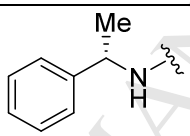
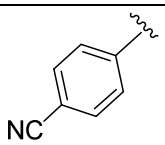
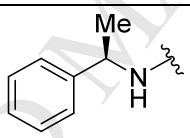
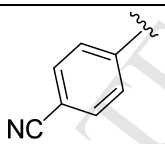
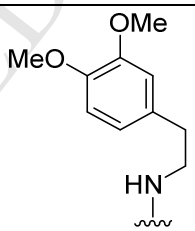
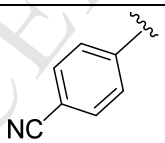
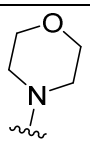
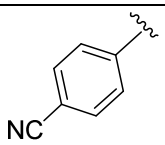
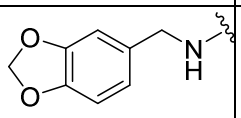
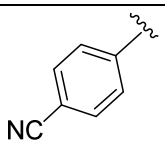
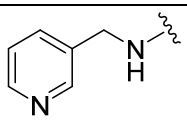
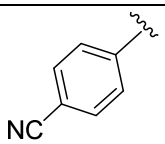
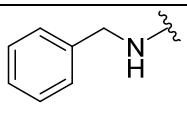
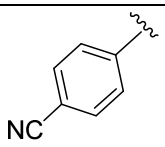
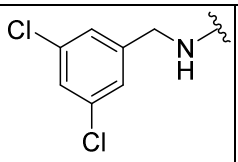
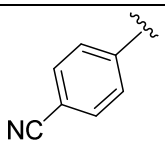
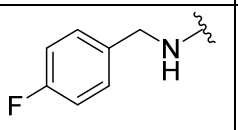
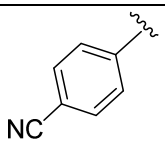
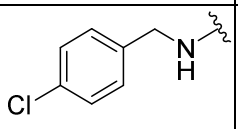
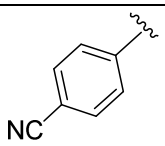
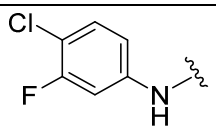
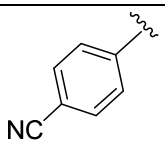
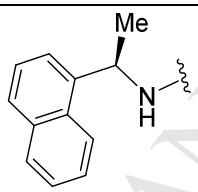
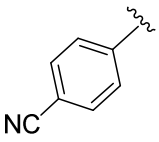
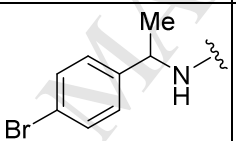
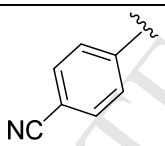
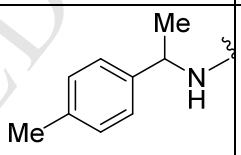
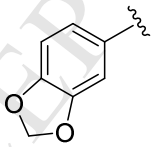
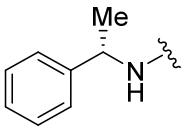
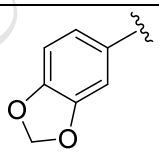
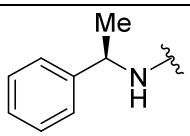
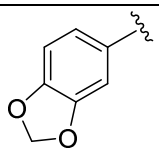
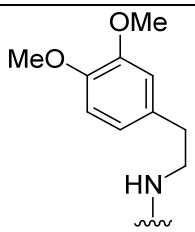


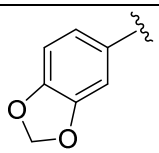
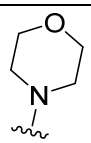
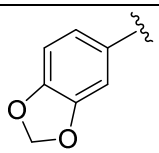
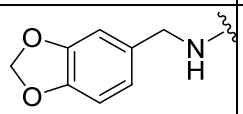
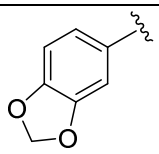
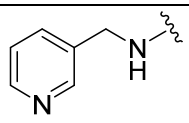
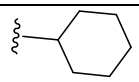
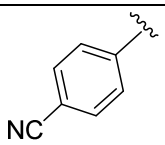
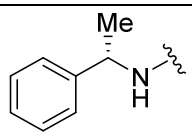
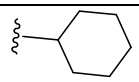
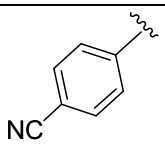
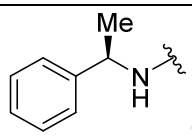
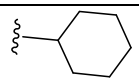
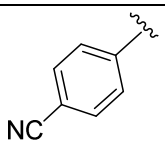
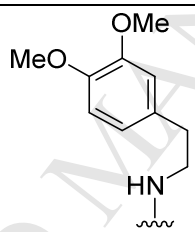
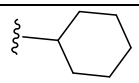
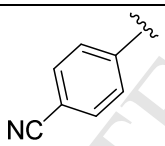
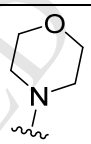
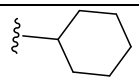
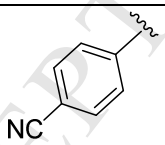
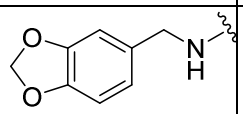
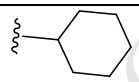
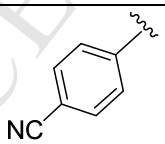
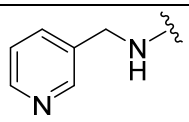
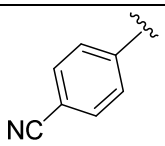
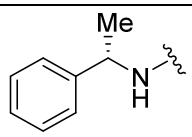
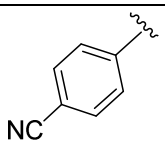
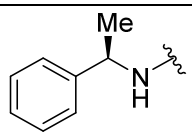
14-17

Comp. no.	Substituents			MIC (µg/mL)[a]	%inhibition (10µM)[b]	cLogP
	R_1	R_2	R_3			
13a			-	7.9	90.13	3.6
13b			-	>34	NS	3.0

13c			-	16.3	NS	4.0
13d			-	4.0	80.54	4.0
13e			-	8.1	19.53	3.4
13f			-	15.0	NS	3.6
13g			-	15.0	NS	3.5
13h			-	1.8	82.74	3.5
13i			-	8.9	92.01	4.3
13j			-	19.3	NS	3.7
13k			-	4.5	95.97	4.6
13l			-	4.5	86.52	4.8
13m			-	4.5	93.26	4.1

3n			-	4.2	91.73	4.2
13o			-	4.2	90.34	4.2
13p			-	2.1	90.55	4.2
13q			-	13.6	NS	2.9
13r			-	14.5	20.22	2.9
14a				18.7	73.25	4.4
14b				9.3	86.73	4.4
14c				5.4	89.37	4.4
14d				>34	NS	2.9
14e				>34	NS	4.0
14f				>34	NS	3.4
14g				>34	NS	4.2

4h				>34	NS	5.1
14i				>34	NS	4.5
14j				>34	NS	4.6
14k				>34	NS	5.0
14l				>34	NS	5.4
14m				>34	NS	5.0
14n				>34	NS	4.8
15a				4.9	90.76	4.3
15b				4.9	90.90	4.5
15c				5.6	84.92	4.4

15d				>34	NS	2.9
15e				10.6	82.21	3.9
15f				9.5	87.14	3.4
16a				20.7	NS	5.2
16b				10.3	57.75	5.1
16c				5.9	71.58	5.1
16d				>34	NS	3.6
16e				>34	NS	4.7
16f				>34	NS	4.1
17a				>34	73.45	3.8
17b				>34	74.01	3.8

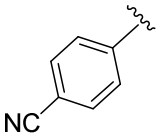
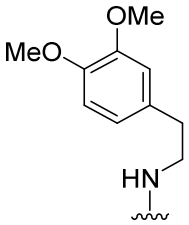
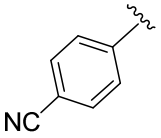
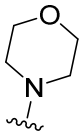
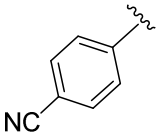
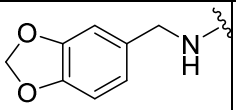
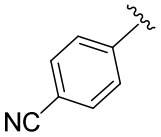
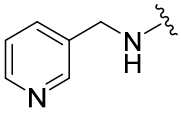
17c				>34	67.34	3.8
17d				>34	NS	2.2
17e				>34	NS	3.4
17f				>34	NS	2.8
Rifampicine				0.2	NS	-

Table 1: (a) Thiazole analogs with their activity against replicating *M. tuberculosis* H37Rv. (b) percent inhibition of dormant *M. tuberculosis* H37Ra. (c) cLogP is calculated using SwissADME. NS: Not screened.

Upon having deciphered the importance of R_1 and R_2 substituents, we decided to prepare analogs with different R_3 substituents. Accordingly, 32 analogs were prepared and screened against *M. tuberculosis* H37Rv (Table 1). Compound **14b**, **14c**, **15a**, **15b**, **15c**, **15f** and **16c** showed MIC of less than 10 µg/mL while rest other molecules showed weaker inhibition or were inactive. This indicates that the amide substitution as R_3 is not favorable when compared to ester functionality at this position (compare series **14-17** vs **13a-13r**). The SAR along with cLogP analysis (figure 3) identified compound **13d**, **13h**, **13n**, **13o** and **13p** potent inhibitors with MIC ≤ 4.2 µg/mL and cLogP lower than 5. LogP is one of the important parameter in Lipinski's rule of five[33-34] which determines the drug-likeness of compounds. Further, the compounds were screened for their ability to inhibit dormant *M. tuberculosis* H37Ra (Table 1). Compounds **13a**, **13i**, **13k**, **13m-13p**, **15a**, and **15b** showed more than 90% inhibition of dormant *M. tuberculosis* H37Ra at 10 µM concentration.

