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Structure-activity relationship (SAR) studies of N-(3-methylpyridin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine (SRI-22819) as NF-κB activators for the treatment of ALS

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ABSTRACT

ALS is a rare type of progressive neurological disease with unknown etiology. It results in the gradual degeneration and death of motor neurons responsible for controlling the voluntary muscles. Identification of mutations in the superoxide dismutase (SOD) 1 gene has been the most significant finding in ALS research. SOD1 abnormalities have been associated with both familial as well as sporadic ALS cases. SOD2 is a highly inducible SOD that performs in concurrence with SOD1 to detoxify ROS. Induction of SOD2 can be obtained through activation of NF-κBs. We previously reported that SRI-22819 increases NF-κB expression and activation *in vitro*, but it has poor ADME properties in general and has no oral bioavailability. Our initial studies were focused on direct modifications of SRI-22819. There were active compounds identified but no improvement in microsomal stability was observed. In this context, we focused on making more significant structural changes in the core of the molecule. Ataluren, an oxadiazole compound that promotes read-through and expression of dystrophin in patients with Duchenne muscular dystrophy, bears some structural similarity to SRI-22819. Thus, we synthesized a series of SRI-22819 and Ataluren (PTC124) hybrid compounds. Several compounds from this series exhibited improved activity, microsomal stability and lower calculated polar surface area (PSA). This manuscript describes the synthesis and biological evaluation of SRI-22819 analogs and its hybrid combination with Ataluren.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a rare, progressive and incurable neurodegenerative disease. It is also known as Lou Gehrig's disease or motor neuron disease, and it generally destroys nerve cells responsible for controlling the voluntary muscles. ALS causes irreversible degeneration of motor neurons which is accompanied by paralysis of voluntary muscle and leads to respiratory failure. ALS usually affects people between 40 and 60 years of age with an incidence of 2 in 100,000 adults. Death occurs within 5 years on average from diagnosis. Approximately 10% of ALS cases are familial (f-ALS) and the remaining 90% of ALS is sporadic (s-ALS), meaning it occurs without any family history [1].

The etiology of this disease is unknown, but examples of possible causes of this disease that are reported are glutamate toxicity [2], mitochondrial dysfunctions [3], exposures to environmental toxins and toxic chemicals [4], and superoxide dismutase [Cu–Zn] or superoxide dismutase 1 (SOD1) abnormalities [5–7]. Here we focused on the SOD1 gene abnormalities and this gene mutation has been identified in both familial as well as sporadic ALS cases [8]. SOD1 converts superoxide free radicals into hydrogen peroxide which is then eliminated by catalases and glutathione peroxidases. Thus, SOD1 abnormalities can cause hyper-generation of ROS (Reactive Oxygen Species) which can lead to oxidative stress. Transgenic animals carrying high number of mutated SOD1 develop a disease similar to human ALS [9]. SOD2, another Mn2+-dependent superoxide dismutase, is highly inducible and is unaffected in ALS, and thus, can be a novel approach to ALS treatment

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Abbreviations

ALS	Amyotrophic lateral sclerosis
SOD	superoxide dismutase
NF-κB	nuclear factor kappa light chain enhancer of activated B cells
ROS	reactive oxygen species
SAR	structure-activity relationship
DMD	Duchenne muscular dystrophy
ADME	Absorption, Distribution, Metabolism, and Excretion
EtOH	Ethanol
F	Fluorine
Cl	Chlorine
H	Hydrogen
OMe	Methoxy
OH	Hydroxy
Me	Methyl
DIEA	*N*,*N*-Di*iso*propylethylamine
DIAD	Di*iso*propyl azodicarboxylate
NaOH	Sodium hydroxide
BOP	benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate
THF	Tetrahydrofuran
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate
MeCN	Acetonitrile
DCM	Dichloromethane
TEA	Triethylamine
DMAP	4-Dimethylaminopyridine
EC_{50}	half maximal effective concentration
Emax	Maximal Efficacy
Std Dev	Standard Deviation
DMF	Dimethylformamide
HLM	Human Liver Microsome
MLM	Mouse Liver Microsome
PK	pharmacokinetic
iv	Intravenous
po	oral administration
Cmax	maximum concentration
$t_{1/2}$	Half-life
TMS	tetramethylsilane

[10–13]. It is localized in the mitochondria and works in conjunction with SOD1 to detoxify ROS. Induction of SOD2 can be achieved through activation of NF-κBs (nuclear factor kappa light chain enhancer of activated B cells) [10]. The p65 subunit of NF-κB (which consists of 75% of brain NF-κBs) activates SOD2 transcription by binding a specific sequence on the SOD2 promoter region [11]. The development of potent and selective small molecule activators of NF-κB can be used as a strategy for a novel treatment of ALS [14,15].

In our earlier publication, we reported that SRI-22819 (Fig. 1) increases NF-kB activation *in vitro* [14]. However, it had a short half-life of <30 min when tested in human and mouse microsomes. In addition, SRI-22819 had a half-life of less than 1-h IV (intravenous) and had no significant oral bioavailability (Table 6). We therefore set out to identify novel compounds that up-regulate SOD2 levels by activating NF-κB and improved drug-like properties, including oral bioavailability.

Our initial optimization studies were focused on modifications of SRI-22819 in an effort to enhance activity and drug-like properties. However, no improvement in these properties was observed (Tables 1 and 5). Moving forward, we modeled our medicinal chemistry optimization studies based upon the structural similarities of SRI-22819 and ataluren (PTC124) [16], a known oral bioavailable drug for Duchenne Muscular Dystrophy (DMD) in Europe (Fig. 1). Hybrid combinations of SRI-22819 and Ataluren were designed with the goal of identifying a series of compounds with the desired activity and physiochemical properties.

Our general approach is outlined in Fig. 1. Our first set of compounds (**1**–**18,** X = CH) consisted of the replacement of the 2-

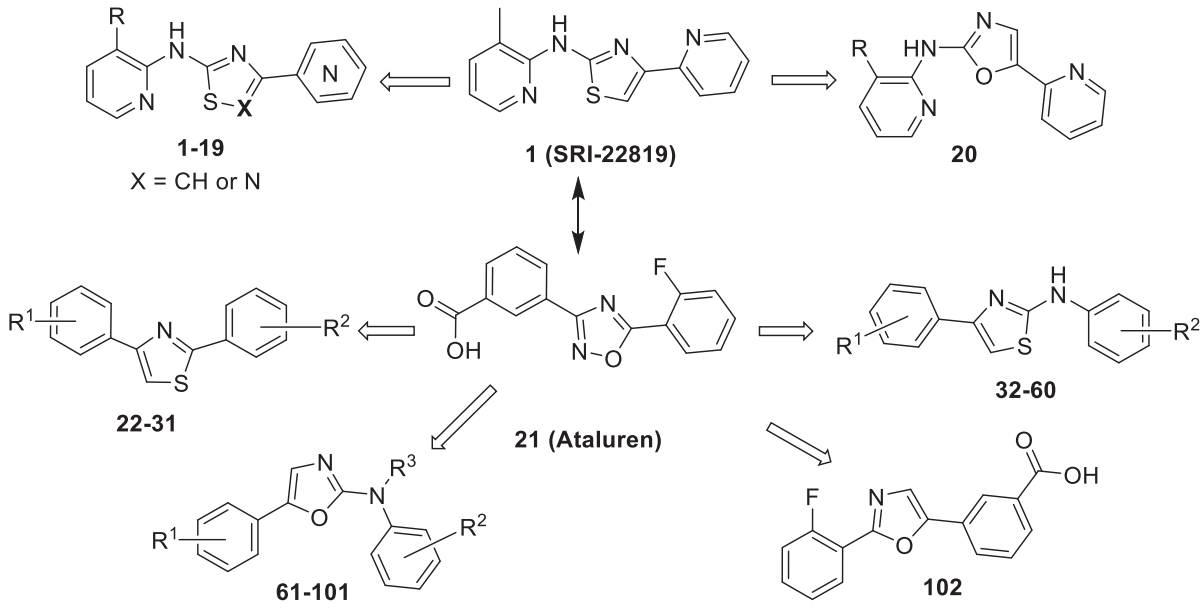


Fig. 1. Overview of SAR studies.

methyl group and/or rotation of the nitrogen atom on the pyridine ring, that directly attached to the thiazole ring. We also replaced the thiazole ring of SRI-22819 with thiadiazole (**19**, X = N) and oxazole (**20**) ring systems. Subsequently, we carried out detailed studies on hybrid combinations of SRI-22819 and ataluren (**22**–**102**). For example, compounds **22**–**31** have a thiazole ring in lieu of oxadiazole ring found in ataluren along with various substituents on both phenyl rings. Compounds **32**–**60** contain an amino-thiazole group similar to SRI-22819, but with substitutions on each phenyl ring. Replacement of the oxadiazole ring in Ataluren with amino-oxazole or oxazole and phenyl substitutions (compounds **61**–**102**) were also carried out. Herein, we report the synthesis and biological evaluation of these compounds.

2. Results and discussion

2.1. Chemistry

Compounds **1**–**18** were synthesized starting with substituted 2-pyridyl thiourea (**I**) and 2-,3-, or 4-pyridyl-2-bromoethanone (**II**) by utilizing a published procedure (Scheme 1) [17]. Substituted 2-pyridyl thioureas, if not commercially available, were synthesized from substituted 2-pyridyl amine and benzoyl *iso*thiocyanate in two steps [17].

Thiadiazole analog (**19**) was prepared from 2-*iso*thiocyanato-3-methylpyridine (**19a**) [18] and picolinimidamide hydrochloride (**19b**) as shown in Scheme 2 [19].

Oxazole analog, **20** was prepared from 2-azido-1-(pyridin-2-yl) ethanone (**20a**) [20] and 2-*iso*thiocyanato-3-methylpyridine (**20b**) [18] in presence of triphenylphosphine in 1,4-dioxane under reflux conditions (Scheme 3) [21].

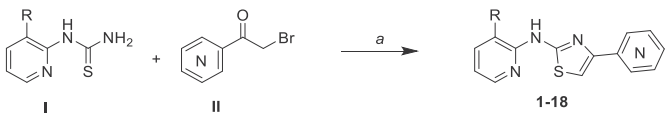
The general synthetic route used to prepare the biaryl thiazoles is shown in Scheme 4 [22]. In some cases, the biaryl thiazole esters (**29**–**31**) were isolated rather than corresponding acids and hydrolyzed to biaryl thiazole acids (**22**–**27**) [23].

A similar synthetic route was followed for the synthesis of biaryl aminothiazoles (Scheme 5) [24]. Commercially available aryl thioureas (**V**) combined with various substituted phenyl-2-bromoethanone (**III**) provided the biaryl aminothiazoles in good yields.

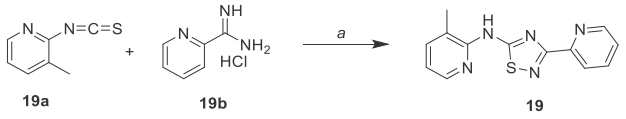
The syntheses of **45-47**, **51** and **54** were all achieved from biaryl aminothiazole, 3-(2-((2-fluorophenyl)amino)thiazol-4-yl)benzoic acid (**32**), as shown in Scheme 6. Treatment of **32** with thionyl chloride and methanol gave methyl ester **45** [25]. Reduction of **32** using sodium borohydride and BOP reagent gave alcohol **46** [26], which was converted to methyl ether **47** by reacting with sodium hydride and methyl iodide [27]. Lastly, acid **32** was amidated under HATU coupling conditions to give **51** [28] and **32** was also treated with *N′*-hydroxyacetimidamide in presence of HATU to give **54** [29].

Compounds **55**–**58** were synthesized from the corresponding cyano compounds, **55a-58a** (prepared from fluorophenylthiourea and 2-bromoacetylbenzonitrile [23]) using lithium aluminum hydride [30]. Compound **55** was further acetylated in the presence of acetic anhydride and Hünigs base to give **59** (Scheme 7) [31].

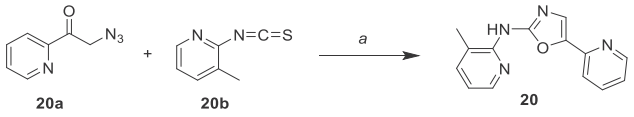
Reaction of 2-chloro-*N*-(2-fluorophenyl)acetamide (**60a**) and 3-carbamothioylbenzoic acid (**60b**) afforded compound **60** which is the reverse analog of **32** (Scheme 8) [32].



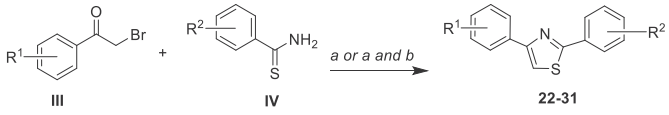
Scheme 1. Synthesis of bipyridyl aminothiazoles 1-18
Conditions: (a) EtOH, 80 °C.



Scheme 2. Synthesis of bipyridyl aminothiadiazole 19
Conditions: (a) DIEA, DIAD, DMF, rt.



Scheme 3. Synthesis of bipyridyl aminoxazole 20
Conditions: (a) Triphenylphosphine, 1,4-Dioxane, 100 °C.