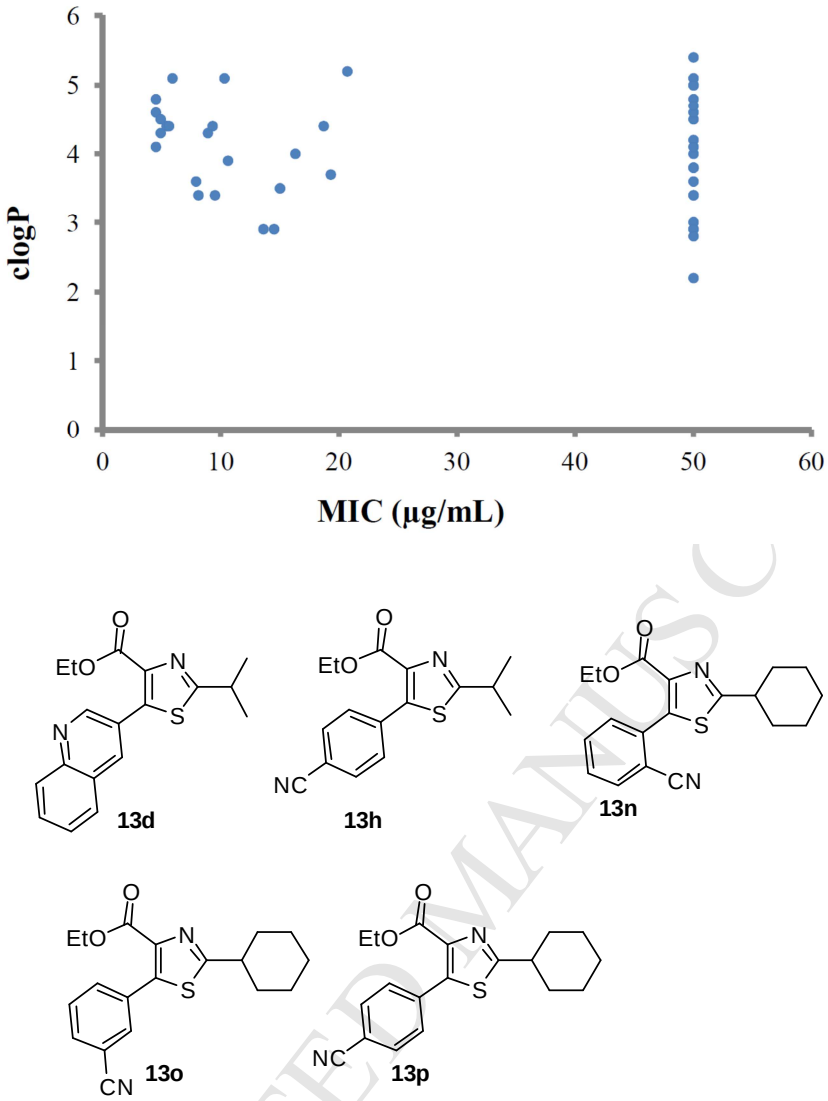


Figure 3: Correlation of antitubercular activity of compounds with cLogP. The MIC >34 µg/mL is taken as 50 µg/mL for simplicity in graphical presentation. Structures of compounds with MIC≤4.2 µg/mL against *M. tuberculosis* H37Rv with cLogP <5 are shown.

2.2.2. Cytotoxicity

The compounds showing MIC ≤ 4.2 µg/mL against *M. tuberculosis* H37Rv were further screened for cytotoxicity against CHO-KI cells. The cytotoxicity data for compounds is shown in table 2. All the compounds were non-toxic to CHO cells. Importantly, compound **13h** and **13P** showed selectivity index of 22 and 35 respectively. Of note, compounds presented in table 2 did not show any inhibition of B16-F10 and MCF7 cell lines at 10 µM concentration (data not shown).

Table 2: Effect of thiazole analogous against CHO-K1 (Chinese hamster ovary cells)

Comp. no.	IC_{50} (µg/mL) CHO-KI	SI Index (IC_{50}/MIC)
13d	>50	>12.5
13h	40.47	22.4
13n	>50	>11.9
13o	>50	>11.9
13p	75.23	35.8
Mitomycin C	13.10	-

2.2.3. Effect on ESKAPE pathogen and other bacteria

The compounds showing MIC ≤ 4.2 µg/mL against *M. tuberculosis* H37Rv were screened against a panel of bacteria consisting of ESKAPE pathogens namely *Escherichia coli, Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The results are presented in supporting information. None of the derivatives showed any inhibition except *Staphylococcus aureus*. *Staphylococcus aureus* was weakly sensitive to **13n**, **13o** and **13p** with MIC of 50 µM . Furthermore, these compounds were tested against nontuberculous mycobacteria namely *Mycobacterium fortuitum*, *Mycobacterium chelonae*, and *Mycobacterium abscessus* (data not shown). None of the thiazole derivatives showed inhibition indicating their selective inhibition of *M. tuberculosis* H37Rv.

2.2.4. Effect against MDR-TB isolates

The compound **13p** was profiled against a panel of drug-resistant TB isolates (Table 3). This compound showed MIC of 8 µg/mL against clinical isolate 1, 2, 5 and 6. Important to note that the isolate 4 is resistant to four TB drugs, *i.e.* isoniazid, streptomycin, ethionamide and ethambutol. Compound **13P** showed MIC of 16, 6 and 16 µg/mL against MDR-TB isolate 3,4 and 7 respectively. Thus , compound **13P** showed limited activity against clinical isolate 1 to 7 whereas it was ineffective against pre-extensively drug resistant (Pre-XDR)[35] isolate 8. Compound **13p** was non toxic to CHO

cells at 8 µg/mL and hence has possibility for further development to render it more efficacious against MDR-TB.

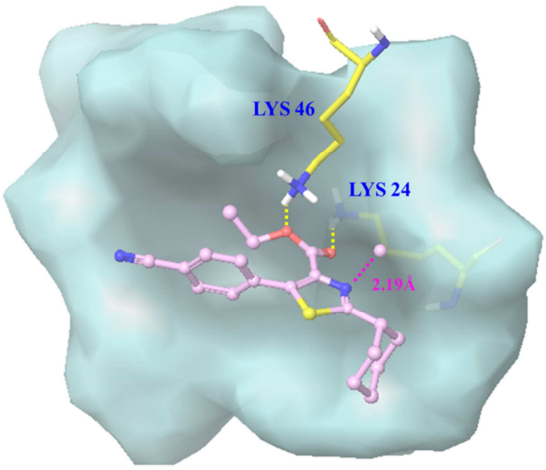
Table 3: Activity of **13p** against drug resistant tuberculosis isolates

Clinical isolate	Description	MIC (µg/mL)
Isolate 1	Resistant to isoniazid, streptomycin, ethionamide and ethambutol	8
Isolate 2	Resistant to isoniazid and ethionamide	8
Isolate 3	Resistant to isoniazid, streptomycin and rifampicin	16
Isolate 4	Resistant to isoniazid and rifampicin	4
Isolate 5	Resistant to isoniazid and ethionamide	8
Isolate 6	Resistant to isoniazd, streptomycin and ethionamide	8
Isolate 7	Resistant to isoniazid, streptomycin, ethambutol, rifampicin, ethionamide	16
Isolate 8	Resistant to isoniazid, streptomycin, ethionamide, ofloxacin, ethambutol and rifampicin	>32

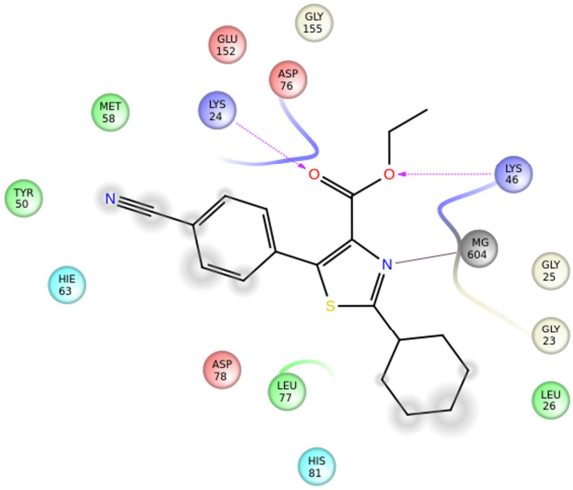
3. Molecular Docking study

Finally, in order to understand the possible binding mode of these thiazole analogs, we carried out docking of **13p** and **13d** in the active site of CTP (cytidine triphosphate) synthase PyrG (Maestro 9.8, Schrodinger, New York, U.S.A). Recently PyrG has shown to be a relevant target in tuberculosis drug discovery.[36] Further, *Chiarelli et al.*[37] showed that the thiazole-based GSK compounds inhibit PyrG. Figure 4 shows interaction of **13p** and **13d** with amino acid residues of the ATP binding site of PyrG. The thiazole-nitrogen of **13p** interacts with magnesium ion whereas ester functionality is involved in hydrogen bond interactions with protonated Lys24 and Lys46 residues of PyrG. In the case of **13d**, the interaction between protonated Lys46 of PyrG with carbonyl of ester is preserved, while Gly155 interacts with ester side chain. Interesting to note that the quinoline nitrogen of **13d** interacts with the magnesium ion. Further, we docked compounds in the active site of PyrG and determined the docking score. No correlation was observed between the docking score and MIC of compounds against *M. tuberculosis* H37Rv (supporting information).

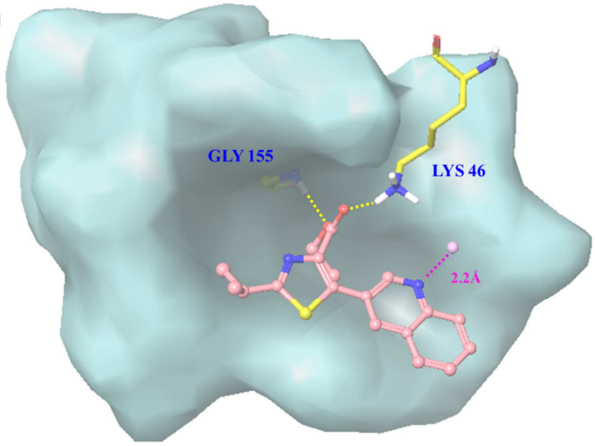
A)


LYS 46
LYS 24
2.19Å

B)


GLY 155
GLU 152
ASP 76
MET 58
LYS 24
TYR 50
N
O
O
LYS 46
MG 604
N
S
HIE 63
GLY 25
GLY 23
ASP 78
LEU 77
LEU 26
HIS 81

C)


GLY 155
LYS 46
2.2Å

D)

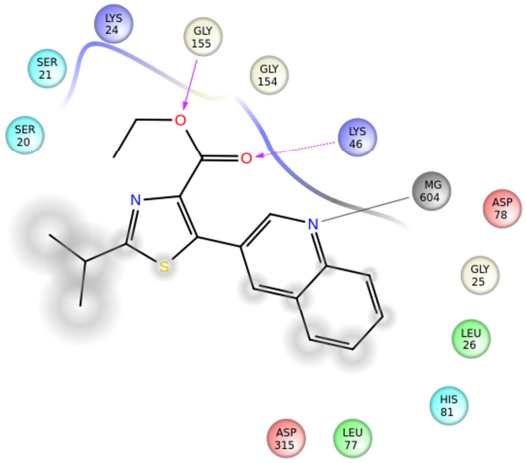


Figure 4: Docking of the thiazole derivatives in the active site of CTP synthase PyrG. A) The three dimensional representation of interaction of **13p** with CTP synthase PyrG , docking (XP G) score is -5.61 kcal/mol; B) The two dimensional interaction map of **13P** with CTP synthase PyrG; C) The three dimensional representation of interaction of **13d** with CTP synthase PyrG , docking (XP G) score is -6.04 kcal/mol; D) The two dimensional interaction map of **13d** with CTP synthase PyrG.

4. Conclusion

In summary, the thiazole derivatives with antitubercular properties on drug sensitive and dormant mycobacterial strains are reported. The SAR study identified a requirement of hydrophobic substituent at C2, ester functionality at C4, and various groups with hydrogen bond acceptor character at C5 of thiazole scaffold. These derivatives selectively inhibited *M. tuberculosis* H37Rv while docking study revealed key interactions of thiazole derivative **13p** with Lys24 and Lys46 residues of CTP synthase PyrG. Importantly, **13P** was active against multidrug-resistant tuberculosis isolates.

5. Experimental

5.1. General methods for the synthesis of compounds

Synthesis of 2a-2c thiazole

To a solution of phosphorus pentasulfide (P_2S_5) (4.58 mmol) in ether (8ml) was added isobutylamide **11a** (1gm, 11 mmol) and the reaction mixture was stirred for 2h at room temperature. The reaction mixture was diluted with brine and extracted with ether. The organic layer was dried over Na_2SO_4 and evaporated to give crude thioamide. The mixture of crude thioamide and ethyl α-bromopyruvate (11.42 mmol) in EtOH (10ml) was stirred at reflux temperature for 30 min. The solvent was evaporated under vaccum, diluted with EtOAc and washed with 7% aqueous $NaHCO_3$ (3×30 mL), the organic layer was dried over Na_2SO_4 and evaporated to get crude product, which was purified by column chromatography (n-hexane/EtOAc) to afford **12a**.

In an analogous way **12b, 12c** were synthesized.

Synthesis of 13a-13r

In round bottom flask, added 1**2a** (100 mg, 0.5mmol) followed by 4-bromo-1,2-(methylenedioxy)benzene (0.45 mmol), $PdCl_2(PPh_3)_2$ (5mol%) and KOAc (0.5mmol) sequentially in dry DMA (10ml). The reaction mixture was stirred at 150 ºC for 18h. The reaction mixture was diluted with saturated $NaHCO_3$ and extracted with EtOAc. The organic layer dried over Na_2SO_4, filtered and evaporated to give crude product which was finally purified by column chromatography to afford **13a**.

In an analogous way **13b-13r** were synthesized.

Synthesis of 14a-17f

In round bottom flask, 200 mg of **13a** was dissolved in 8 ml of THF:MeOH (3:1), the solution of 2 equivalent aq. NaOH (1.5ml) was added slowly at 0 ºC and reaction mixture allowed to stir for 3h at room temperature. The solvent was evaporated under vaccum and the residue was diluted with water (2ml) and cooled to 0 ºC. The reaction mixture was acidified with 4M HCl. Resulting Solid was filtered and dried to afford acid which was used in the next step without purification.

To the solution of acid in DMF (7ml), were added EDC.HCl (1 mmol) and HOBt (1 mmol) respectively at 0 ºC. The solution was stirred for 30 min followed by addition of (*S*)-1-phenylethan-1-amine (0.8 mmol) and NEt_3 (1.33 mmol). The reaction mixture was stirred for 1h at 0 ºC and then for 12 h at room temperature. The reaction mixture was quenched by saturated $NaHCO_3$ and then

extracted with EtOAc. The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography to obtain pure **15a**.

In an analogous way, **14-17** were synthesized.

5.2 Analytical data of the compounds

Ethyl 2-isopropylthiazole-4-carboxylate (12a)

The compound is synthesized according to the literature procedure.[38] Yellow liquid (1.26 gm, 61%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 (s, 1H), 4.41 (q, J = 7.19, 2H), 3.42 (sept, J = 6.8 Hz, 1H), 1.41 (d, J = 6.8 Hz, 6H), 1.39 (t, J =7.1,3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 178.5, 161.1, 146.2, 126.1, 60.9, 33.1, 22.9 (X2), 14.0.

Ethyl 2-cyclohexylthiazole-4-carboxylate (12b)

The compound is synthesized according to the reported literature.[39] Yellow liquid (1.62 gm, 86%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.01 (s, 1H), 4.37 (q, J = 7.1 Hz, 2H), 3.06 (tt, J = 11.7, 3.6 Hz, 1H), 2.12 (dd, J = 13.1, 1.8 Hz, 2H), 1.83 – 1.78 (m, 2H), 1.72 – 1.68 (m, 1H), 1.46 (m, 2H), 1.40 – 1.31 (m, 2H), 1.35 (t, J = 7.1 Hz, 3H), 1.28 – 1.21 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 178.1, 161.4, 146.2, 126.3, 61.2, 42.6, 33.7 (X2), 25.9 (X2), 25.5, 14.3.

Ethyl 2-cyclohexylthiazole-4-carboxylate (12c)

White solid (1.5 gm, 53%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.01 (s, 1H), 4.39 (q, J = 7.1 Hz, 2H), 2.74 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.8, 161.4, 146.9, 127.3, 61.4, 19.4, 14.4; HRMS (ESI-MS):Calc. for $C_7H_{10}NO_2S$ [$(M+H)^+$]: 172.0432, Found: 172.0426.

Ethyl 5-(benzo[*d*][1,3]dioxol-5-yl)-2-isopropylthiazole-4-carboxylate (13a)

White solid (70 mg, 43%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 6.97 – 6.91 (m, 2H), 6.82 (d, J = 7.9 Hz, 1H), 6.00 (s, 2H), 4.30 (q, J = 7.1 Hz, 2H), 3.38 (sept, J = 6.9 Hz, 1H), 1.41 (d, J = 6.9 Hz, 6H), 1.27 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 176.1, 162.4, 148.4, 147.4, 145.1, 139.6,

124.4, 124.0, 110.5, 108.1, 101.5, 61.3, 33.7, 23.4 (X2), 14.2; HRMS (ESI-MS):Calc. for $C_{16}H_{18}NO_4S$ $[(M+H)^+]$: 320.0957, Found: 320.0965.

Ethyl 2-isopropyl-5-(3-oxo-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-6-yl)thiazole-4-carboxylate (13b)

Brown solid (60 mg, 37%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.76 (s, 1H), 7.08 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.09 – 6.96 (m, 2H), 4.65 (s, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.38 (sept, *J* = 6.9 Hz, 1H), 1.42 (d, *J* = 6.9 Hz, 6H), 1.27 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.6, 165.7 (X2), 162.4, 144.3, 139.8, 126.2, 125.9, 125.4, 117.7, 116.6, 67.3, 61.5, 33.8, 23.4 (X2), 14.3; HRMS (ESI-MS):Calc. for $C_{17}H_{19}N_2O_4S$ $[(M+H)^+]$: 347.1066, Found: 347.1065.

Ethyl 2-isopropyl-5-(isoquinolin-5-yl)thiazole-4-carboxylate (13c)

Yellow solid (83 mg, 50%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 9.30 (s, 1H), 8.50 (d, *J* = 6.0 Hz, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.70 (dd, *J* = 7.1, 1.3 Hz, 1H), 7.67 – 7.61 (m, 1H), 7.43 (d, *J* = 6.0 Hz, 1H), 4.00 (q, *J* = 7.1 Hz, 2H), 3.48 (sept, *J* = 6.9 Hz, 1H), 1.48 (d, *J* = 6.9 Hz, 6H), 0.76 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.1, 161.5, 152.8, 143.9, 142.8, 140.7, 135.1, 132.3, 128.9, 128.4, 128.3, 126.4, 118.2, 61.1, 33.8, 23.4 (X2), 13.6; HRMS (ESI-MS):Calc. for $C_{18}H_{19}N_2O_2S$ $[(M+H)^+]$: 327.1178, Found: 327.1167.