Scheme 4. Synthesis of biaryl thiazoles 22-31
Conditions: (a) EtOH, 80 °C; (b) NaOH (1N), EtOH, 60 °C.

Scheme 9 outlines the general synthetic route for the preparation of biaryl aminooxazoles **61**–**92**, **94**, **98** and **101**. These compounds were prepared *via* the cyclization of the appropriately substituted 2-azidoacetylbenzoates (**VI**) [20] with commercially available substituted *iso*thiocyanatobenzenes (**VII**) to provide the corresponding amino-oxazoles, **75**–**88**, **94** and **98** in good yields [21]. The esters were hydrolyzed to give the corresponding acids (**61**–**74**) in average yields [23]. Subsequent *N*-alkylation of methyl 3-(2-((4-fluorophenyl)amino)oxazol-5-yl)benzoate (**77**) in the presence of an alkyl halide and sodium hydride provided compounds **89** and **91A** which were then hydrolyzed to the corresponding *N*-alkyl amino-oxazole acids, **90**–**91** in good yields [33]. Compounds **92** and **101** were prepared from **77** and **89** by treating with methyl amine (Scheme 9) [34].

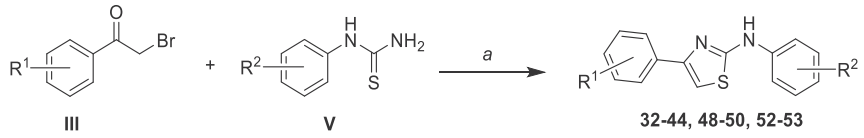
Next, we replaced the carboxylic acid group in **63** and **90** with an oxadiazole ring as a bioisosteric replacement to give compounds **93** and **100**. This was achieved by treating the amino-oxazole acids, **63** and **90**, with (*E*)-*N′*-hydroxyacetimidamide in presence of propylphosphonic anhydride and triethylamine (Scheme 10) [35].

The preparation of **95-97** and **99** is shown in Scheme 11. Cyano aminooxazole **94** was treated with sodium azide and ammonium chloride for the introduction of tetrazole ring to get **95** [36]. Compound **94** was converted to **96** by a lithium aluminum hydride catalyzed reduction and then **96** was further acetylated to **97** in good yields [30,31]. Deacetylation of **98** under acidic conditions provided **99** in 38% yield (Scheme 11) [37].

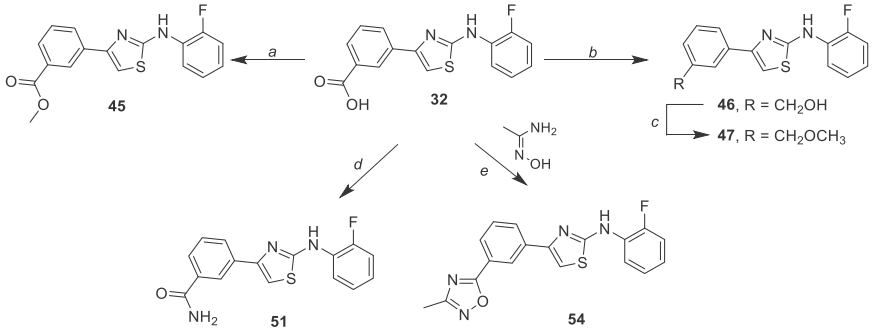
The oxazole analog was prepared by reacting 3-(2-bromoacetyl) benzoic acid (**102a**) with 2-fluorobenzylamine (**102b**) in presence of iodine and potassium carbonate to afford biaryl oxazole acid, **102** (Scheme 12) [38].

2.2. Biological evaluation

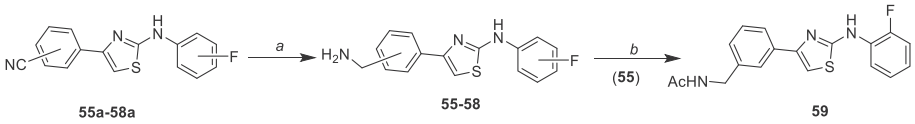
The compounds were screened for their ability to activate NF-κB [14,15] and the EC_{50} and E_{max} results are summarized in Tables 1–4 It was important to look at both the activation *vis* the EC_{50} and the magnitude by the E_{max}. As previously discussed, compound **1** was identified as a lead compound for the studies and was used as the basis for newly synthesized compounds. Furthermore, some



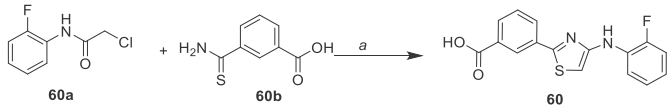
Scheme 5. Synthesis of biaryl aminothiazoles 32–44, 48–50, 52-53
Conditions: (a) EtOH, 80 °C.



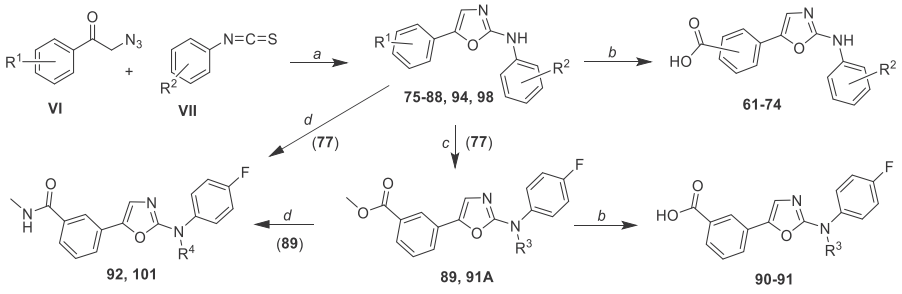
Scheme 6. Synthesis of biaryl aminothiazoles 45–47, 51, 54
Conditions: (a) Thionyl chloride, MeOH, rt; (b) DIEA, BOP, Sodium borohydride, THF, rt; (c) Sodium hydride, Methyl iodide, THF, 0 °C-rt; (d) HATU, DIEA, Ammonium chloride, MeCN, rt; (e) HATU, DIEA, DMF, rt.



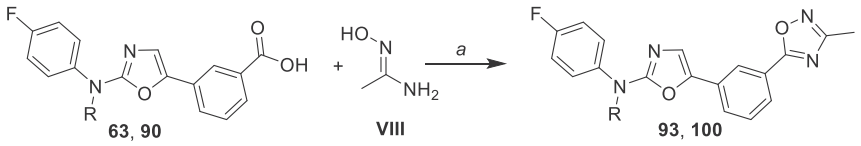
Scheme 7. Synthesis of biaryl aminothiazoles 55-59
Conditions: (a) Lithium aluminum hydride, Ether, 0 °C-rt; (b) Ac_2O, DIEA, DCM, 0 °C-rt.



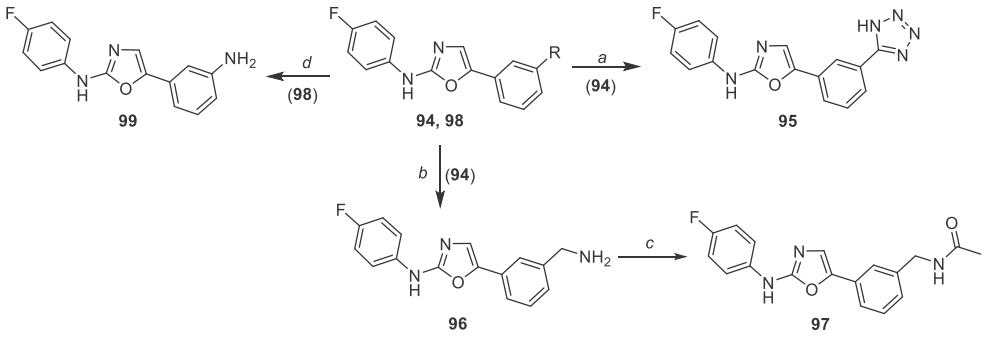
Scheme 8. Synthesis of biaryl aminothiazole 60
Conditions: (a) DMF, 80 °C.



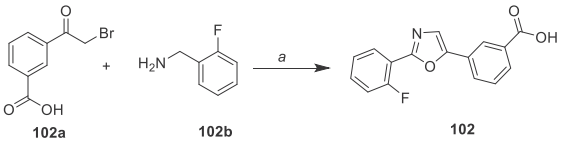
Scheme 9. Synthesis of biaryl aminooxazoles 61–92, 94, 98, 101
Conditions: (a) Triphenylphosphine, 1,4-Dioxane, 100 °C; (b) NaOH (1N), EtOH, 60 °C; (c) Sodium hydride, Alkyl halide, DMF, rt; (d) Methyl amine (2M), MeOH, 60 °C.



Scheme 10. Synthesis of biaryl aminooxazoles 93, 100
Conditions: (a) Propylphosphonic anhydride, TEA, DMF, 80 °C.



Scheme 11. Synthesis of biaryl aminooxazoles 95–97, 99
Conditions: (a) Sodium azide, Ammonium chloride, DMF, 120 °C; (b) Lithium aluminum hydride, Ether, 0 °C-rt; (c) Acetic anhydride, DMAP, DCM, −15 °C; (d) Hydrochloric acid (4N), EtOH, 78 °C.



Scheme 12. Synthesis of biaryl oxazole 102
Conditions: (a) Iodine, Potassium carbonate, DMF, 80 °C, MW.

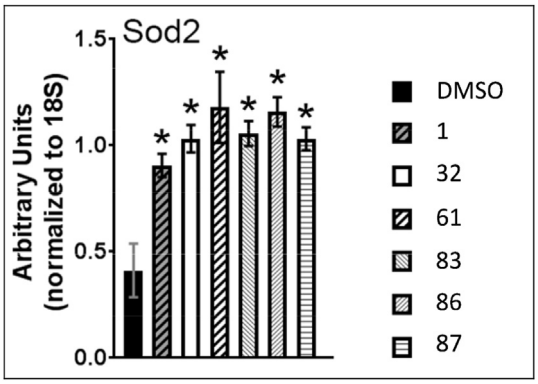


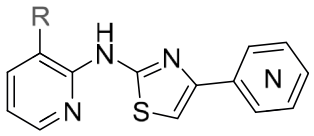
Fig. 2. SRI-22819 and selected compounds (**32**, **61**, **83**, **86** and **87**) induce SOD2 mRNA expression. Treatment of SH-SY5Y neuroblastoma cells with compounds (1 μM, 6 h) induced SOD2 mRNA expression >2 fold, as detected by q-RT-PCR. N = 4/group, mean+/-SEM, 2-way ANOVA, post-hoc *t*-test.

potential compounds were tested for their ability to increase SOD2 mRNA expression *in vitro* (Fig. 2). Additionally, selected compounds from each series were tested for metabolic stability in rodent and human liver microsomes and for solubility (Table 5). Selected compounds with acceptable activity, metabolic stability and solubility advanced to pharmacokinetic (PK) studies (Tables 6 and 7).

The biological data for compounds **1**–**20** is illustrated in Table 1. These compounds include 2-pyridyl aminothiazoles (**1**–**6**), 3-pyridyl aminothiazoles (**7**–**12**), 4-pyridyl aminothiazoles (**13**–**18**), thiadiazole (**19**) and oxazole (**20**) analogs of **1**. For compounds **2**–**4**, in which the methyl group was replaced with Br, H or F, little change in activity was seen compared to **1**. However, for compound **5** in which the methyl group of **1** is replaced with chlorine, 3-fold reduction in activity versus the parent compound was observed. The methoxy analog was the least active compound in this group with an EC_{50} of 9.80 μM. The 3-pyridyl analogs (**7**–**12**) were overall less active than the corresponding 2-pyridyl analogs and the 4-pyridyl compounds, **13**–**18,** were overall the least active. We also prepared the thiadiazole analog (**19**) and the oxazole analog (**20**) of **1** and found that these modifications resulted in compounds that had a 15- to 23-fold loss in activity.

Ataluren (**21**) contains a biaryl oxadiazole structure with a carboxylic group at the meta position of the phenyl ring attached to

Table 1
NF-κB activation data for SRI-22819 (1) and compounds 2–20.



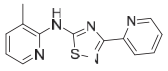
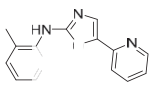
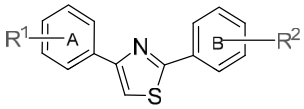
No	R	N	EC_{50} (μM)	Std Dev	E_{max}
1	Me	2	0.48	0.44	40
2	Br	2	0.25		13
3	H	2	0.35	0.04	211
4	F	2	0.73	0.45	67
5	Cl	2	1.40		110
6	OMe	2	9.80		33
7	F	3	0.80		12
8	H	3	1.50		7.5
9	Br	3	4.40		19
10	Me	3	5.30		14
11	Cl	3	7.60		21
12	OMe	3	>20		5
13	Cl	4	2.50		8
14	Br	4	3.60		7
15	F	4	4.70		13
16	H	4	5.60		15
17	Me	4	>40		8
18	OMe	4	>40		4
19			7.40		32
20			11.13	1.59	26

Table 2
NF-κB activation data for Ataluren (21) and compounds 22–31.