Ethyl 2-isopropyl-5-(quinolin-3-yl)thiazole-4-carboxylate (13d)

Yellow semisolid (60 mg, 36%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.94 (d, *J* = 2.2 Hz, 1H), 8.22 (d, *J* = 2.0 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.72 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.55 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.41 (sept, *J* = 6.9 Hz, 1H), 1.43 (d, *J* = 6.9 Hz, 6H), 1.13 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 177.5, 161.9, 150.8, 147.6, 141.3, 140.9, 136.6, 130.3, 129.3, 128.0, 127.3, 127.0, 124.5, 61.4, 33.7, 23.3 (X2), 14.1; HRMS (ESI-MS):Calc. for $C_{18}H_{19}N_2O_2S$ $[(M+H)^+]$: 327.1167, Found: 327.0978.

Ethyl 2-isopropyl-5-(quinoxalin-6-yl)thiazole-4-carboxylate (13e)

Yellow solid (70 mg, 42%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.88 (s, 2H), 8.21 (d, *J* = 1.9 Hz, 1H), 8.14 (d, *J* = 8.7 Hz, 1H), 7.89 (dd, *J* = 8.7, 2.0 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.45 (sept, *J* = 6.9 Hz, 1H), 1.47 (d, *J* = 6.9 Hz, 6H), 1.20 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 177.6, 162.1, 145.8, 145.7, 143.4, 143.0, 142.5, 140.7, 133.2, 132.2, 130.7, 129.2, 61.6, 33.9, 23.4 (X2), 14.2; HRMS (ESI-MS):Calc. for $C_{17}H_{18}N_3O_2S$ $[(M+H)^+]$: 328.1120, Found: 328.1121.

Ethyl 5-(2-cyanophenyl)-2-isopropylthiazole-4-carboxylate (13f)

Yellow solid (50 mg, 33%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.74 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.62 (td, *J* = 7.7, 1.4 Hz, 1H), 7.51 (td, *J* = 7.7, 1.3 Hz, 1H), 7.46 (dd, *J* = 7.7, 0.8 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.43 (sept, *J* = 6.9 Hz, 1H), 1.44 (d, *J* = 6.9 Hz, 6H), 1.16 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.2, 161.5, 142.4, 139.8, 135.2, 132.9, 132.3, 131.2, 129.2, 117.4, 113.9, 61.5, 33.8, 23.3 (X2), 14.0; HRMS (ESI-MS):Calc. for $C_{16}H_{17}N_2O_2S$ $[(M+H)^+]$: 301.1011, Found: 301.1034.

Ethyl 5-(3-cyanophenyl)-2-isopropylthiazole-4-carboxylate (13g)

White solid (45 mg, 30%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.77 (t, *J* = 1.4 Hz, 1H), 7.73 – 7.66 (m, 2H), 7.52 (t, *J* = 8.0 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.42 (sept, *J* = 6.9 Hz, 1H), 1.44 (d, *J* = 6.9 Hz, 6H), 1.23 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.6, 161.9, 142.2, 140.8, 134.4, 133.5, 132.6, 132.4 129.0, 118.3, 112.6, 61.6, 33.8, 23.4 (X2), 14.2; HRMS (ESI-MS):Calc. for $C_{16}H_{17}N_2O_2S$ $[(M+H)^+]$: 301.1011, Found: 301.1019.

Ethyl 5-(4-cyanophenyl)-2-isopropylthiazole-4-carboxylate (13h)

White solid (60 mg, 40%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.69 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.6 Hz, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.42 (sept, *J* = 6.9 Hz, 1H), 1.44 (d, *J* = 6.9 Hz, 6H), 1.23 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 177.8, 161.9, 142.6, 140.8, 135.9, 131.8 (X2), 130.8 (X2), 118.4, 112.6, 61.6, 33.7, 23.3 (X2), 14.1; HRMS (ESI-MS):Calc. for $C_{16}H_{17}N_2O_2S$ $[(M+H)^+]$: 301.1011, Found: 301.1014.

Ethyl 5-(benzo[*d*][1,3]dioxol-5-yl)-2-cyclohexylthiazole-4-carboxylate (13i)

White solid (40 mg, 26%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 6.97 – 6.91 (m, 2H), 6.82 (d, *J* = 7.9 Hz, 1H), 6.00 (s, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.11 – 3.00 (m, 1H), 2.17 (d, *J* = 12.1 Hz, 2H), 1.89 – 1.81 (m, 2H), 1.80 – 1.70 (m, 1H), 1.55 – 1.32 (m, 5H), 1.26 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.0, 162.3, 148.2, 147.3, 145.0, 139.3, 124.3, 123.9, 110.4, 107.9, 101.4, 61.1, 42.8, 33.9 (X2), 26.0 (X2), 25.6, 14.2; HRMS (ESI-MS):Calc. for $C_{19}H_{22}NO_4S$ [$(M+H)^+$]: 360.1270, Found: 360.1288.

Ethyl 2-cyclohexyl-5-(3-oxo-3,4-dihydro-2*H*-benzo[b][1,4]oxazin-6-yl)thiazole-4-carboxylate (13j)

Yellow solid (60 mg, 37%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.97 (bs, 1H), 7.07 (dd, J = 8.4, 1.9 Hz, 1H), 7.00 – 6.96 (m, 2H), 4.65 (s, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.07 (tt, J = 11.6, 7.02, 3.5 Hz, 1H), 2.17 (d, *J* = 12.1 Hz, 2H), 1.87 – 1.83 (m, 2H), 1.77 – 1.73 (m, 1H), 1.54 – 1.35 (m, 5H), 1.27 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125MHz, $CDCl_3$) δ 175.6, 165.8, 162.4, 144.3, 144.2, 139.7, 126.2, 125.9, 125.5, 117.7, 116.6, 67.3, 61.4, 43.0, 34.0 (X2), 26.1 (X2), 25.8, 14.3; HRMS (ESI-MS):Calc. for $C_{20}H_{23}N_2O_4S$ [$(M+H)^+$]: 387.1379, Found: 387.1385.

Ethyl 2-cyclohexyl-5-(isoquinolin-5-yl)thiazole-4-carboxylate (13k)

White solid (65 mg, 42%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 9.30 (s, 1H), 8.49 (d, *J* = 5.6 Hz, 1H), 8.04 (dt, *J* = 8.06, 1.0 Hz, 1H), 7.69 (dd, *J* = 7.1, 1.4 Hz, 1H), 7.67 – 7.61 (m, 1H), 7.43 (d, *J* = 5.9 Hz, 1H), 4.01 (q, *J* = 7.1 Hz, 2H), 3.15 (tt, *J* = 11.7, 3.6 Hz, 1H), 2.25 (dd, *J* = 13.0, 2.1 Hz, 2H), 1.92 – 1.85 (m, 2H), 1.81 – 1.73 (m, 1H), 1.56 (qd, *J* = 12.3, 3.1 Hz, 2H), 1.43 (qt, *J* = 12.3, 3.1 Hz, 2H), 1.36 – 1.23 (m, 1H), 0.78 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.0, 161.5, 152.8, 143.8, 142.7, 140.5, 135.0, 132.2, 128.9, 128.3, 126.4, 118.1, 61.0, 43.0, 33.9 (X2), 26.1 (X2), 25.7, 13.6; HRMS (ESI-MS):Calc. for $C_{21}H_{23}N_2O_2S$ [$(M+H)^+$]: 367.1480, Found: 367.1507.

Ethyl 2-cyclohexyl-5-(quinolin-3-yl)thiazole-4-carboxylate (13l)

White solid (58 mg, 38%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.97 (d, *J* = 2.2 Hz, 1H), 8.26 (d, *J* = 2.0 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.80 – 7.73 (m, 1H), 7.63 – 7.56 (m,

1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.13 (tt, *J* = 11.7, 3.5 Hz, 1H), 2.22 (dd, *J* = 13.1, 1.8 Hz, 2H), 1.93 – 1.83 (m, 2H), 1.80 – 1.74 (m, 1H), 1.54 (qd, *J* = 12.3, 3.1 Hz, 2H), 1.43 (qt, *J* = 12.3, 3.1 Hz, 2H), 1.35 – 1.27 (m, 1H), 1.17 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.7, 162.1, 151.0, 147.7, 141.3, 141.0, 136.7, 130.5, 129.5, 128.2, 127.4, 127.1, 124.7, 61.6, 43.1, 34.0 (X2), 26.1 (X2), 25.8, 14.2; HRMS (ESI-MS):Calc. for $C_{21}H_{23}N_2O_2S$ [$(M+H)^+$]: 367.1480, Found: 367.1267.

Ethyl 2-cyclohexyl-5-(quinoxalin-6-yl)thiazole-4-carboxylate (13m)

Yellow solid (50mg, 32%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.88 (s, 2H), 8.20 (d, *J* = 1.8 Hz, 1H), 8.13 (d, *J* = 8.7 Hz, 1H), 7.89 (dd, *J* = 8.7, 1.9 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.13 (tt, *J* = 11.7, 3.5 Hz, 1H), 2.23 (d, *J* = 11.5 Hz, 2H), 1.93 – 1.87 (m, 2H), 1.80 – 1.75 (m, 1H), 1.54 (qd, *J* = 12.4, 3.0 Hz, 2H), 1.45 (qt, *J* = 12.5, 3.0 Hz, 2H), 1.35 – 1.30 (m, 1H), 1.20 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.7, 162.2, 145.8, 145.7, 143.3, 143.0, 142.6, 140.6, 133.2, 132.2, 130.6, 129.1, 61.6, 43.1, 34.0 (X2), 26.1 (X2), 25.8, 14.2; HRMS (ESI-MS):Calc. for $C_{20}H_{22}N_3O_2S$ [$(M+H)^+$]:368.1433, Found: 368.1440.

Ethyl 5-(2-cyanophenyl)-2-cyclohexylthiazole-4-carboxylate (13n)

Yellow solid (70 mg, 50%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.75 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.63 (td, *J* = 7.7, 1.3 Hz, 1H), 7.51 (td, *J* = 7.7, 1.3 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.12 (tt, *J* = 11.7, 3.5 Hz, 1H), 2.22 (dd, *J* = 13.1, 2.0 Hz, 2H), 1.87 (dt, *J* = 13.2, 3.3 Hz, 2H), 1.80 – 1.72 (m, 1H), 1.52 (qd, *J* = 12.3, 3.2 Hz, 2H), 1.42 (qt, *J* = 12.5, 3.1 Hz, 2H), 1.34 – 1.26 (m, 1H), 1.18 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.3, 161.6, 142.3, 139.7, 135.3, 133.0, 132.3, 131.2, 129.2, 117.4, 114.0, 61.5, 43.0, 33.9 (X2), 26.0 (X2), 25.7, 14.1; HRMS (ESI-MS):Calc. for $C_{19}H_{21}N_2O_2S$ [$(M+H)^+$]: 341.1324, Found: 341.1343.

Ethyl 5-(3-cyanophenyl)-2-cyclohexylthiazole-4-carboxylate (13o)

White solid (60 mg, 42%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.76 (t, *J* = 1.4 Hz, 1H), 7.69 (tt, *J* = 7.6, 1.2 Hz, 2H), 7.52 (t, *J* = 7.9 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.10 (tt, *J* = 11.6, 3.5 Hz, 1H), 2.30 – 2.13 (m, 2H), 1.86 (dt, *J* = 13.2, 3.3 Hz, 2H), 1.80 – 1.71 (m, 1H), 1.56 – 1.35 (m, 4H), 1.34 – 1.26

(m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.6, 161.9, 142.1, 140.7, 134.4, 133.5, 132.6, 132.3, 129.0, 118.3, 112.6, 61.5, 43.0, 34.0 (X2), 26.1 (X2), 25.7, 14.2; HRMS (ESI-MS):Calc. for $C_{19}H_{21}N_2O_2S$ [$(M+H)^+$]: 341.1324, Found: 341.1329.

Ethyl 5-(4-cyanophenyl)-2-cyclohexylthiazole-4-carboxylate (13p)

White solid (70 mg, 50%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.69 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.6 Hz, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.10 (tt, *J* = 11.7, 3.5 Hz, 1H), 2.18 (dd, *J* = 10.5, 8.6 Hz, 2H), 1.87 (dt, *J* = 13.1, 3.3 Hz, 2H), 1.80 – 1.72 (m, 1H), 1.51 (qd, *J* = 12.3, 3.2 Hz, 2H), 1.41 (qt, *J* = 12.5, 3.1 Hz, 2H), 1.34 – 1.26 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 176.7, 161.9, 142.5, 140.6, 135.9, 131.8 (X2), 130.8 (X2), 118.4, 112.6, 61.5, 43.0, 33.9 (X2), 26.0 (X2), 25.7, 14.2; HRMS (ESI-MS):Calc. for $C_{19}H_{21}N_2O_2S$ [$(M+H)^+$]: 341.1324, Found: 341.1351.

Ethyl 5-(benzo[*d*][1,3]dioxol-5-yl)-2-methylthiazole-4-carboxylate (13q)

White solid (70 mg, 41%). **^{1}H NMR** (500 MHz, CDCl3) δ ppm 6.96 – 6.91 (m, 2H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.00 (s, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 2.71 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.0, 162.0, 148.4, 147.4, 146.3, 139.7, 124.0, 123.9, 110.5, 108.1, 101.5, 61.3, 19.3, 14.2; HRMS (ESI-MS):Calc. for $C_{14}H_{14}NO_4S$ [$(M+H)^+$]: 292.0644, Found: 292.0649.

Ethyl 5-(4-cyanophenyl)-2-methylthiazole-4-carboxylate (13r)

White solid (100 mg, 43%). **^{1}H NMR** (500 MHz, CDCl3) δ ppm 7.70 (d, *J* = 8.3 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 2.78 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 165.7, 161.6, 143.7, 140.9, 135.5, 131.8 (X2), 130.8 (X2), 118.4, 112.7, 61.6, 19.4, 14.1; HRMS (ESI-MS):Calc. for $C_{14}H_{13}N_2O_2S$ [$(M+H)^+$]: 273.0698, Found: 273.0700.

(*S*)-5-(4-cyanophenyl)-2-isopropyl-*N*-(1-phenylethyl)thiazole-4-carboxamide (14a)

White solid (140 mg, 56%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.79 (d, *J* = 8.5 Hz, 1H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.65 (d, *J* = 8.6 Hz, 2H), 7.39 – 7.32 (m, 4H), 7.29 – 7.26 (m, 1H), 5.22 (qn, *J* =7.0 Hz, 1H), 3.29 (sept, *J* = 6.9 Hz, 1H), 1.58 (d, *J* = 6.9 Hz, 3H), 1.44 (d, *J* = 1.6 Hz, 3H), 1.42 (d, *J* = 1.6

Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.4, 160.5, 143.3, 142.0, 139.8, 135.8, 131.7 (X2), 131.1 (X2), 128.8 (X2), 127.4, 126.3 (X2), 118.7, 112.3, 48.6, 33.4, 23.1 (X2), 22.2; HRMS (ESI-MS):Calc. for $C_{22}H_{22}N_3OS$ $[(M+H)^+]$: 376.1484, Found: 376.1490.

(*R*)-5-(4-cyanophenyl)-2-isopropyl-*N*-(1-phenylethyl)thiazole-4-carboxamide (14b)

White solid (125 mg, 50%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.80 (d, *J* = 8.3 Hz, 1H), 7.71 – 7.68 (m, 2H), 7.67 – 7.63 (m, 2H), 7.40 – 7.32 (m, 4H), 7.29 – 7.25 (m, 1H), 5.22 (qn, *J* =7.0 Hz, 1H), 3.29 (sept, *J* = 6.9 Hz, 1H), 1.58 (d, *J* = 6.9 Hz, 3H), 1.44 (d, *J* = 1.6 Hz, 3H), 1.42 (d, *J* = 1.6 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 176.4, 160.5, 143.3, 142.0, 139.7, 135.8, 131.6 (X2), 131.1 (X2), 128.8 (X2), 127.4, 126.3 (X2), 118.7, 112.3, 48.6, 33.4, 23.1 (X2), 22.2; HRMS (ESI-MS):Calc. for $C_{22}H_{22}N_3OS$ $[(M+H)^+]$: 376.1494, Found: 376.1492.

5-(4-cyanophenyl)-*N*-(3,4-dimethoxyphenethyl)-2-isopropylthiazole-4-carboxamide (14c)

Yellow solid (80 mg, 55%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.71 – 7.65 (m, 4H), 7.64 – 7.61 (m, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.79 – 6.74 (m, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.59 (q, *J* = 7.0 Hz, 2H), 3.24 (sept, *J* = 6.9 Hz, 1H), 2.83 (t, *J* = 7.2 Hz, 2H), 1.41 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.2, 161.4, 149.1, 147.8, 142.1, 139.6, 135.8, 131.7 (X2), 131.6, 131.1 (X2), 120.8, 118.7, 112.3, 112.1, 111.5, 56.0, 55.9, 40.8, 35.6, 33.4, 23.0 (X2); HRMS (ESI-MS):Calc. for $C_{24}H_{26}N_3O_3S$ $[(M+H)^+]$: 436.1695, Found: 436.1700.

4-(2-isopropyl-4-(morpholine-4-carbonyl)thiazol-5-yl)benzonitrile (14d)

White solid (55 mg, 24%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.68 (d, *J* = 8.6 Hz, 2H), 7.62 (d, *J* = 8.6 Hz, 2H), 3.78 – 3.66 (m, 4H), 3.44 (t, *J* = 4.6 Hz, 2H), 3.32 (sept, *J* = 6.9 Hz, 1H), 3.24 (t, *J* = 4.9 Hz, 2H), 1.43 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 178.6, 164.21, 144.8, 135.2, 133.5, 132.8 (X2), 129.0 (X2), 118.3, 112.3, 66.8, 66.7, 47.3, 42.5, 33.6, 23.1 (X2); HRMS (ESI-MS):Calc. for $C_{18}H_{20}N_3O_2S$ $[(M+H)^+]$: 342.1276, Found: 342.1283.

***N*-(benzo[*d*][1,3]dioxol-5-ylmethyl)-5-(4-cyanophenyl)-2-isopropylthiazole-4-carboxamide (14e)**

White solid (100 mg, 37%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.80 (t, *J* = 5.8 Hz, 1H), 7.72 (d, *J* = 8.6 Hz, 2H), 7.67 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 1.5 Hz, 1H), 6.82 – 6.74 (m, 2H), 5.94 (s, 2H), 4.47 (d, *J* = 6.1 Hz, 2H), 3.26 (sept, *J* = 6.9 Hz, 1H), 1.41 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.4, 161.2, 147.9, 147.0, 141.9, 139.9, 135.7, 132.1, 131.6 (X2), 131.1 (X2), 121.1, 118.7, 112.8, 108.5, 108.3, 101.1, 43.0, 33.4, 23.0 (X2); HRMS (ESI-MS):Calc. for $C_{22}H_{20}N_3O_3S$ [$(M+H)^+$]: 406.1225, Found: 406.1229.