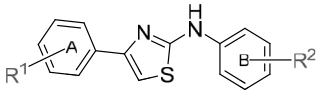


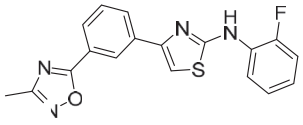
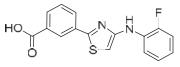
No	R^1	R^2	EC_{50} (μM)	Std Dev	E_{max}
21	Ataluren		1.10	0.77	36
22	3-CO_2H	2-F	6.36	0.84	17
23	3-CO_2H	3-F	7.49	2.19	37
24	3-CO_2H	4-F	5.39	2.42	37
25	3-CO_2H	H	4.23	0.64	29
26	4-CO_2H	2-F	0.90	0.16	28
27	2-CO_2H	2-F	5.02	1.17	7
28	H	2-F	15.29	1.89	50
29	3-$CO_2CH_2CH_3$	2-F	11.30	6.62	12
30	3-$CO_2CH_2CH_3$	3-F	17.18	2.45	9
31	3-$CO_2CH_2CH_3$	4-F	15.04	6.73	23

3rd position of the oxadiazole ring (Fig. 1) and has an EC_{50} of 1.10 μM in our primary assay of NF-κB activation. Additional compounds where the replacement of oxadiazole ring of Ataluren with a thiazole ring are shown in Table 2. The most active compound in this series, **26** (EC_{50} = 0.90 μM), contains a carboxylic acid at the 4-position of the A-ring while maintaining fluorine at the 2-position of the B-ring. The direct Ataluren variant, **22**, showed a 6-fold decrease in activity versus ataluren. Similar acid analogs (**23**–**25**, **27**) in this series had a comparable activity profile to **22**. When the carboxylic acid group of **22** was replaced with a hydrogen (**28**), the activity was reduced by 2.5-fold. However, the ethyl ester analogs (**29**–**31**) were less active when compared to the corresponding parent acid compounds, **22**–**24**.

Since changes of the oxadiazole ring in Ataluren to a thiazole resulted in compounds that were significantly less active with an exception of compound **26** (Table 2), we decided to prepare a series of compounds that contained an amino linker at the 2-position of the thiazole ring (Table 3) as similar to **1**. In this series, compounds containing modifications to both aryl groups were prepared while the aminothiazole linker was kept constant. Compounds **32**–**41** include variations on amino aryl ring while keeping carboxylic acid group at the 3-position of the A-ring. Among these ten compounds, **32**, **35** and **36** exhibited excellent activity similar to ataluren and SRI-22819 (EC_{50} = 0.90, 1.30 and 0.94 μM, respectively). Incorporating a fluorine substituent at both the 3- and 4-position of amino aryl ring in compounds **33** and **34** reduced the activity by 2- to 4-fold as compared to **32**. Addition of a second fluorine substituent on the A-ring also decreased the activity (**37**–**41**). In compounds **42** and **43**, the carboxylic group was shifted to the 4- and 2-position, respectively while keeping 2-fluorophenyl aminothiazole group same. Of these two compounds, **43** with an acid group at the 2-position is more active than **42** which has the acid group at the 4-position. Replacing the carboxylic group of **32** (EC_{50} = 0.90 μM) with a hydrogen on the A-ring gave **44** which had a slight decrease in activity with an EC_{50} = 1.59 μM. Compounds **45**–**55**, in which substitutions for the acid group in the 3-position of the A ring while keeping the fluorine substituent constant at the 2-position of the B ring, yielded analogs with less activity versus **32**, the direct aminothiazole analogs of Ataluren. The activity of these compounds ranged from 3 μM to ˃40 μM with the exception of **49** which showed comparable activity with an EC_{50} of 2.05 μM. The

Table 3
NF-κB activation data for compounds 32–60.

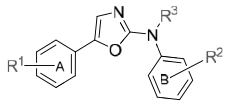


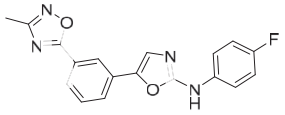
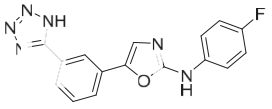
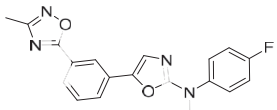
No	R^1	R^2	EC_{50} (μM)	Std Dev	E_{max}
32	3-CO_2H	2-F	0.90	0.54	23.2
33	3-CO_2H	3-F	3.50	0.80	27.8
34	3-CO_2H	4-F	1.50	0.28	30.5
35	3-CO_2H	H	1.30	0.39	31.5
36	3-CO_2H	2-CH_3	0.94	0.36	16.9
37	3-CO_2H	2,6-*diF*	10.17		36.5
38	3-CO_2H	2,3-*diF*	˃10		22.2
39	3-CO_2H	2,4-*diF*	2.50		25.0
40	3-CO_2H	3,5-*diF*	5.01		8.7
41	3-CO_2H	2,5-*diF*	3.08		23.7
42	4-CO_2H	2-F	4.08	1.83	23.0
43	2-CO_2H	2-F	1.98	0.81	20.7
44	H	2-F	1.59	0.41	33.5
45	3-CO_2CH_3	2-F	4.47	0.96	15.3
46	3-CH_2OH	2-F	4.19	1.81	25.1
47	3-CH_2OCH_3	2-F	7.60		14.9
48	3-OH	2-F	5.53	1.13	35.8
49	3-OCH_3	2-F	2.05	1.48	13.7
50	3-F	2-F	3.71	0.95	26.8
51	3-$CONH_2$	2-F	˃10		
52	3-OCH_2CF_3	2-F	˃10		
53	3-CF_3	2-F	˃10		
54			˃40		
55	3-CH_2NH_2	2-F	3.27	1.99	20.3
56	3-CH_2NH_2	3-F	˃10		
57	3-CH_2NH_2	4-F	22.71		35.7
58	4-CH_2NH_2	2-F	36.24		30.9
59	3-CH_2NHAc	2-F	˃10		
60			1.20	0.04	22.3

introduction of amino methyl group in place of carboxylic group at the 3-position of the A-ring (**55**) reduced the activity by 3.5-fold. Rotation of amino methyl or fluorine substituents in **55** on the phenyl rings gave compounds **56**–**58** which were showed no activity (EC_{50} = ˃20 μM). In addition, *N*-acetylated analog of **55** (**59**) was also inactive. Compound **60**, the reverse analog of **32**, exhibited slightly less activity (EC_{50} = 1.20 μM) versus the parent amino thiazole compound, **32**.

Similar studies focused on the biaryl aminooxazole and oxazole analogs of Ataluren. Illustrated in Table 4 is the NF-κB activity of the aminooxazole analogs (**61**–**101**) as well as an oxazole compound **102** which is a direct analog of Ataluren. Replacement of the

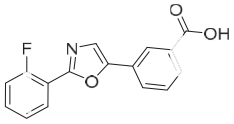
Table 4
NF-κB activation data for compounds 61–102.



No	R^1	R^2	R^3	EC_{50} (μM)	Std Dev	E_{max}
61	3-CO_2H	2-F	H	1.58	0.55	25.5
62	3-CO_2H	3-F	H	4.76		20.1
63	3-CO_2H	4-F	H	6.67		30.4
64	3-CO_2H	H	H	8.28		17.4
65	3-CO_2H	2,6-*di*F	H	>10		
66	3-CO_2H	2,4-*di*F	H	1.60		26.4
67	3-CO_2H	2,5-*di*F	H	2.92		25.5
68	3-CO_2H	2,3-*di*F	H	3.27		46.5
69	4-CO_2H	2-F	H	>10		10.2
70	4-CO_2H	3-F	H	>40		
71	4-CO_2H	4-F	H	>40		
72	4-CO_2H	2,5-*di*F	H	5.60		11.6
73	4-CO_2H	2,6-*di*F	H	>40		
74	2-CO_2H	2-F	H	>10		
75	3-CO_2Me	2-F	H	>40		
76	3-CO_2Me	3-F	H	0.49	0.11	17.2
77	3-CO_2Me	4-F	H	1.21	0.32	24.3
78	3-CO_2Me	H	H	0.29	0.12	14.5
79	3-CO_2Me	2,6-*di*F	H	2.06		19.8
80	3-CO_2Me	2,4-*di*F	H	0.37		9.1
81	3-CO_2Me	2,5-*di*F	H	0.18		7.6
82	3-CO_2Me	2,3-*di*F	H	3.41		8.6
83	4-CO_2Me	2-F	H	1.20		63.2
84	4-CO_2Me	3-F	H	>10		6.7
85	4-CO_2Me	4-F	H	>40		
86	4-CO_2Me	2,5-*di*F	H	0.40		34.1
87	4-CO_2Me	2,6-*di*F	H	0.16		42.5
88	2-CO_2Me	2-F	H	>10		
89	3-CO_2Me	4-F	Me	2.58		28.6
90	3-CO_2H	4-F	Me	2.16		36.9
91	3-CO_2H	4-F	$CH(CH_3)_2$	>10		
92	3-CONHMe	4-F	H	1.93		17.4
93				7.15		18.1
94	3-CN	4-F	H	2.59	0.11	14.2
95				>10		
96	3-CH_2NH_2	4-F	H	1.31	0.85	20.2
97	3-CH_2NHAc	4-F	H	>10		
98	3-NHAc	4-F	H	1.05		15.0
99	3-NH_2	4-F	H	3.06	1.10	15.8
100				>10		
101	3-CONHMe	4-F	Me	4.89		19.7

(*continued on next page*)

Table 4 (*continued*)

No	R^1	R^2	R^3	EC_{50} (μM)	Std Dev	E_{max}
102				2.55		15.01

thiazole ring in **32** with an oxazole ring (**61**) did show slight reduction in NF-κB activity. Compounds **62**–**68**, mono- and difluoro analogs of **61**, displayed EC_{50} range between 1.60->10 μM. 2,4-Difluoro-analog **66** being the most active of these analogs and having an EC_{50} of 1.60 μM. Interestingly, the des-fluoro analog (**64**) is 5-fold less active than **61** and 2,6-difluoro analog (**65**) was inactive (EC_{50} > 10 μM). Analogs in which the carboxylic acid group was moved to the 2-position (**74**) or the 4-position (**69**–**73**) showed no activity, with an exception of **72** (EC_{50} = 5.60 μM). However, a series of carboxylic acid esters (**75**–**88**) presented a different activity pattern versus the related acid analogs (**61**–**74**). For example, compound **75**, the direct ester analog of **61**, was totally inactive, but esters **76**–**83** and **86**–**87** exhibited excellent activity. Among these ten active ester analogs, compound **77**, having a 3-methyl ester (A-ring) and 4-fluoro substituent (B-ring) was selected for further investigation. We began with *N*-alkylation (R^3) of amine linker (**89**–**91**) and found that substitution at R^3 resulted in compounds with decreasing activity when the alkyl group size was increased (**90** versus **91**). This result was once again different in acid and ester series. For example, compound **90**, which has a methyl group at the amine linker, was 3-fold more active than the corresponding des-methyl compound, **63**. However, the ester compound, **89**, with a methyl group at the amino linker, had 2-fold decrease in potency than its corresponding des-methyl ester compound, **77**. We next explored the effect on activity at the 3-position of the A-ring while keeping the remaining structure constant (**92**–**99**). In this small series of analogs, compounds **92**, **96** and **98** displayed activity below 2 μM and **93**, **94** and **99** showed activity below 10 μM. *N*-Methylation of **92** and **93** gave **101** and **100** that showed reduced (**101**) or no (**100**) activity. The oxazole analog of Ataluren (**102**) was around 2-fold less active than Ataluren.

While a number of new compounds derived from Ataluren and SRI-22819 were shown to increase NF-kB reporter activity, we wanted to determine whether they were capable of inducing SOD2 mRNA expression *in vitro* to the same extent as the original compound, SRI-22819. We found that all the compounds tested (**1**, **32**, **61**, **83**, **86** & **87**) increased SOD2 mRNA expression, similar to the original compound (Fig. 2).

The metabolic stability in both mouse and human microsomes and solubility were evaluated on selected compounds (Table 5). As noted, the lead compound, SRI-22819 had a short half-life in microsomal preps and *in vivo* pharmacokinetic (PK) studies. Since a goal of the program was to identify compounds with oral bioavailability and CNS penetration, the criteria for half-lives in both mouse and human microsomal preps and solubility in simulated intestinal fluid were >60 min and >20 μM, respectively. From the initial series (**1**–**20**, Table 1), compounds **1**, **4**, **6** and **20** were evaluated for mouse and human microsomal stability, but none of the compounds were better than the parent compound, **1**. However, compounds **4** and **20** had marginal improvement in solubility (45.4 μM 72.5 μM) versus the parent compound (1.2 μM). Ataluren exhibited an excellent target profile (EC_{50} = 1.10 μM) with good metabolic stability (HLM = 300 min and MLM = 253.2 min) and solubility (70.5 μM). Of the biaryl thiazole series (**22**–**31**, Table 2),

Table 5
Microsomal Stability and Solubility data of selected compounds.

Compounds	Microsomal Stability* (minutes)		Solubility† (μM)
	HLM‡	MLM§	
1 (SRI-22819)	10.1	2.8	1.2
4	6.2	<1	45.4
6	8.7	2.1	1.2
20	7.7	1.4	72.5
21 (Ataluren)	300	253.2	70.5
22	188.6	204.2	55.2
26	194.6	86.3	38.4
32	96.7	31.9	80.9
34	80.8	38.1	77.7
35	85.8	48.1	70.2
44	21.6	2.9	<1
46	7.2	9.8	30.9
49	8.2	3.8	49.3
50	22.8	11.4	<1
60	83.8	38.9	˃100
61	259.4	102.4	55.6
66	279.2	33.9	69.0
76	<1	<1	<1
77	<1	1.1	<1
83	1.6	1.5	<1
90	202.2	87.1	276.9
92	25.4	1.5	3.1
93	34.5	23.0	0
96	49.1	24.2	50.8
98	114.3	10.4	5.0
99	2.8	4.3	15.2
101	37.2	3.9	60.4
102	207.3	133.2	69.5

*Diclofenac was used as a positive control.
†Estradiol (haloperidol) was used as a control standard and data were normalized.
‡HLM = Human Liver Microsome.
§MLM = Mouse Liver Microsome.

compound **26** with carboxylic acid group at the 4-position of the A-ring had the best overall activity profile (EC_{50} = 0.90 μM) and ADME properties (194.6 min in HLM and 86.3 min in MLM; solubility = 38.4 μM). Selected compounds from the aminothiazole series (**32**–**60**, Table 3), **32**, **34**, **35** and **60** showed good metabolic stability (˃60 min in HLM and ˃30 min in MLM) and solubility (˃70 μM), whereas **44**, **46**, **49** and **50** had poor solubility and/or microsomal stability (<10 μM solubility and/or <30 min in MLM). These results (**21**, **22**, **26**, **32**, **34**, **35** and **60**) implied that carboxylic acid group is crucial for compounds to demonstrate high metabolic stability and solubility. Of the oxazole series (**61**–**102**, Table 4), a select group of thirteen compounds were examined for ADME properties. Acid analogs **61**, **66**, **90** and **102** stood out as having high metabolic stability (˃60 min in HLM and ˃30 min in MLM) and solubility (˃70 μM), that again gave a clear indication that the carboxylic acid group allows for less metabolism and induces high solubility. In addition, the amino methyl compound **96** showed modest ADME properties (49 min in HLM and 24 min in MLM; 50.8 μM solubility) and the ester compounds **76**, **77** and **83** gave very poor ADME results (<1 min metabolic stability and <1 μM solubility).

Docking results of selected compounds at mouse P65: Potential interaction modes of active compounds at P65 were further investigated *via* computational docking [14,39]. Compounds **61** and **1** were docked to a putative binding site in the mouse P65 crystal structure. Since mouse and human P65 are highly similar (92% sequence similarity), mouse P65 was used as a surrogate of human P65 in our docking studies. The docking poses imply both **61** and **1** are compatible at the binding site (Fig. 3). Specifically, the shape of

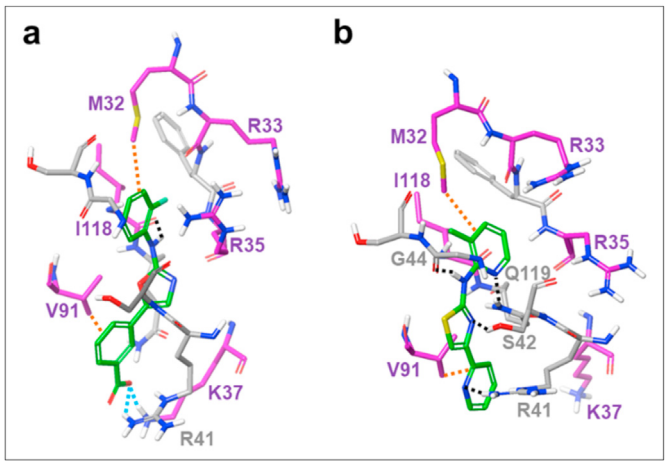


Fig. 3. Docking poses of compounds **61** (a) and **1** (b) at mouse P65 crystal structure. Compounds and residues used to define the docking center are represented by green and purple carbons respectively. Hydrogen bonds, salt-bridges, and hydrophobic contacts are indicated by black, cyan, and orange dashed lines respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

the small molecule scaffold fits in the groove of the binding site. Besides, each of **61** and **1** could form hydrogen bonds at this binding site to increase the binding specificity. Moreover, the aromatic rings of **61** and **1** could form hydrophobic contacts with non-polar residues such as V91 to increase the binding affinity. Noticeably, the carboxylic acid group in **61** could also form salt bridges with K37 and R41, which may further increase its binding affinity at this site. However, compared to **1**, the carboxylic acid group in **61** may cause poor cell permeability and off-target binding to other positively charged proteins, which may decrease its cell-level potency. Indeed, the apparent potency of **1** (EC_{50} = 0.48 μM) is slightly better than **61** (EC_{50} = 1.58 μM) in the cell-based NF-κB reporter assay. Overall, the docking studies do imply that the small molecular scaffold exemplified by **61** and **1** is compatible at the putative target P65.

Pharmacokinetic studies: The selected compounds **1**, **32** and **61** were advanced to pharmacokinetic (PK) studies to evaluate the drug-like properties *in vivo*. These compounds were administered IV (Intravenous) and PO (oral administration) and the results are presented in Table 6. Compound **32** exhibited the highest half-life ($t_{½}$) of 4 h when administered IV and **32** and **61** had comparable half-life of around 3 h for PO administration. Furthermore, compounds **32** and **61** showed similar C_{max} (maximum concentration) and had an oral bioavailability (%F) of 27 and 16%, respectively. This results revealed that a significant increase of PK properties were observed for **32** and **61** as compared to the original parent compound, **1**.

Furthermore, compounds **90**, **93**, **96** and **101** were examined for the determination of brain-to-plasma ratio using cassette dosing or N-in-1 dosing. These compounds were administered IV

Table 6
PK results of 1, 32 and 61.

Compounds	IV administration $t_{1/2}$ (h)	PO administration		
		$t_{1/2}$ (h)	C_{max} (ng/mL)	%F
1	0.36	1.92	13.0	5.34
32	4.04	2.51	101	26.6
61	0.96	2.86	92	15.6

Table 7
Brain penetration results of 90, 93, 96 and 101.

Compounds	Brain Concentration (ng/g)		Plasma Concentration (ng/mL)		Brain/Plasma ratio	
	Time (h)		Time (h)		Time (h)	
	0.25	0.5	0.25	0.5	0.25	0.5
90	16.4	7.27	788	529	0.0213	0.0137
93	821	357	119	74.4	6.93	4.81
96	473	297	32.8	21.0	14.5	14.3
101	200	30.9	164	31.1	1.21	1.02

(Intravenous) with 1 mg/kg/compound dosing and the results are summarized in Table 7. The results indicated that compound **96** exhibited better brain-to-plasma ratio than other three compounds.

3. Conclusion

In summary, herein we have presented the design and synthesis of SR-22819 analogs that showed a wide range of their ability to activate NF-κB and selected compounds were tested for the drug like properties. More specifically, we have developed SAR on the direct modification of SRI-22819 and hybrid combinations of SRI-22819 and Ataluren. The first series (Table 1) exhibited significant activity, but had poor ADME results. In an effort to increase the ADME properties, hybrid compounds of SRI-22819 and Ataluren (Tables 2–4) were designed and showed excellent activity (around 1 μM) with good metabolic stability and solubility (˃60 min in HLM; ˃60 min MLM; ˃20 μM solubility). Moreover, selected compounds were shown to induce SOD2 mRNA expression *in vitro*. We also investigated the role of a carboxylic group and its effect on metabolic stability and solubility. Biaryl aminothiazole **32** and biaryl aminooxazole **61** were advanced to *in vivo* pharmacokinetic studies and showed improved half-life and oral bioavailability than the original lead, SRI-22819 (**1**) and compound **96**, 3-aminomethylphenyl-4-fluorophenylaminooxazole, showed good brain permeability. Thus, our results from this study on these small molecules and their effect on NF-κB activation and SOD2 induction provide compounds suitable for investigation as therapeutics for the treatment of ALS.

4. Experimental

4.1. High throughput assay for NF-kB reporter activity

SH-SY5Y human neuroblastoma cell line was obtained from the American Tissue Culture collection (ATCC). A commercially available expression vector containing the NF-kB promoter enhancer region driving the firefly luciferase gene expression and a second plasmid containing the gene conferring resistance to blasticidin were used in a dual transfection approach to obtain a stable cell line. SH-SY5Y cells stably transfected with pNF-κB-luc/pEF6 were plated at 8000 per well in a volume of 40 μl DMEM in either Corning white opaque, 384-well plates (Cat. No. 3570, Corning, Inc., Corning, NY) or Corning black clear bottom, 384-well plates (Cat. No. 3712, Corning, Inc., Corning, NY) and treated with test compounds for 24 h at 37 °C. Luciferase activity was measured as a reporter of NF-kB activation using the Bright-Glo Luciferase assay kit (Cat. No. E2620, Promega, Madison, WI) according to the manufacturer's instructions. Cell viability was measured using the CellTiter-Glo Luminescent Cell Viability assay kit (Cat. No. G7572, Promega, Madison, WI) according to the manufacturer's instructions. Briefly, cells were equilibrated at room temperature for 30 min prior to the addition of Bright-Glo to the white opaque plates or CellTiter-Glo to the black clear bottom plates. A volume of assay buffer equal to the volume of cell media was added to each well and incubated for 5 min to allow complete cell lysis. All procedures were performed in the dark. Luminescence was measured by the Synergy4 Multi-detection microplate reader (BioTek, Winooski, VT) within 15 min of lysis.

4.2. SOD2 assay

SH-SY5Y neuroblastoma cells (ATCC#CRL-2266; passages 5–10) were maintained in DMEM (cat#: 11965–092; Gibco) with 10% fetal bovine serum, plated on 10 cm plates, and grown to 70–80% confluency before treatment. Cells were treated with compounds for 6 h, rinsed in PBS (pH 7.4), and harvested in Trizol on ice [40]. Total RNA was isolated using chloroform and isopropanol, with glycogen as a carrier (cat#10901393001; Roche Applied Science). RNA was re-suspended in DNAase-RNAse-free water and frozen at −80 °C until needed. 1 μg RNA was DNAse-treated and reverse transcribed (cat#4368813, Applied Biosystems), and cDNA was amplified using inventoried Taqman primer/probe sets from ThermoFisher (human 18s: HS99999901_s1; human SOD2: HS00167309_m1) and JumpStart Taq (cat#P2893; Sigma), using the calibrator method for relative expression analysis. SOD2 data were normalized to 18s data and expressed as+/-standard error of the mean. One-way ANOVA and Tukey's post-hoc *t*-test were used to assess statistical significance amongst groups (GraphPad Prism 8.2).

4.3. ADME evaluation

A standard panel of *in vitro* ADME assays available at Southern Research was utilized to assess drug-like properties of compounds and to inform subsequent *in vivo* PK studies. These assays include:

(a) *Metabolic Stability*: The potential for a high metabolic clearance compound was estimated using a liver microsome assay. The compounds were incubated in human and mouse liver microsomes with the co-factor NADPH which has oxidative, esterase and protease metabolic activity. The disappearance of the parent molecule was measured by liquid chromatography/mass spectroscopy (LC/MS) detection. Stability of the parent compound was reported as half-life. Diclofenac was used as a positive control.
(b) *Solubility*: Kinetic solubility is an important parameter for accurate determinations of the dose response. This was estimated using the shake flask method with a μSol Explorer (PION, Billerica, MA) at pH 7.4. Compounds were added as a DMSO solution to buffer. The average of two determinations at pH 7.4 were reported. Estradiol (haloperidol) was used as a control standard.

4.4. In vivo PK studies

PK studies are routinely performed by Pharmaron using CD1 mice. The test compounds were administered at 1.0 mg/kg (IV) and 5.0 mg/kg (PO). The brain:plasma ratio was determined subsequent to IV and PO dosing; samples were collected at four-to-six time points post-dose, n = 3 animals/time point. Compound quantities in plasma and brain tissue were determined following protein precipitation and LC/MS/MS analysis. The use of unbound brain concentration was shown to provide the best correlations with

pharmacological data. Therefore, PK assay of equilibrium dialysis of brain homogenates were used in buffer to determine the free unbound compound concentration in mouse brain *via* LC/MS/MS analysis. All PK data were analyzed using WinNonlin software (Pharsight, St. Louis, MO) to obtain PK parameters including oral bioavailability (%F), T_{max}, C_{max}, $t_{½}$, AUC_{last}, AUC_{inf}, Cl, and Vss.

4.5. Computational docking

The docking studies were performed using the induced-fit docking protocol implemented in Schrödinger Small Molecule Drug Discovery Suite [39]. Mouse P65 crystal structure (PDB ID 1VKX) was used as the receptor. The compounds binding site was defined according to a previous docking study [14]. The 3D structures of compounds were generated using the LigPrep module in Schrödinger. These compounds were then docked to the defined binding site.