5-(4-cyanophenyl)-2-isopropyl-*N*-(pyridin-3-ylmethyl)thiazole-4-carboxamide (14f)

White solid (110 mg, 41%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.60 (s, 1H), 8.53 (d, *J* = 4.3 Hz, 1H), 7.93 (t, *J* = 5.8 Hz, 1H), 7.71 (d, *J* = 8.5 Hz, 2H), 7. 69 – 7.65 (m, 3H), 7.27 – 7.40 (m, 1H), 4.58 (d, *J* = 6.3 Hz, 2H), 3.27 (sept, *J* = 6.9 Hz, 1H), 1.41 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.4, 161.4, 149.1, 148.8, 141.5, 140.1, 135.5, 134.0, 131.6 (X2), 131.0 (X2), 123.5, 118.5, 112.2, 40.6, 33.3, 22.9 (X2); HRMS (ESI-MS):Calc. for $C_{20}H_{19}N_4OS$ [$(M+H)^+$]: 363.1280, Found: 363.1308.

***N*-benzyl-5-(4-cyanophenyl)-2-isopropylthiazole-4-carboxamide (14g)**

White solid (160 mg, 66%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.80 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.32 – 7.16 (m, 5H), 4.52 (d, *J* = 6.1 Hz, 2H), 3.20 (sept, *J* = 6.9 Hz, 1H), 1.35 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 176.4, 161.3, 141.9, 139.9, 138.3, 135.8, 131.7 (X2), 131.2 (X2), 128.8 (X2), 127.9 (X2), 127.6, 118.7, 112.3, 43.3, 33.4, 23.0 (X2); HRMS (ESI-MS):Calc. for $C_{21}H_{20}N_3OS$ [$(M+H)^+$]:362.1327, Found:362.1328.

(4-cyanophenyl)-*N*-(3,5-dichlorobenzyl)-2-isopropylthiazole-4-carboxamide (14h)

White solid (125 mg, 55%). **1H NMR** (400 MHz, $CDCl_3$) δ ppm 8.01 (t, *J* = 6.1 Hz, 1H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.66 (d, *J* = 8.6 Hz, 2H), 7.39 (d, *J* = 2.1 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.20 (dd, *J* = 8.2, 2.1 Hz, 1H), 4.61 (d, *J* = 6.4 Hz, 2H), 3.28 (sept, *J* = 6.9 Hz, 1H), 1.43 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.5, 161.4, 141.6, 140.2, 135.6, 134.4, 134.3, 134.0, 131.7 (X2), 131.1

(X2), 130.8, 129.5, 127.4, 118.7, 112.5, 40.7, 33.4, 23.0 (X2); HRMS (ESI-MS):Calc. for $C_{21}H_{18}N_3OSCl_2$ [$(M+H)^+$]: 430.0548, Found: 430.551.

5-(4-cyanophenyl)-*N*-(4-fluorobenzyl)-2-isopropylthiazole-4-carboxamide (14i)

White solid (180 mg, 71%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.86 (t, J = 5.6 Hz, 1H), 7.72 (d, J = 8.6 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.35 – 7.27 (m, 2H), 7.02 (t, J = 8.6 Hz, 2H), 4.53 (d, J = 6.2 Hz, 2H), 3.27 (sept, J = 6.9 Hz, 1H), 1.41 (d, J = 6.9 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 176.5, 162.3 (d, $^1J_{C,F}$ = 245.5Hz), 161.3, 141.8, 140.0, 135.7, 134.2, 134.1, 131.7 (X2), 131.1 (X2), 129.5 (d, $^3J_{C,F}$ = 8.0 Hz), 118.7, 115.6 (d, $^2J_{C,F}$ = 21.4 Hz), 112.4, 42.5, 33.4, 23.0 (X2); HRMS (ESI-MS):Calc. for $C_{21}H_{19}N_3OSF$ [$(M+H)^+$]: 380.1233, Found: 380.1234.

***N*-(4-chlorobenzyl)-5-(4-cyanophenyl)-2-isopropylthiazole-4-carboxamide (14j)**

White solid (180 mg, 68%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.87 (t, J = 5.5 Hz, 1H), 7.72 (d, J = 8.5 Hz, 2H), 7.67 (d, J = 8.5 Hz, 2H), 7.32 – 7.24 (m, 4H), 4.53 (d, J = 6.2 Hz, 2H), 3.27 (sept, J = 6.9 Hz, 1H), 1.42 (d, J = 6.9 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 176.5, 161.4, 141.7, 140.1, 136.9, 135.7, 133.4, 131.7 (X2), 131.2 (X2), 129.2 (X2), 128.9 (X2), 118.7, 112.4, 42.6, 33.4, 23.0 (X2); HRMS (ESI-MS):Calc. for $C_{21}H_{19}N_3OSCl$ [$(M+H)^+$]: 396.0937, Found: 396.0943.

***N*-(4-chloro-3-fluorophenyl)-5-(4-cyanophenyl)-2-isopropylthiazole-4-carboxamide (14k)**

White solid (160 mg, 54%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 9.44 (s, 1H), 7.85 (dd, J = 6.5, 2.6 Hz, 1H), 7.76 – 7.66 (m, 4H), 7.45 (ddd, J = 8.9, 4.1, 2.7 Hz, 1H), 7.09 (t, J = 8.8 Hz, 1H), 3.34 (sept, J = 6.9 Hz 1H), 1.48 (d, J = 6.9 Hz, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.7, 159.1, 154.9 (d, $^1J_{C,F}$ = 246.3Hz), 141.4, 141.2, 135.3, 134.4, 134.4, 131.8 (X2), 131.1 (X2), 122.0, 121.3 (d, $^2J_{C,F}$ = 18.5Hz), 119.5 (d, $^3J_{C,F}$ = 6.7 Hz), 118.6, 116.6 (d, $^2J_{C,F}$ = 21.4Hz), 112.7, 33.5, 23.0 (X2); HRMS (ESI-MS):Calc. for $C_{20}H_{16}N_3OFClS$ [$(M+H)^+$]: 400.0697, Found: 400.0693.

(*R*)-5-(4-cyanophenyl)-2-isopropyl-*N*-(1-(naphthalen-1-yl)ethyl)thiazole-4-carboxamide (14l)

White solid (145 mg, 51%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.88 (d, *J* = 8.5 Hz, 1H), 7.86 – 7.80 (m, 4H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.65 (d, *J* = 8.6 Hz, 2H), 7.52 – 7.43 (m, 3H), 5.38 (qn, *J* =7.0 Hz, 1H), 3.30 (sept, *J* = 6.9 Hz, 1H), 1.68 (d, *J* = 6.9 Hz, 3H), 1.44 (d, *J* = 1.9 Hz, 3H), 1.42 (d, *J* = 1.9 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.4, 160.6, 142.0, 140.7, 139.8, 135.8, 133.5, 132.8, 131.7 (X2), 131.1 (X2), 128.6, 128.0, 127.7, 126.3, 126.0, 124.9, 124.7, 118.7, 112.3, 48.8, 33.5, 23.1 (X2), 22.1; HRMS (ESI-MS):Calc. for $C_{26}H_{24}N_3OS$ [$(M+H)^+$]: 426.1640, Found: 426.1646.

***N*-(1-(4-bromophenyl)ethyl)-5-(4-cyanophenyl)-2-isopropylthiazole-4-carboxamide (14m)**

White solid (165 mg, 54%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.77 (d, *J* = 8.2 Hz, 1H), 7.68 (d, *J* = 8.6 Hz, 2H), 7.65 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H), 5.15(qn, *J* =7.0 Hz, 1H), 3.29 (sept, *J* = 6.9 Hz, 1H), 1.55 (d, *J* = 7.0 Hz, 3H), 1.43 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.5, 160.5, 142.5, 141.8, 140.0, 135.7, 131.8 (X2), 131.7 (X2), 131.1 (X2), 128.0 (X2), 121.2, 118.7, 112.3, 48.2, 33.4, 23.1 (X2), 22.1; HRMS (ESI-MS):Calc. for $C_{22}H_{21}N_3OSBr$ [$(M+H)^+$]: 454.0589, Found: 454.0586.

5-(4-cyanophenyl)-2-isopropyl-*N*-(1-(p-tolyl)ethyl)thiazole-4-carboxamide (14n)

White solid (180 mg, 69%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.76 (d, *J* = 8.3 Hz, 1H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.65 (d, *J* = 8.6 Hz, 2H), 7.27 (d, *J* = 7.9 Hz, 2H), 7.16 (d, *J* = 7.9 Hz, 2H), 5.18 (qn, *J* =7.5 Hz, 1H), 3.28 (Sept, *J* = 6.9 Hz, 1H), 2.33 (s, 3H), 1.56 (d, *J* = 6.9 Hz, 3H), 1.43 (d, *J* = 1.5 Hz, 3H), 1.41 (d, *J* = 1.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.3, 160.5, 142.1, 140.3, 139.7, 137.1, 135.8, 131.7 (X2), 131.2 (X2), 129.4 (X2), 126.2 (X2), 118.7, 112.2, 48.4, 33.4, 23.1 (X2), 22.2, 21.2; HRMS (ESI-MS):Calc. for $C_{23}H_{24}N_3OS$ [$(M+H)^+$]: 390.1640, Found: 390.1645.