4.6. Chemistry

The reactions were performed under a dry argon atmosphere and reaction temperatures were measured externally. Anhydrous solvents and reagents from Aldrich were used without further drying. The reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel ($60F_{254}$) aluminium plates (0.25 mm) from E. Merck and visualized using UV light (254 nm). Purification of all compounds was carried out by utilizing a Teledyne Isco Combiflash® R_f automated chromatography machine. Universal RediSep solid sample loading pre-packed cartridges were used to absorb crude product and purified on silica RediSep Rf Gold Silica (20–40 μm spherical silica) columns using appropriate solvent gradients. Pure samples were dried overnight under high vacuum over P_2O_5 at 78 °C before analyses. Compounds **1** and ataluren were purchased from Aurora Fine Chemicals and Combi-Blocks, respectively and purity was checked. The exact mass spectral data were obtained with an Agilent LC-MSTOF or with Bruker BIOTOF II by electrospray ionization (ESI). ^{1}HNMR spectra were recorded on Agilent/Varian MR-400 spectrometer operating at 399.930 MHz. The chemical shifts (δ) are in ppm downfield from standard tetramethylsilane (TMS). Chemical shifts (δ) listed for multiplets were measured from the approximate centers, and relative integrals of peak areas agreed with those expected for the assigned structures. Determination of % purity were obtained by HPLC using an Agilent 1100 LC equipped with a diode array UV detector and monitored at multiple wavelengths. ESI-MS spectra were recorded on a BioTof-2 time-of-flight mass spectrometer.

4.6.1. Procedure 1: general procedure for the synthesis of amino thiazoles and thiazoles (1–18, 22–31, 32–34, 48–50, 52–53)

A solution of appropriate arylthiourea (1 eq.) or arylthioamide (1 eq.) and aryl-2-bromoethanone (1 eq.) in anhydrous ethanol was heated in a sealed tube at 80 °C for 2 h. The progress of reaction was monitored by TLC. Ethanol was removed from the reaction mixture and the resulted residue was washed with aq. $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 times) and the combined organic layer was dried over anhydrous Na_2SO_4. The filtrate was concentrated *in vacuo* and the crude product was purified on Teledyne Isco Combiflash® R_f purification machine to afford corresponding thiazoles in moderate to good yields.

4.6.2. Procedure 2: general procedure for the hydrolysis of esters (22–27, 61–74, 90–91)

A solution of thiazole ethyl esters or oxazole methyl esters (1 eq.) in ethanol was added sodium hydroxide (3 eq.) and heated at 60 °C for overnight. Neutralize with 1N HCl and extracted with ethyl acetate (3 × 20 mL). Combined organic layer was dried over anhydrous Na_2SO_4. The drying agent was filtered off and the filtrate was concentrated under *vacuum*. The crude product was purified on Teledyne Isco Combiflash® R_f purification machine to provide corresponding acids in moderate yields.

4.6.3. Procedure 3: Reduction of cyano group (55–58, 96)

LAH (5 eq.) was added to a dry round-bottom flask under argon and diluted with diethyl ether. The mixture was cooled to 0 °C, then a solution of cyano compound (1 eq.) in diethyl ether was added dropwise. The mixture was slowly warmed to room temperature, and stirred under argon for 4 h. The reaction was quenched by adding aqueous NaOH (10%) at 0 °C, and after 30 min, water was added. The aqueous phase was extracted with diethyl ether (5 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4 and the filtrate was concentrated *in vacuo*. The crude residue was purified on Teledyne Isco Combiflash® R_f purification machine to afford corresponding benzyl amine in good yields.

4.6.4. Procedure 4: Synthesis of aminooxazoles (20, 75–88, 94, 98)

Step 1. Sodium azide (3 eq) was added to a solution of appropriate methyl (2-bromoacetyl)benzoate (1 eq.) in acetone/water (2:1).and the reaction mixture was allowed to stir at room temperature for 1 h. Water was added to the reaction mixture and extracted with CH_2Cl_2 (thrice). Combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The drying agent was filtered and the filtrate was concentrated under *vacuum* to obtain corresponding azide in good yields. Crude product was dried and used for next step without any further purification.

Step:2. A solution of appropriate methyl (azidoacetyl)benzoate (1 eq.), appropriate fluoro *iso*thiocyanatobenzene (1 eq.) and triphenylphosphine (1 equivalent) in anhydrous dioxane (2 ml) under nitrogen was taken in a microwave tube and the reaction mixture was heated at 100 °C for 30 min under microwave conditions. Progress of the reaction was monitored by TLC. Reaction mixture was concentrated under *vacuum* and purified on Teledyne Isco Combiflash® R_f purification machine to provide aminooxazole esters in moderate to good yields.

4.6.5. Procedure 5: Synthesis of N-alkyl aminooxazole esters (89, 91a)

Sodium hydride (2 eq.) was added to a solution of appropriate amino oxazole esters (1 eq.) in DMF (1 mL) at room temperature under argon atmosphere. The resulted reaction mixture was stirred for 15 min and was added methyl iodide (2 eq.) and stirred for 1 h. Water (1 mL) was added to neutralize the reaction mixture and extracted with CH_2Cl_2 (3 times). The combined organic layer was dried over anhydrous Na_2SO_4. The drying agent was filtered off and the filtrate was concentrated under *vacuum*. The crude product was purified on Teledyne Isco Combiflash® R_f purification machine to provide corresponding N-alkyl amino oxazole esters in good yields.

4.6.6. N-(3-bromopyridin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine (2)

By following procedure 1, the title compound **2** was obtained from 1-(3-bromopyridin-2-yl)thiourea and 2-bromo-1-(pyridin-2-yl)ethanone as a colorless solid in 65% yield (HPLC purity: 99.5%). TLC $R_f = 0.25$ (30% EtOAc in Hexanes). M. P. = 201–203 °C. ESI-MS *m/z*: 333.0. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 8.61–8.59 (m, 1H), 8.38 (dd, J = 6.2, 2.4 Hz, 1H), 8.11–8.05 (m, 2H), 7.90–7.85 (m, 1H), 7.76 (s, 1H), 7.34–7.31 (m, 1H), 6.99 (dd, J = 7.6, 4.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.3, 152.2, 149.4, 148.5, 145.3, 141.7, 137.2, 122.7, 120.1, 110.0, 117.9, 110.7, 105.7.

4.6.7. N,4-Di(pyridin-2-yl)thiazol-2-amine (3)

By following procedure 1, the title compound **3** was obtained from 1-(pyridin-2-yl)thiourea and 2-bromo-1-(pyridin-2-yl)ethanone as a colorless solid in 48% yield (HPLC purity: 99.2%). TLC $R_f = 0.30$ (50% EtOAc in Hexanes). M. P. = 194–196 °C. ESI-MS *m/z*: 255.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.66 (s, 1H), 8.80–8.73 (m, 1H), 8.57–8.33 (m, 3H), 8.30–8.17 (m, 1H), 7.91–7.73 (m, 2H), 7.26–7.18 (m, 1H), 7.06–7.00 (m, 1H).

4.6.8. N-(3-fluoropyridin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine (4)

By following procedure 1, the title compound **4** was obtained from 1-(3-fluoropyridin-2-yl)thiourea and 2-bromo-1-(pyridin-2-yl)ethanone as a colorless solid in 81% yield (HPLC purity: 100%). TLC $R_f = 0.30$ (50% EtOAc in Hexanes). M. P. = 195–197 °C. ESI-MS *m/z*: 273.0. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.78–8.73 (m, 1H), 8.47–8.30 (m, 2H), 8.28–8.11 (m, 2H), 7.85–7.67 (m, 2H), 7.12–7.06 (m, 1H).

4.6.9. N-(3-chloropyridin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine (5)

By following procedure 1, the title compound **5** was obtained from 1-(3-chloropyridin-2-yl)thiourea and 2-bromo-1-(pyridin-2-yl)ethanone as a colorless solid in 25% yield (HPLC purity: 100%). TLC $R_f = 0.30$ (50% EtOAc in Hexanes). M. P. = 180–182 °C. ESI-MS *m/z*: 289.0. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.68 (s, 1H), 8.64–8.55 (m, 1H), 8.33 (dd, $J = 4.8$, 1.5 Hz, 1H), 8.06 (dt, $J = 7.9$, 1.2 Hz, 1H), 7.97–7.83 (m, 2H), 7.75 (s, 1H), 7.32 (ddd, $J = 7.5$, 4.7, 1.3 Hz, 1H), 7.10–6.98 (m, 1H).

4.6.10. N-(3-methoxypyridin-2-yl)-4-(pyridin-2-yl)thiazol-2-amine (6)

By following procedure 1, the title compound **6** was obtained from 1-(3-methoxypyridin-2-yl)thiourea and 2-bromo-1-(pyridin-2-yl)ethanone as a colorless solid in 85% yield (HPLC purity: 100%). TLC $R_f = 0.25$ (50% EtOAc in Hexanes). M. P. = 159–161 °C. ESI-MS *m/z*: 285.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.56 (s, 1H), 8.76–8.70 (m, 1H), 8.44–8.28 (m, 2H), 8.18 (d, $J = 6.5$ Hz, 1H), 7.98 (dt, $J = 5.2$, 1.4 Hz, 1H), 7.76–7.67 (m 1H), 7.50 (dt, $J = 8.1$, 1.7 Hz, 1H), 7.19–7.02 (m, 1H), 3.96 (s, 3H).

4.6.11. N-(3-fluoropyridin-2-yl)-4-(pyridin-3-yl)thiazol-2-amine (7)

By following procedure 1, the title compound **7** was obtained from 1-(3-fluoropyridin-2-yl)thiourea and 2-bromo-1-(pyridin-3-yl)ethanone as a colorless solid in 22% yield (HPLC purity: 99.6%). TLC $R_f = 0.30$ (50% EtOAc in Hexanes). M. P. = 239–241 °C. ESI-MS *m/z*: 273.0. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.50 (s, 1H), 9.16 (dd, $J = 2.3$, 1.1 Hz, 1H), 8.51 (dd, $J = 4.8$, 1.5 Hz, 1H), 8.27 (dt, $J = 8.1$, 1.7 Hz, 1H), 8.18 (dt, $J = 4.9$, 1.3 Hz, 1H), 7.76–7.61 (m, 2H), 7.46 (ddd, $J = 8.0$, 4.8, 1.1 Hz, 1H), 7.06–6.99 (m, 1H).

4.6.12. N,4-Di(pyridin-3-yl)thiazol-2-amine (8)

By following procedure 1, the title compound **8** was obtained from 1-(pyridin-2-yl)thiourea and 2-bromo-1-(pyridin-3-yl)ethanone as a colorless solid in 59% yield (HPLC purity: 95%). TLC $R_f = 0.30$ (50% EtOAc in Hexanes). M. P. = 216–218 °C. ESI-MS *m/z*: 255.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.46 (s, 1H), 9.13 (dd, $J = 2.3$, 1.1 Hz, 1H), 8.57–8.43 (m, 1H), 8.34–8.29 (m, 1H), 8.26–8.20 (m, 1H), 7.76–7.69 (m, 1H), 7.60 (s, 1H), 7.49–7.39 (m, 1H), 7.13–7.08 (m, 1H), 6.97–6.91 (m, 1H).

4.6.13. N-(3-bromopyridin-2-yl)-4-(pyridin-3-yl)thiazol-2-amine (9)

By following procedure 1, the title compound **9** was obtained from 1-(3-bromopyridin-2-yl)thiourea and 2-bromo-1-(pyridin-3-yl)ethanone as a colorless solid in 33% yield (HPLC purity: 99.2%). TLC $R_f = 0.25$ (30% EtOAc in Hexanes). M. P. = 148–150 °C. ESI-MS *m/z*: 333.0. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.28 (s, 1H), 9.17 (d, $J = 3.4$Hz, 1H), 8.52 (dd, $J = 4.8$, 1.5 Hz, 1H), 8.38 (dd, $J = 5.6$, 2.0 Hz, 1H), 8.28–8.21 (m, 1H), 8.11 (dd, $J = 6.8$, 4.2 Hz, 1H), 7.73 (s, 1H), 7.50–7.42 (m, 1H), 7.02–6.97 (m, 1H).

4.6.14. N-(3-methylpyridin-2-yl)-4-(pyridin-3-yl)thiazol-2-amine (10)

By following procedure 1, the title compound **10** was obtained from 1-(3-methylpyridin-2-yl)thiourea and 2-bromo-1-(pyridin-3-yl)ethanone as a colorless solid in 37% yield (HPLC purity: 98.4%). TLC $R_f = 0.25$ (30% EtOAc in Hexanes). M. P. = 162–164 °C. ESI-MS *m/z*: 269.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.52 (s, 1H), 9.17 (dd, $J = 2.3$, 1.1 Hz, 1H), 8.54–8.45 (m, 1H), 8.33–8.12 (m, 2H), 7.66–7.51 (m, 2H), 7.50–7.37 (m, 1H), 6.92 (dd, $J = 7.2$, 5.0 Hz, 1H), 2.37 (s, 3H).

4.6.15. N-(3-chloropyridin-2-yl)-4-(pyridin-3-yl)thiazol-2-amine (11)

By following procedure 1, the title compound **11** was obtained from 1-(3-chloropyridin-2-yl)thiourea and 2-bromo-1-(pyridin-3-yl)ethanone as a colorless solid in 57% yield (HPLC purity: 100%). TLC $R_f = 0.30$ (50% EtOAc in Hexanes). M. P. = 168–170 °C. ESI-MS *m/z*: 289.0. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.73 (s, 1H), 9.18 (dt, $J = 2.3$, 1.1 Hz, 1H), 8.52 (dt, $J = 4.8$, 1.4 Hz, 1H), 8.39–8.23 (m, 2H), 7.94 (dt, $J = 7.8$, 1.4 Hz, 1H), 7.72 (s, 1H), 7.49–7.43 (m, 1H), 7.08–7.01 (m, 1H).

4.6.16. N-(3-methoxypyridin-2-yl)-4-(pyridin-3-yl)thiazol-2-amine (12)

By following procedure 1, the title compound **12** was obtained from 1-(3-methoxypyridin-2-yl)thiourea and 2-bromo-1-(pyridin-3-yl)ethanone as a colorless solid in 31% yield (HPLC purity: 98.1%). TLC $R_f = 0.25$ (70% EtOAc in Hexanes). M. P. = 126–128 °C. ESI-MS *m/z*: 285.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.23 (s, 1H), 9.15 (dd, $J = 2.2$, 1.0 Hz, 1H), 8.50 (dd, $J = 4.8$, 1.6 Hz, 1H), 8.26 (dt, $J = 8.0$, 1.9 Hz, 1H), 7.91 (dt, $J = 5.1$, 1.3 Hz, 1H), 7.64 (d, $J = 1.3$ Hz, 1H), 7.48–7.33 (m, 2H), 7.04–6.89 (m, 1H), 3.91 (d, $J = 1.4$ Hz, 3H).

4.6.17. N-(3-chloropyridin-2-yl)-4-(pyridin-4-yl)thiazol-2-amine (13)

By following procedure 1, the title compound **13** was obtained from 1-(3-chloropyridin-2-yl)thiourea and 2-bromo-1-(pyridin-4-yl)ethanone as a colorless solid in 45% yield (HPLC purity: 100%). TLC $R_f = 0.25$ (50% EtOAc in Hexanes). M. P. = 167–169 °C. ESI-MS *m/z*: 289.0. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.78 (s, 1H), 8.67–8.56 (m, 2H), 8.34 (dt, $J = 4.9$, 1.3 Hz, 1H), 7.99–7.84 (m, 4H), 7.07–7.04 (m, 1H).

4.6.18. N-(3-bromopyridin-2-yl)-4-(pyridin-3-yl)thiazol-2-amine (14)

By following procedure 1, the title compound **14** was obtained from 1-(3-bromopyridin-2-yl)thiourea and 2-bromo-1-(pyridin-4-yl)ethanone as a colorless solid in 64% yield (HPLC purity: 99.3%). TLC $R_f = 0.20$ (30% EtOAc in Hexanes). M. P. = 182–184 °C. ESI-MS *m/z*: 333.0. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.33 (s, 1H), 8.65–8.60 (m, 2H), 8.38 (dd, $J = 4.8$, 1.6 Hz, 1H), 8.12 (dd, $J = 8.6$, 2.2 Hz, 1H), 7.94–7.88 (m, 3H), 7.00 (dd, $J = 8.8$, 4.6 Hz, 1H).

4.6.19. N-(3-fluoropyridin-2-yl)-4-(pyridin-4-yl)thiazol-2-amine (15)

By following procedure 1, the title compound **15** was obtained from 1-(3-fluoropyridin-2-yl)thiourea and 2-bromo-1-(pyridin-4-yl)ethanone as a colorless solid in 61% yield (HPLC purity: 96.3%). TLC $R_f = 0.30$ (50% EtOAc in Hexanes). M. P. = 216–218 °C. ESI-MS

m/z: 273.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.78 (s, 1H), 9.11–8.77 (m, 2H), 8.53–8.33 (m, 3H), 8.21 (dt, J = 4.9, 1.2 Hz, 1H), 7.75 (ddd, J = 11.2, 8.0, 1.4 Hz, 1H), 7.11–7.04 (m, 1H).

4.6.20. N,4-Di(pyridin-3-yl)thiazol-2-amine (16)

By following procedure 1, the title compound **16** was obtained from 1-(pyridin-2-yl)thiourea and 2-bromo-1-(pyridin-4-yl)ethanone as a colorless solid in 13% yield (HPLC purity: 98.6%). TLC R_f = 0.25 (50% EtOAc in Hexanes). M. P. = 228–230 °C. ESI-MS *m/z*: 255.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.71 (s, 1H), 8.94 (d, J = 6.9 Hz, 2H), 8.54–8.39 (m, 3H), 8.35 (ddd, J = 5.1, 1.9, 1.0 Hz, 1H), 7.81–7.74 (m, 1H), 7.15 (dd, J = 8.3, 1.0 Hz, 1H), 7.03–6.98 (m, 1H).

4.6.21. N-(3-methylpyridin-2-yl)-4-(pyridin-4-yl)thiazol-2-amine (17)

By following procedure 1, the title compound **17** was obtained from 1-(3-methylpyridin-2-yl)thiourea and 2-bromo-1-(pyridin-4-yl)ethanone as a colorless solid in 74% yield (HPLC purity: 97.8%). TLC R_f = 0.25 (50% EtOAc in Hexanes). M. P. = 213–215 °C. ESI-MS *m/z*: 269.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.56 (s, 1H), 8.67–8.54 (m, 2H), 8.24–8.15 (m, 1H), 7.89 (dd, J = 4.7, 1.5 Hz, 2H), 7.80 (s, 1H), 7.61–7.53 (m, 1H), 6.93 (dd, J = 7.2, 5.0 Hz, 1H), 2.37 (s, 3H).

4.6.22. N-(3-methoxypyridin-2-yl)-4-(pyridin-4-yl)thiazol-2-amine (18)

By following procedure 1, the title compound **18** was obtained from 1-(3-methoxypyridin-2-yl)thiourea and 2-bromo-1-(pyridin-4-yl)ethanone as a colorless solid in 56% yield (HPLC purity: 97.1%). TLC R_f = 0.25 (70% EtOAc in Hexanes). M. P. = 164–166 °C. ESI-MS *m/z*: 285.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.70 (s, 1H), 9.04–8.86 (m, 2H), 8.62–8.36 (m, 3H), 7.94 (dd, J = 5.1, 1.4 Hz, 1H), 7.43 (dd, J = 8.0, 1.3 Hz, 1H), 7.04 (dd, J = 7.9, 5.0 Hz, 1H), 3.92 (s, 3H).

4.6.23. N-(3-methylpyridin-2-yl)-3-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine (19)

A solution of 2-*iso*thiocyanato-3-methylpyridine (150 mg, 1 mmol) and picolinimidamide hydrochloride (157 mg, 1 mmol) in DMF (1 mL) were added *N,N*-di*iso*propylethyl amine (0.19 mL, 1.1 mmol) followed by DIAD (0.21 mL, 1.1 mmol) at room temperature under argon atmosphere. The resulted reaction mixture was stirred for overnight. Water was added to the reaction mixture and extracted with CH_2Cl_2 (3 × 20 mL). Combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The drying agent was filtered and the filtrate was concentrated under *vacuum*. The crude product was purified on Teledyne Isco Combiflash® R_f purification machine to provide *N*-(3-methylpyridin-2-yl)-3-(pyridin-2-yl)-1,2,4-thiadiazol-5-amine, **19** as a colorless solid in 11% yield (HPLC purity: 99.1%). TLC R_f = 0.15 (75% EtOAc in Hexanes). M. P. = 227–229 °C. ESI-MS *m/z*: 270.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.84 (s, 1H), 8.70 (ddt, J = 4.8, 1.8, 0.8 Hz, 1H), 8.40–8.16 (m, 2H), 8.03–7.86 (m, 1H), 7.68 (ddt, J = 7.4, 1.8, 0.9 Hz, 1H), 7.48 (ddt, J = 7.6, 4.7, 1.0 Hz, 1H), 7.05 (dd, J = 7.3, 5.0 Hz, 1H), 2.41 (s, 3H).

4.6.24. N-(3-methylpyridin-2-yl)-5-(pyridin-2-yl)oxazol-2-amine (20)

By following procedure 4, the title compound **20** was obtained from 2-azido-1-(pyridin-2-yl)ethanone and 2-*iso*thiocyanato-3-methylpyridine as a colorless solid in 52% yield (HPLC purity: 98.3%). TLC R_f = 0.20 (50% EtOAc in Hexanes). M. P. = 175–177 °C. ESI-MS *m/z*: 253.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.60–8.52 (m, 1H), 7.90 (s, 1H), 7.88–7.80 (m, 1H), 7.66 (s, 1H), 7.60–7.55 (m, 2H), 7.80 (s, 1H), 7.29–7.22 (m, 1H), 6.63 (s, 1H), 2.23 (s, 3H).

4.6.25. 3-(2-(2-Fluorophenyl)thiazol-4-yl)benzoic acid (22) and ethyl 3-(2-(2-fluorophenyl)thiazol-4-yl)benzoate (29)

By following procedure 1, the title compound **29** was obtained from 2-fluorobenzothioamide and 3-(2-bromoacetyl)benzoic acid as a colorless solid in 49% yield (HPLC purity: 100%). TLC R_f = 0.70 (10% EtOAc in Hexanes). M. P. = 91–93 °C. ESI-MS *m/z*: 328.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.62 (t, J = 1.8 Hz, 1H), 8.47 (s, 1H), 8.39–8.29 (m, 2H), 7.96 (dt, J = 7.8, 1.4 Hz, 1H), 7.68–7.53 (m, 2H), 7.49–7.38 (m, 2H), 4.36 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H). HRMS calcd for $[C_{18}H_{15}FNO_2S + H]^+$: 328.0802, Found: 328.0797.

Compound **29** was hydrolyzed by following procedure 2 to get compound **22** as a colorless solid in 91% yield (HPLC purity: 100%). TLC R_f = 0.20 (30% EtOAc in Hexanes). M. P. = 264–268 °C. ESI-MS *m/z*: 300.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.63 (t, J = 1.7 Hz, 1H), 8.45 (s, 1H), 8.41–8.26 (m, 2H), 7.94 (dt, J = 7.8, 1.4 Hz, 1H), 7.66–7.52 (m, 2H), 7.50–7.36 (m, 2H). HRMS calcd for $[C_{16}H_{10}FNO_2S + H]^+$: 300.0489, Found: 300.04925.

4.6.26. 3-(2-(3-Fluorophenyl)thiazol-4-yl)benzoic acid (23) and ethyl 3-(2-(3-fluorophenyl)thiazol-4-yl)benzoate (30)

By following procedure 1, the title compound **30** was obtained from 3-fluorobenzothioamide and 3-(2-bromoacetyl)benzoic acid as a colorless solid in 55% yield (HPLC purity: 100%). TLC R_f = 0.80 (10% EtOAc in Hexanes). M. P. = 97–99 °C. ESI-MS *m/z*: 328.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.59 (t, J = 1.7 Hz, 1H), 8.39 (s, 1H), 8.31 (ddd, J = 7.8, 1.9, 1.2 Hz, 1H), 7.96 (dt, J = 7.8, 1.4 Hz, 1H), 7.90–7.80 (m, 2H), 7.68–7.53 (m, 2H), 7.41–7.32 (m, 1H), 4.36 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H). HRMS calcd for $[C_{18}H_{15}FNO_2S + H]^+$: 328.0802, Found: 328.0798.

Compound **30** was hydrolyzed by following procedure 2 to get compound **23** as a colorless solid in 91% yield (HPLC purity: 100%). TLC R_f = 0.20 (30% EtOAc in Hexanes). M. P. = 211–213 °C. ESI-MS *m/z*: 300.0. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.13 (s, 1H), 8.59 (t, J = 1.7 Hz, 1H), 8.38 (s, 1H), 8.28 (dt, J = 7.8, 1.4 Hz, 1H), 7.99–7.79 (m, 3H), 7.66–7.53 (m, 2H), 7.41–7.31 (m, 1H). HRMS calcd for $[C_{16}H_{10}FNO_2S + H]^+$: 300.0489, Found: 300.04889.

4.6.27. 3-(2-(4-Fluorophenyl)thiazol-4-yl)benzoic acid (24) and ethyl 3-(2-(4-fluorophenyl)thiazol-4-yl)benzoate (31)

By following procedure 1, the title compound **31** was obtained from 3-fluorobenzothioamide and 3-(2-bromoacetyl)benzoic acid as a colorless solid in 48% yield (HPLC purity: 100%). TLC R_f = 0.80 (10% EtOAc in Hexanes). M. P. = 97–99 °C. ESI-MS *m/z*: 328.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.59 (t, J = 1.8 Hz, 1H), 8.36–8.26 (m, 2H), 8.14–8.03 (m, 2H), 7.95 (dt, J = 7.8, 1.3 Hz, 1H), 7.63 (t, J = 7.8 Hz, 1H), 7.43–7.31 (m, 2H), 4.36 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H). HRMS calcd for $[C_{18}H_{15}FNO_2S + H]^+$: 328.0802, Found: 328.0800.

Compound **31** was hydrolyzed by following procedure 2 to get compound **24** as a colorless solid in 91% yield (HPLC purity: 100%). TLC R_f = 0.20 (30% EtOAc in Hexanes). M. P. = 252–254 °C. ESI-MS *m/z*: 300.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.12 (s, 1H), 8.59 (t, J = 1.7 Hz, 1H), 8.35–8.22 (m, 2H), 8.13–8.04 (m, 2H), 7.93 (dt, J = 7.7, 1.4 Hz, 1H), 7.60 (t, J = 7.8 Hz, 1H), 7.42–7.31 (m, 2H). HRMS calcd for $[C_{16}H_{10}FNO_2S + H]^+$: 300.0489, Found: 300.04838.