(*S*)-5-(benzo[d][1,3]dioxol-5-yl)-2-isopropyl-*N*-(1-phenylethyl)thiazole-4-carboxamide (15a)

Yellow semisolid (120 mg, 48%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.74 (d, *J* = 8.2 Hz, 1H), 7.38 (d, *J* = 7.2 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.28 – 7.22 (m, 1H), 7.10 (d, *J* = 1.6 Hz, 1H), 7.04 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 5.97 (s, 1H), 5.25 (qn, *J* =7.0 Hz, 1H), 3.24 (sept, *J* = 6.9 Hz, 1H), 1.57 (d, *J* = 6.9 Hz, 3H), 1.41 (d, *J* = 1.5 Hz, 3H), 1.39 (d, *J* = 1.5 Hz, 3H); **^{13}C NMR** (100

MHz, $CDCl_3$) δ 174.5, 160.9, 148.2, 147.3, 143.6, 142.2, 140.7, 128.7 (X2), 127.2, 126.3 (X2), 124.3, 124.2, 111.0, 107.9, 101.4, 48.4, 33.3, 23.1 (X2), 22.2; HRMS (ESI-MS):Calc. for $C_{22}H_{23}N_2O_3S$ [$(M+H)^+$]: 395.1429, Found: 395.1459.

(*R*)-5-(benzo[d][1,3]dioxol-5-yl)-2-isopropyl-*N*-(1-phenylethyl)thiazole-4-carboxamide (15b)

White solid (125 mg, 50%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.74 (d, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 7.0 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.29 – 7.23 (m, 1H), 7.11 (d, *J* = 1.7 Hz, 1H), 7.04 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 5.97 (s, 2H), 5.25 (qn, *J* =7.0 Hz, 1H), 3.24 (sept, *J* = 6.9 Hz, 1H), 1.57 (d, *J* = 6.9 Hz, 3H)1.41 (d, *J* = 1.3 Hz, 3H), 1.39 (d, *J* = 1.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.5, 160.9, 148.2, 147.3, 143.6, 142.2, 140.7, 128.7 (X2), 127.2, 126.3 (X2), 124.3, 124.2, 111.0, 107.9, 101.4, 48.4, 33.3, 23.1 (X2), 22.2; HRMS (ESI-MS):Calc. for $C_{22}H_{23}N_2O_3S$ [$(M+H)^+$]: 395.1429, Found: 395.1438.

5-(benzo[d][1,3]dioxol-5-yl)-*N*-(3,4-dimethoxyphenethyl)-2-isopropylthiazole-4-carboxamide (15c)

Yellow solid (165 mg, 58%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.58 (t, *J* = 5.8 Hz, 1H), 7.11 (d, *J* = 1.7 Hz, 1H), 7.04 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 2H), 6.78 (d, *J* = 1.8 Hz, 1H), 6.76 (s, 1H), 5.99 (s, 2H), 3.86 (s, 3H)), 3.85 (s, 3H), 3.60 (q, *J* = 6.7 Hz, 2H), 3.21 (sept, *J* = 6.9 Hz, 1H), 2.84 (t, *J* = 7.2 Hz, 2H), 1.38 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.3, 161.8, 149.0, 148.2, 147.6, 147.3, 142.0, 140.8, 131.8, 124.3, 124. 2, 120.8, 112.1, 111.4, 111.0, 107.9, 101.4, 56.0, 55.9, 40.8, 35.6, 33.2, 22.9 (X2); HRMS (ESI-MS):Calc. for $C_{24}H_{27}N_2O_5S$ [$(M+H)^+$]: 455.1641, Found: 455.1650.

(5-(benzo[*d*][1,3]dioxol-5-yl)-2-isopropylthiazol-4-yl)(morpholino)methanone (15d)

White solid (133 mg, 59%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 6.99 – 6.94 (m, 2H), 6.82 (dd, *J* = 7.7, 0.7 Hz, 1H), 6.00 (s, 2H), 3.73 (t, *J* = 4.8 Hz, 2H), 3.65 (t, *J* = 5.0 Hz, 2H), 3.32 (t, *J* = 4.8 Hz, 2H), 3.32 – 3.23 (m, 1H), 3.19 ((t, *J* = 5.0 Hz, 2H), 1.41 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.8, 164.9, 148.3, 148.28, 142.6, 135.8, 124.2, 122.7, 108.9 (X2), 101.6, 66.6, 66.5, 47.2,

42.4, 33.5, 23.2 (X2); HRMS (ESI-MS):Calc. for $C_{18}H_{21}N_2O_4S$ [$(M+H)^+$]: 361.1222, Found: 361.1221.

5-(benzo[*d*][1,3]dioxol-5-yl)-*N*-(benzo[d][1,3]dioxol-5-ylmethyl)-2-isopropylthiazole-4-carboxamide (15e)

Brown semisolid (120 mg, 45%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.78 (bs, 1H), 7.12 (d, *J* = 1.6 Hz, 1H), 7.05 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.84 (s, 1H), 6.82 – 6.78 (m, 2H), 6.75 (d, *J* = 7.9 Hz, 1H), 5.97 (s, 2H), 5.92 (s, 2H), 4.47 (d, *J* = 6.1 Hz, 2H), 3.21 (sept, *J* = 6.9 Hz, 1H), 1.38 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.4, 161.5, 148.6, 147.8, 147.2, 146.8, 142.3, 140.5, 132.4, 124.2, 124.1, 121.0, 110.9, 108.4, 108.2, 107.8, 101.3, 100.9, 42.9, 33.1, 22.9 (X2); HRMS (ESI-MS):Calc. for $C_{22}H_{21}N_2O_5S$ [$(M+H)^+$]: 425.1171, Found: 425.1175.

5-(benzo[*d*][1,3]dioxol-5-yl)-2-isopropyl-*N*-(pyridin-3-ylmethyl)thiazole-4-carboxamide (15f)

Brown solid (110 mg, 46%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.59 (d, *J* = 1.6 Hz, 1H), 8.51 (dd, *J* = 4.7, 1.3 Hz, 1H), 7.88 (t, *J* = 5.8 Hz, 1H), 7.69 (dt, *J* = 7.8, 1.8 Hz, 1H), 7.26 – 7.23 (m, 1H), 7.11 (d, *J* = 1.7 Hz, 1H), 7.05 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 5.98 (s, 2H), 4.59 (d, *J* = 6.3 Hz, 2H), 3.22 (sept, *J* = 6.9 Hz, 1H), 1.39 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.6, 161.8, 149.1, 148.6, 148.2, 147.2, 142.6, 140.2, 135.7, 134.4, 124.2, 124.0, 123.6, 110.9, 107.9, 101.3, 40.5, 33.2, 22.9 (X2); HRMS (ESI-MS):Calc. for $C_{20}H_{20}N_3O_3S$ [$(M+H)^+$]: 382.1225, Found: 382.1232.

(*S*)-5-(4-cyanophenyl)-2-cyclohexyl-*N*-(1-phenylethyl)thiazole-4-carboxamide (16a)

White solid (175 mg, 70%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.80 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.39 – 7.36 (m, 2H), 7.36 – 7.32 (m, 2H), 7.28 – 7.24 (m, 1H), 5.21 (qn, *J* = 7.0 Hz, 1H), 2.96 (tt, *J* = 11.5, 3.6 Hz, 1H), 2.16 (d, *J* = 12.5 Hz, 2H), 1.90 – 1.86 (m, 2H), 1.79 – 1.75 (m, 1H), 1.56 (d, *J* = 10.8 Hz, 3H), 1.55 – 1.38 (m, 4H), 1.35 – 1.27 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.4, 160.5, 143.3, 141.9, 139.5, 135.8, 131.6 (X2), 131.1 (X2), 128.7

(X2), 127.3, 126.2 (X2), 118.7, 112.2, 48.6, 42.6, 33.6, 29.8, 26.0 (X2), 25.7, 22.2; HRMS (ESI-MS):Calc. for $C_{25}H_{26}N_3OS$ [$(M+H)^+$]: 416.1797, Found: 416.1805.

(*R*)-5-(4-cyanophenyl)-2-cyclohexyl-*N*-(1-phenylethyl)thiazole-4-carboxamide (16b)

White solid (150 mg, 61%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.79 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 8.5 Hz, 2H), 7.39 – 7.36 (m, 2H), 7.36 – 7.31 (m, 2H), 7.29 – 7.24 (m, 1H), 5.21 (qn, J = 7.0 Hz, 1H), 2.96 (tt, J = 11.5, 3.6 Hz, 1H), 2.16 (d, J = 12.5 Hz, 2H), 1.90 – 1.86 (m, 2H), 1.79 – 1.75 (m, 1H), 1.56 (d, J = 10.8 Hz, 3H), 1.55 – 1.38 (m, 4H), 1.35 – 1.27 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.4, 160.6, 143.4, 142.0, 139.6, 135.9, 131.7 (X2), 131.2 (X2), 128.8 (X2), 127.4, 126.3 (X2), 118.8, 112.3, 48.7, 42.7, 33.7, 29.8, 26.1 (X2), 25.8, 22.2; HRMS (ESI-MS):Calc. for $C_{25}H_{26}N_3OS$ [$(M+H)^+$]:416.1797, Found: 416.1800.