4.6.28. 3-(2-Phenylthiazol-4-yl)benzoic acid (25)

By following procedure 1, the title compound **25** was obtained from benzothioamide and 3-(2-bromoacetyl)benzoic acid as a colorless solid in 9% yield (HPLC purity: 99.1%). TLC R_f = 0.25 (30% EtOAc in Hexanes). M. P. = 200–202 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.64 (td, J = 1.8, 0.5 Hz, 1H), 8.35 (d, J = 0.4 Hz, 1H), 8.33–8.28 (m, 1H), 8.09–8.03 (m, 2H), 7.98–7.95 (m, 1H), 7.67–7.50 (m, 4H). HRMS calcd for $[C_{16}H_{11}NO_2S + H]^+$: 282.0583, Found: 282.059.

4.6.29. 4-(2-(2-Fluorophenyl)thiazol-4-yl)benzoic acid (26)

By following procedure 1, the title compound **26** was obtained from 2-fluorobenzothioamide and 4-(2-bromoacetyl)benzoic acid as a colorless solid in 58% yield (HPLC purity: 100%). TLC $R_f = 0.25$ (30% EtOAc in Hexanes). M. P. = 219–221 °C. ESI-MS *m/z*: 300.1.^{1}H NMR (400 MHz, DMSO-d_6): δ 13.01 (bs, 1H), 8.49 (s, 1H), 8.38 (td, $J = 7.8, 1.8$ Hz, 1H), 8.24–8.14 (m, 2H), 8.08–7.97 (m, 2H), 7.60–7.53 (m, 1H), 7.50–7.36 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.5, 160.1, 160.0, 159.9 (d, $J_{C\text{-}F} = 251.3$ Hz), 153.6, 138.1, 132.5 (d, $J_{C\text{-}F} = 8.6$ Hz), 130.7, 130.4, 129.0, 126.6, 125.7, 120.8 (d, $J_{C\text{-}F} = 11.4$ Hz), 118.6 (d, $J_{C\text{-}F} = 16.0$ Hz), 118.6, 116.9 (d, $J_{C\text{-}F} = 21.3$ Hz). HRMS calcd for $[C_{16}H_{10}FNO_2S + H]^+$: 300.0489, Found: 300.0481.

4.6.30. 2-(2-(2-Fluorophenyl)thiazol-4-yl)benzoic acid (27)

By following procedure 1, the title compound **27** was obtained from 2-fluorobenzothioamide and 2-(2-bromoacetyl)benzoic acid as a colorless solid in 13% yield (HPLC purity: 100%). TLC $R_f = 0.35$ (30% EtOAc in Hexanes). M. P. = 157–159 °C. ESI-MS *m/z*: 300.1.^{1}H NMR (400 MHz, DMSO-d_6): δ 8.23 (td, $J = 7.8, 1.8$ Hz, 1H), 8.05 (s, 1H), 7.75 (dd, $J = 7.7, 1.2$ Hz, 1H), 7.66–7.34 (m, 6H). HRMS calcd for $[C_{16}H_{10}FNO_2S + H]^+$: 300.0489, Found: 300.0483.

4.6.31. 2-(2-Fluorophenyl)-4-phenylthiazole (28)

By following procedure 1, the title compound **28** was obtained from 2-fluorobenzothioamide and 2-bromo-1-phenylethanone as a colorless solid in 48% yield (HPLC purity: 100%). TLC $R_f = 0.70$ (10% EtOAc in Hexanes). M. P. = 77–79 °C. ESI-MS *m/z*: 256.1.^{1}H NMR (400 MHz, DMSO-d_6): δ 8.37 (td, $J = 7.8, 1.8$ Hz, 1H), 8.31 (s, 1H), 8.12–8.02 (m, 2H), 7.59–7.52 (m, 1H), 7.51–7.33 (m, 5H). HRMS calcd for $[C_{15}H_{11}FNS + H]^+$: 256.0591, Found: 256.0591.

4.6.32. 3-(2-((2-Fluorophenyl)amino)thiazol-4-yl)benzoic acid (32)

By following procedure 1, the title compound **32** was obtained from 1-(2-fluorophenyl)thiourea and 3-(2-bromoacetyl)benzoic acid as a colorless solid in 37% yield (HPLC purity: 96.3%). TLC $R_f = 0.20$ (30% EtOAc in Hexanes). M. P. = 259–261 °C. ESI-MS *m/z*: 315.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.08 (s, 1H), 8.58–8.38 (m, 2H), 8.12 (ddd, $J = 7.7, 1.9, 1.2$ Hz, 1H), 7.86 (ddd, $J = 7.7, 1.7, 1.2$ Hz, 1H), 7.59–7.45 (m, 2H), 7.32–7.15 (m, 2H), 7.09–6.96 (m, 1H). HRMS calcd for $[C_{16}H_{11}FN_2O_2S + H]^+$: 315.0598, Found: 315.05916.

4.6.33. 3-(2-((3-Fluorophenyl)amino)thiazol-4-yl)benzoic acid (33)

By following procedure 1, the title compound **33** was obtained from 1-(3-fluorophenyl)thiourea and 3-(2-bromoacetyl)benzoic acid as a colorless solid in 37% yield (HPLC purity: 96.2%). TLC $R_f = 0.20$ (30% EtOAc in Hexanes). M. P. = 274–276 °C. ESI-MS *m/z*: 315.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.04 (s, 1H), 10.55 (s, 1H), 8.46 (t, $J = 1.7$ Hz, 1H), 8.13 (dt, $J = 7.8, 1.5$ Hz, 1H), 7.91–7.75 (m, 2H), 7.61–7.49 (m, 2H), 7.42–7.26 (m, 2H), 6.80–6.73 (m, 1H). HRMS calcd for $[C_{16}H_{11}FN_2O_2S + H]^+$: 315.0598, Found: 315.05968.

4.6.34. 3-(2-((4-Fluorophenyl)amino)thiazol-4-yl)benzoic acid (34)

By following procedure 1, the title compound **34** was obtained from 1-(4-fluorophenyl)thiourea and 3-(2-bromoacetyl)benzoic acid as a colorless solid in 44% yield (HPLC purity: 99.6%). TLC $R_f = 0.20$ (30% EtOAc in Hexanes). M. P. = 228–230 °C. ESI-MS *m/z*: 315.0. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.32 (s, 1H), 8.43 (t, $J = 1.8$ Hz, 1H), 8.14 (dt, $J = 7.9, 1.4$ Hz, 1H), 7.86 (dt, $J = 7.7, 1.4$ Hz, 1H), 7.75–7.65 (m, 2H), 7.55 (t, $J = 7.7$ Hz, 1H), 7.45 (s, 1H), 7.25–7.11 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.7, 163.9 (2C), 157.4 (d, $J_{C\text{-}F} = 238.9$ Hz), 149.5 (2C), 138.1 (d, $J_{C\text{-}F} = 2.3$ Hz), 135.2, 131.7, 130.4, 129.4, 128.8, 126.8, 118.9 (d, $J_{C\text{-}F} = 7.7$ Hz), 116.0 (d, $J_{C\text{-}F} = 22.4$ Hz), 104.8 (d, $J_{C\text{-}F} = 2.1$ Hz). HRMS calcd for $[C_{16}H_{11}FN_2O_2S + H]^+$: 315.0598, Found: 315.05974.

4.6.35. 3-(2-(Phenylamino)thiazol-4-yl)benzoic acid (35)

By following procedure 1, the title compound **35** was obtained from 1-phenylthiourea and 3-(2-bromoacetyl)benzoic acid as a colorless solid in 63% yield (HPLC purity: 100%). TLC $R_f = 0.20$ (30% EtOAc in Hexanes). M. P. = 288–290 °C. ESI-MS *m/z*: 297.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.03 (s, 1H), 10.30 (s, 1H), 8.45 (t, $J = 1.8$ Hz, 1H), 8.14 (dt, $J = 7.8, 1.5$ Hz, 1H), 7.87 (dt, $J = 7.7, 1.4$ Hz, 1H), 7.73–7.64 (m, 2H), 7.55 (t, $J = 7.8$ Hz, 1H), 7.46 (s, 1H), 7.39–7.27 (m, 2H), 6.96 (tt, $J = 7.3, 1.2$ Hz, 1H). HRMS calcd for $[C_{16}H_{12}N_2O_2S + H]^+$: 297.06922, Found: 297.06860.

4.6.36. 3-(2-(o-Tolylamino)thiazol-4-yl)benzoic acid (36)

By following procedure 1, the title compound **36** was obtained from 1-(*o*-tolyl)thiourea and 3-(2-bromoacetyl)benzoic acid as a colorless solid in 95% yield (HPLC purity: 96.7%). TLC $R_f = 0.25$ (30% EtOAc in Hexanes). M. P. = 221–223 °C. ESI-MS *m/z*: 311.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.46 (s, 1H), 8.43 (t, $J = 1.7$ Hz, 1H), 8.09 (ddd, $J = 7.8, 1.9, 1.2$ Hz, 1H), 7.94–7.82 (m, 2H), 7.59–7.48 (m, 1H), 7.39 (s, 1H), 7.29–7.18 (m, 2H), 7.05 (td, $J = 7.5, 1.3$ Hz, 1H), 2.30 (s, 3H). HRMS calcd for $[C_{17}H_{14}N_2O_2S + H]^+$: 311.08487, Found: 311.08485.

4.6.37. 3-(2-((2,6-Difluorophenyl)amino)thiazol-4-yl)benzoic acid (37)

By following procedure 1, the title compound **37** was obtained from 1-(2,6-difluorophenyl)thiourea and 3-(2-bromoacetyl)benzoic acid as a colorless solid in 48% yield (HPLC purity: 97.0%). TLC $R_f = 0.20$ (30% EtOAc in Hexanes). M. P. = 180–182 °C. ESI-MS *m/z*: 333.0. ^{1}H NMR (400 MHz, D_2O): δ 8.34–8.33 (m, 1H), 8.13–8.10 (m, 1H), 7.93–7.91 (m, 1H), 7.63–7.22 (m, 5H). HRMS calcd for $[C_{16}H_{10}F_2N_2O_2S + H]^+$: 333.05038, Found: 333.04979.

4.6.38. 3-(2-((2,3-Difluorophenyl)amino)thiazol-4-yl)benzoic acid (38)

By following procedure 1, the title compound **38** was obtained from 1-(2,3-difluorophenyl)thiourea and 3-(2-bromoacetyl)benzoic acid as a colorless solid in 44% yield (HPLC purity: 95.8%). TLC $R_f = 0.20$ (30% EtOAc in Hexanes). M. P. = 250–252 °C. ESI-MS *m/z*: 333.0. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.33 (s, 1H), 8.44 (t, $J = 3.2$ Hz, 1H), 8.40–8.35 (m, 1H), 8.17–8.14 (m, 1H), 7.90–7.87 (m, 1H), 7.59–7.55 (m, 1H), 7.26–7.20 (m, 1H), 7.07–7.01 (m, 1H). HRMS calcd for $[C_{16}H_{10}F_2N_2O_2S + H]^+$: 333.05038, Found: 333.04995.

4.6.39. 3-(2-((2,4-Difluorophenyl)amino)thiazol-4-yl)benzoic acid (39)

By following procedure 1, the title compound **39** was obtained from 1-(2,4-difluorophenyl)thiourea and 3-(2-bromoacetyl)benzoic acid as a colorless solid in 68% yield (HPLC purity: 98.7%). TLC $R_f = 0.20$ (30% EtOAc in Hexanes). M. P. = 235–237 °C. ESI-MS *m/z*: 333.0. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.02 (s, 1H), 10.05 (s, 1H), 8.54–8.36 (m, 2H), 8.14–8.12 (m, 1H), 7.89–7.86 (m, 1H), 7.62–7.45 (m, 2H), 7.37–7.31 (m, 1H), 7.19–7.06 (m, 1H). HRMS calcd for $[C_{16}H_{10}F_2N_2O_2S + H]^+$: 333.05038, Found: 333.04973.

4.6.40. 3-(2-((3,5-Difluorophenyl)amino)thiazol-4-yl)benzoic acid (40)

By following procedure 1, the title compound **40** was obtained from 1-(3,5-difluorophenyl)thiourea and 3-(2-bromoacetyl)benzoic acid as a colorless solid in 24% yield (HPLC purity: 100%). TLC $R_f = 0.20$ (30% EtOAc in Hexanes). M. P. = 272–274 °C. ESI-MS *m/z*: 333.0. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.06 (s, 1H), 10.78 (s, 1H), 8.49 (t, $J = 1.8$ Hz, 1H), 8.15 (dt, $J = 7.7, 1.5$ Hz, 1H), 7.91 (dt, $J = 7.6, 1.4$ Hz, 1H), 7.64–7.55 (m, 2H), 7.50–7.40 (m, 2H), 6.80 (tt, $J = 9.2, 2.3$ Hz, 1H). HRMS calcd for $[C_{16}H_{10}F_2N_2O_2S + H]^+$: 333.05038, Found: 333.04956.