(4-cyanophenyl)-2-cyclohexyl-N-(3,4-dimethoxyphenethyl)thiazole-4-carboxamide (16c)

White solid (170 mg, 60%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.75 – 7.58 (m, 5H), 6.86 – 6.70 (m, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.59 (q, J = 6.8 Hz, 2H), 2.92 (tt, J = 11.6, 3.5 Hz, 1H), 2.83 (t, J = 7.1 Hz, 2H), 2.13 (d, J = 11.9 Hz, 2H), 1.87 (d, J = 12.6 Hz, 2H), 1.77 (d, J = 12.6 Hz, 1H), 1.62 – 1.36 (m, 4H), 1.35 – 1.24 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 175.0, 161.2, 148.8, 147.5, 141.9, 139.1, 135.6, 131.4 (X2), 130.9 (X2), 120.6, 118.5, 112.0, 111.9, 111.2, 55.8, 55.7, 42.2, 40.6, 35.3, 33.2 (X2), 25.7 (X2), 25.5; HRMS (ESI-MS):Calc. for $C_{27}H_{30}N_3O_3S$ [$(M+H)^+$]: 476.2008, Found: 476.2020.

4-(2-cyclohexyl-4-(morpholine-4-carbonyl)thiazol-5-yl)benzonitrile (16d)

White solid (130 mg, 58%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.68 (d, J = 8.5 Hz, 2H), 7.62 (d, J = 8.5 Hz, 2H), 3.76 (t, J = 3.9 Hz, 2H), 3.70 (t, J = 4.9 Hz, 2H), 3.45 (t, J = 4.6 Hz, 2H), 3.25 (t, J = 5.0 Hz, 2H), 3.00 (tt, J = 11.4, 3.5 Hz, 1H), 2.20 – 2.12 (m, 2H), 1.91 – 1.82 (m, 2H), 1.79 – 1.70 (m, 1H), 1.60 – 1.35 (m, 4H), 1.34 – 1.25 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.6, 164.2, 144.7, 135.2, 134.1, 132.7 (X2), 129.0 (X2), 118.3, 112.2, 66.8, 66.6, 47.3, 42.8, 42.5, 33.7 (X2), 26.0 (X2), 25.7; HRMS (ESI-MS):Calc. for $C_{21}H_{24}N_3O_2S$ [$(M+H)^+$]: 382.1289, Found: 382.1591.

***N*-(benzo[d][1,3]dioxol-5-ylmethyl)-5-(4-cyanophenyl)-2-cyclohexylthiazole-4-carboxamide (16e)**

White solid (125 mg, 47%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.79 (t, *J* = 5.0 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 6.83 (s, 1H), 6.81 – 6.74 (m, 2H), 5.94 (s, 2H), 4.46 (d, *J* = 6.1 Hz, 2H), 2.94 (tt, *J* = 11.5, 3.4 Hz, 1H), 2.18 – 2.10 (m, 2H), 1.90 – 1.83 (m, 2H), 1.77 – 1.72 (m, 1H), 1.54 – 1.35 (m, 4H), 1.33 – 1.24 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.5, 161.3, 148.0, 147.1, 141.9, 139.7, 135.8, 132.2, 131.7 (X2), 131.2 (X2), 121.2, 118.8, 112.3, 108.6, 108.4, 101.2, 43.1, 42.6, 33.6 (X2), 26.0 (X2), 25.7; HRMS (ESI-MS):Calc. for $C_{25}H_{24}N_3O_3S$ [$(M+H)^+$]: 446.1538, Found: 446.1545.

5-(4-cyanophenyl)-2-cyclohexyl-*N*-(pyridin-3-ylmethyl)thiazole-4-carboxamide (16f)

White solid (120 mg, 50%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.59 (d, *J* = 1.9 Hz, 1H), 8.52 (dd, *J* = 4.7, 1.1 Hz, 1H), 7.93 (t, *J* = 5.8 Hz, 1H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 8.3 Hz, 3H), 7.26 – 7.23 (m, 1H), 4.57 (d, *J* = 6.3 Hz, 2H), 2.93 (tt, *J* = 11.5, 3.6 Hz, 1H), 2.14 (dd, *J* = 13.0, 2.2 Hz, 2H), 1.89 – 1.81 (m, 2H), 1.78 – 1.72 (m, 1H), 1.52 (qd, *J* = 12.3, 3.1 Hz, 2H), 1.41 (qt, *J* = 12.3, 3.1 Hz, 2H), 1.32 – 1.22 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.5, 161.4, 149.1, 148.8, 141.4, 139.9, 135.5, 133.9, 131.6 (X2), 131.0 (X2), 123.5, 118.5, 112.2, 42.4, 40.6, 33.4 (X2), 25.8 (X2), 25.6; HRMS (ESI-MS):Calc. for $C_{23}H_{23}N_4OS$ [$(M+H)^+$]: 403.1593, Found: 403.1607.

(*S*)-5-(4-cyanophenyl)-2-methyl-*N*-(1-phenylethyl)thiazole-4-carboxamide (17a)

White solid (55mg, 70%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.79 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.39 – 7.32 (m, 4H) 7.28 – 7.24 (m, 1H), 5.20 (qn, *J* = 7.0 Hz, 1H), 2.70 (s, 3H), 1.57 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.5, 160.3, 143.3, 142.4, 140.6, 135.5, 131.7 (X2), 131.2 (X2), 128.8 (X2), 127.5, 126.3 (X2), 118.7, 112.4, 48.7, 22.2, 19.2; HRMS (ESI-MS):Calc. for $C_{20}H_{18}N_3OS$ [$(M+H)^+$]: 348.1171, Found: 348.1173.

(*R*)-5-(4-cyanophenyl)-2-methyl-*N*-(1-phenylethyl)thiazole-4-carboxamide (17b)

White solid (110mg, 45%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.79 (d, *J* = 7.9 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 7.0 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.26 (t, *J* =

7.0 Hz, 1H), 5.21 (qn, *J* = 7.0 Hz, 1H), 2.70 (s, 3H), 1.58 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.5, 160.32, 143.2, 142.3, 140.5, 135.4, 131.6 (X2), 131.1 (X2), 128.7 (X2), 127.3, 126.2 (X2), 118.6, 112.2, 48.6, 22.1, 19.1; HRMS (ESI-MS):Calc. for $C_{20}H_{18}N_3OS$ $[(M+H)^+]$: 348.1171, Found: 348.1176.

5-(4-cyanophenyl)-*N*-(3,4-dimethoxyphenethyl)-2-methylthiazole-4-carboxamide (17c)

Brown solid (160 mg, 55%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.70 – 7.64 (m, 4H), 7.59 (t, *J* = 5.8 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 9.9 Hz, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.59 (q, *J* = 6.8 Hz, 2H), 2.83 (t, *J* = 7.2 Hz, 2H), 2.68 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.5, 161.2, 149.0, 147.7, 142.4, 140.4, 135.5, 131.6 (X2), 131.5, 131.1 (X2), 120.7, 118.6, 112.3, 112.0, 111.4, 56.0, 55.9, 40.8, 35.5, 19.1; HRMS (ESI-MS):Calc. for $C_{22}H_{22}N_3O_3S$ $[(M+H)^+]$: 408.1382, Found: 408.1392.

4-(2-methyl-4-(morpholine-4-carbonyl)thiazol-5-yl)benzonitrile (17d)

Yellow solid (120 mg, 52%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.68 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 2H), 3.75 (t, *J* = 5.0 Hz, 2H), 3.68 (t, *J* = 5.0 Hz, 2H), 3.42 (t, *J* = 5.0 Hz, 2H), 3.22 (t, *J* = 5.0 Hz, 2H), 2.74 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.9, 164.1, 145.1, 135.0, 134.9, 132.8 (X2), 129.0 (X2), 118.3, 112.4, 66.8, 66.6, 47.3, 42.5, 19.4; HRMS (ESI-MS):Calc. for $C_{16}H_{16}N_3O_2S$ $[(M+H)^+]$: 314.0963, Found: 314.0963.

***N*-(benzo[*d*][1, 3]dioxol-5-ylmethyl)-5-(4-cyanophenyl)-2-methylthiazole-4-carboxamide (17e)**

Yellow solid (110 mg, 40%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.76 (bs, 1H), 7.71 (d, *J* = 8.6 Hz, 2H), 7.67 (d, *J* = 8.6 Hz, 2H), 6.83 – 6.73 (m, 3H), 5.94 (s, 2H), 4.45 (d, *J* = 6.0 Hz, 2H), 2.68 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.6, 161.0, 148.0, 147.1, 142.2, 140.8, 135.5, 132.1, 131.8 (X2), 131.2 (X2), 121.3, 118.7, 112.5, 108.6, 108.4, 101.2, 43.2, 19.2; HRMS (ESI-MS):Calc. for $C_{20}H_{16}N_3O_3S$ $[(M+H)^+]$: 378.0912, Found: 378.0913.

5-(4-cyanophenyl)-2-methyl-*N*-(pyridin-3-ylmethyl)thiazole-4-carboxamide (17f)

White solid (120 mg, 48%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.59 (s, 1H), 8.53 (d, *J* = 4.1 Hz, 1H), 7.90 (bs, 1H), 7.74 – 7.65 (m, 5H), 7.26 (t, *J* = 6.3 Hz, 1H), 4.57 (d, *J* = 6.2 Hz, 2H), 2.69 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.7, 161.2, 149.1, 148.8, 141.8, 141.0, 135.6, 135.2, 133.9, 131.6 (X2), 131.0 (X2), 123.6, 118.5, 112.3, 40.7, 19.0; HRMS (ESI-MS):Calc. for $C_{18}H_{15}N_4OS$ [$(M+H)^+$]: 335.0967, Found: 335.0974.

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ABBREVIATIONS

MIC, Minimum inhibitory concentration; IC_{50}, Concentration of compound at which 50% cell inhibition occurred; MABA, Microplate Alamar Blue Assay; cLogP, calculated log of partition coefficient.

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- Drug-resistant tuberculosis
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- 2,4,5-trisubstituted thiazoles
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