4.6.41. 3-(2-((2,5-Difluorophenyl)amino)thiazol-4-yl)benzoic acid (41)

By following procedure 1, the title compound **41** was obtained from 1-(2,5-difluorophenyl)thiourea and 3-(2-bromoacetyl)benzoic acid as a colorless solid in 62% yield (HPLC purity: 99.7%). TLC $R_f = 0.20$ (30% EtOAc in Hexanes). M. P. = 242–244 °C. ESI-MS *m/z*: 333.0. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.03 (s, 1H), 10.40 (s, 1H), 8.58 (ddd, J = 11.4, 6.7, 3.2 Hz, 1H), 8.48 (t, J = 1.7 Hz, 1H), 8.14 (ddd, J = 7.8, 1.9, 1.2 Hz, 1H), 7.90 (ddd, J = 7.7, 1.7, 1.2 Hz, 1H), 7.65–7.49 (m, 2H), 7.31 (ddd, J = 11.2, 9.0, 5.2 Hz, 1H), 6.82 (ddt, J = 8.9, 7.8, 3.3 Hz, 1H). HRMS calcd for $[C_{16}H_{10}F_2N_2O_2S + H]^+$: 333.05038, Found: 333.04949.

4.6.42. 4-(2-((2-Fluorophenyl)amino)thiazol-4-yl)benzoic acid (42)

By following procedure 1, the title compound **42** was obtained from 1-(2-fluorophenyl)thiourea and 4-(2-bromoacetyl)benzoic acid as a colorless solid in 20% yield (HPLC purity: 100%). TLC $R_f = 0.20$ (30% EtOAc in Hexanes). M. P. = 234–236 °C. ESI-MS *m/z*: 315.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.12 (s, 1H), 8.56 (td, J = 8.5, 1.7 Hz, 1H), 8.09–7.84 (m, 4H), 7.56 (s, 1H), 7.35–7.11 (m, 2H), 7.04–6.97 (m, 1H). HRMS calcd for $[C_{16}H_{11}FN_2O_2S + H]^+$: 315.0598, Found: 315.05956.

4.6.43. 2-(2-((2-Fluorophenyl)amino)thiazol-4-yl)benzoic acid (43)

By following procedure 1, the title compound **42** was obtained from 1-(2-fluorophenyl)thiourea and 2-(2-bromoacetyl)benzoic acid as a colorless solid in 54% yield (HPLC purity: 100%). TLC $R_f = 0.20$ (30% EtOAc in Hexanes). M. P. = 226–228 °C. ESI-MS *m/z*: 315.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.75 (s, 1H), 9.99 (s, 1H), 8.51 (td, J = 8.5, 1.6 Hz, 1H), 7.64 (dd, J = 7.7, 1.2 Hz, 1H), 7.57–7.46 (m, 2H), 7.40 (td, J = 7.5, 1.3 Hz, 1H), 7.24–7.07 (m, 3H), 6.97–6.90 (m, 1H). HRMS calcd for $[C_{16}H_{11}FN_2O_2S + H]^+$: 315.0598, Found: 315.05946.

4.6.44. N-(2-fluorophenyl)-4-phenylthiazol-2-amine (44)

By following procedure 1, the title compound **44** was obtained from 1-(2-fluorophenyl)thiourea and 2-bromo-1-phenylethanone as a colorless solid in 63% yield (HPLC purity: 100%). TLC $R_f = 0.50$ (10% EtOAc in Hexanes). M. P. = 100–102 °C. ESI-MS *m/z*: 271.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.05 (s, 1H), 8.58 (td, J = 8.6, 1.7 Hz, 1H), 7.98–7.78 (m, 2H), 7.45–7.19 (m, 6H), 7.02–6.96 (m, 1H). HRMS calcd for $[C_{15}H_{11}FN_2S + H]^+$: 271.06997, Found: 271.06958.

4.6.45. Methyl 3-(2-((2-fluorophenyl)amino)thiazol-4-yl)benzoate (45)

Thionyl Chloride (3 eq.) was added to a solution of **32** (1 eq.) in methanol and stirred at room temperature for overnight. Solvent was removed and was washed with aq. $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 times) and the combined organic layer was dried over anhydrous Na_2SO_4. The filtrate was concentrated *in vacuo* and the crude product was purified on Teledyne Isco Combiflash® R_f purification machine to afford the title compound **45** as a colorless solid in 80% yield (HPLC purity: 97.6%). TLC $R_f = 0.40$ (10% EtOAc in Hexanes). M. P. = 142–144 °C. ESI-MS *m/z*: 329.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.11 (s, 1H), 8.55–8.41 (m, 2H), 8.16 (ddd, J = 7.8, 1.9, 1.2 Hz, 1H), 7.94–7.82 (m, 1H), 7.57 (t, J = 8.0 Hz, 1H), 7.52 (s, 1H), 7.31–7.16 (m, 2H), 7.05–6.98 (m, 1H), 3.88 (s, 3H). HRMS calcd for $[C_{17}H_{13}FN_2O_2S + H]^+$: 329.07545, Found: 329.07500.

4.6.46. (3-(2-((2-Fluorophenyl)amino)thiazol-4-yl)phenyl) methanol (46)

Di*iso*propylamine (0.018 ml, 0.124 mmol) was added to a solution of 3-(2-((2-fluorophenyl)amino)thiazol-4-yl)benzoic acid, **32** (30 mg, 0.095 mmol) and (benzotriazol-1-yloxy) tris(dimethylamino)phosphonium hexafluorophosphate (50.7 mg, 0.115 mmol) in THF (1 mL) at room temperature under argon atmosphere and the resulted solution was stirred for 5 min. Then sodium borohydride (7.22 mg, 0.191 mmol) was added to the reaction mixture and stirred for another 30 min under same conditions. Ethanol was removed from the reaction mixture and the resulted residue was washed with water. The aqueous layer was extracted with CH_2Cl_2 (thrice) and the combined organic layer was dried over anhydrous Na_2SO_4. The filtrate was concentrated *in vacuo* and the crude product was purified on Teledyne Isco Combiflash® R_f purification machine to afford (3-(2-((2-fluorophenyl) amino)thiazol-4-yl)phenyl)methanol, **46** as a colorless solid in 70% yield (HPLC purity: 96.9%). TLC $R_f = 0.30$ (30% EtOAc in Hexanes). M. P. = 257–259 °C. ESI-MS *m/z*: 301.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.05 (s, 1H), 8.56 (td, J = 8.6, 1.7 Hz, 1H), 7.88–7.69 (m, 2H), 7.45–7.14 (m, 5H), 7.03–6.97 (m, 1H), 5.23 (t, J = 5.8 Hz, 1H), 4.53 (d, J = 5.7 Hz, 2H). HRMS calcd for $[C_{16}H_{13}FN_2OS + H]^+$: 301.08054, Found: 301.08010.

4.6.47. N-(2-fluorophenyl)-4-(3-(methoxymethyl)phenyl)thiazol-2-amine (47)

Sodium hydride (1.918 mg, 0.080 mmol) was added to a solution of (3-(2-((2-fluorophenyl)amino)thiazol-4-yl)phenyl)methanol, **46** (20 mg, 0.067 mmol) in THF (1 mL) at room temperature under argon and stirred for 30 min. Then the solution was cooled to 0 °C, and methyl iodide (12.49 μl, 0.200 mmol) was added dropwise. Solution was then warmed to room temperature and stirred for another 4 h. Reaction was quenched with saturated NH_4Cl (3 mL), and extracted with EtOAc (5 x 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the filtrate was concentrated *in vacuo*. The crude product was purified on Teledyne Isco Combiflash® R_f purification machine to afford *N*-(2-fluorophenyl)-4-(3-(methoxymethyl)phenyl)thiazol-2-amine, **47** as a yellow oil in 36% yield (HPLC purity: 95.0%). TLC $R_f = 0.30$ (25% EtOAc in Hexanes). ESI-MS *m/z*: 315.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.87–7.86 (m, 1H), 7.79–7.77 (m, 1H), 7.51–7.47 (m, 1H), 7.40–7.20 (m, 5H), 6.73 (s, 1H), 4.74 (s, 2H), 3.58 (s, 3H). HRMS calcd for $[C_{17}H_{15}FN_2OS + H]^+$: 315.09619, Found: 315.09584.

4.6.48. 3-(2-((2-Fluorophenyl)amino)thiazol-4-yl)phenol (48)

By following procedure 1, the title compound **48** was obtained from 1-(2-fluorophenyl)thiourea and 2-bromo-1-(3-hydroxyphenyl)ethanone as a colorless solid in 91% yield (HPLC purity: 99.2%). TLC R_f = 0.20 (25% EtOAc in Hexanes). M. P. = 165–167 °C. ESI-MS *m/z*: 287.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.04 (s, 1H), 8.58 (td, J = 8.2, 1.5 Hz, 1H), 7.35–7.15 (m, 6H), 7.07–6.95 (m, 1H), 6.71 (ddd, J = 8.0, 2.4, 1.1 Hz, 1H). HRMS calcd for $[C_{15}H_{11}FN_2OS + H]^+$: 287.06489, Found: 287.06483.

4.6.49. N-(2-fluorophenyl)-4-(3-methoxyphenyl)thiazol-2-amine (49)

By following procedure 1, the title compound **49** was obtained from 1-(2-fluorophenyl)thiourea and 2-bromo-1-(3-methoxyphenyl)ethanone as a pale yellow sticky solid in 27% yield (HPLC purity: 96.1%). TLC $R_f = 0.30$ (25% EtOAc in Hexanes). ESI-MS *m/z*: 301.1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.43 (m, 1H), 7.41–7.31 (m, 2H), 7.36–7.21 (m, 1H), 7.26 (s, 1H), 7.24–7.16 (m, 3H), 6.78–6.70 (m, 1H), 6.75–6.66 (m, 1H), 3.55 (s, 1H). HRMS calcd for $[C_{16}H_{13}FN_2OS + H]^+$: 301.08054, Found: 301.08119.

4.6.50. N-(2-fluorophenyl)-4-(3-fluorophenyl)thiazol-2-amine (50)

By following procedure 1, the title compound **50** was obtained from 1-(2-fluorophenyl)thiourea and 2-bromo-1-(3-fluorophenyl) ethanone as off-white solid in 35% yield (HPLC purity: 96.8%). TLC $R_f = 0.25$ (10% EtOAc in Hexanes). M. P. = 83–85 °C. ESI-MS *m/z*:

289.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.11 (s, 1H), 8.56 (td, J = 8.6, 1.8 Hz, 1H), 7.77–7.75 (m, 1H), 7.71–7.67 (m, 1H), 7.53–7.44 (m, 2H), 7.30–7.22 (m, 2H), 7.17–7.11 (m, 1H), 7.06–6.99 (m, 1H). HRMS calcd for $[C_{15}H_{10}F_2N_2S + H]^+$: 289.06055, Found: 289.06066.

4.6.51. 3-(2-((2-Fluorophenyl)amino)thiazol-4-yl)benzamide (51)

Ammonium chloride (14.04 mg, 0.262 mmol) and DIEA (92 μl, 0.525 mmol) were added to a rapidly stirring mixture of 3-(2-((2-fluorophenyl)amino)thiazol-4-yl)benzoic acid, **32** (75 mg, 0.239 mmol) in acetonitrile (5 mL). After stirring for 10 min, HATU (100 mg, 0.262 mmol) was added, and the reaction mixture was stirred at room temperature for 24 h. Solvent was removed and was washed with aq. $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (thrice) and the combined organic layer was dried over anhydrous Na_2SO_4. The filtrate was concentrated *in vacuo* and the crude product was purified on Teledyne Isco Combiflash® R_f purification machine to afford 3-(2-((2-fluorophenyl)amino)thiazol-4-yl)benzamide, **51** as a pale yellow sticky solid in 62% yield (HPLC purity: 97.7%). TLC R_f = 0.25 (5% methanol in CH_2Cl_2). ESI-MS m/z: 314.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.10 (d, J = 1.9 Hz, 1H), 8.58 (td, J = 8.2, 1.5 Hz, 1H), 8.37 (td, J = 1.8, 0.6 Hz, 1H), 8.05 (ddd, J = 7.7, 1.8, 1.1 Hz, 2H), 7.80 (ddd, J = 7.7, 1.7, 1.1 Hz, 1H), 7.51 (td, J = 7.8, 0.5 Hz, 1H), 7.43 (d, J = 11.3 Hz, 2H), 7.32–7.18 (m, 2H), 7.08–6.97 (m, 1H). HRMS calcd for $[C_{16}H_{12}FN_3OS + H]^+$: 314.07579, Found: 314.07654.

4.6.52. N-(2-fluorophenyl)-4-(4-(2,2,2-trifluoroethoxy)phenyl) thiazol-2-amine (52)

By following procedure 1, the title compound **52** was obtained from 1-(2-fluorophenyl)thiourea and 2-bromo-1-(4-(2,2,2-trifluoroethoxy)phenyl)ethanone as a pale yellow solid in 66% yield (HPLC purity: 98.0%). TLC R_f = 0.25 (10% EtOAc in Hexanes). M. P. = 211–213 °C. ESI-MS m/z: 369.0. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (td, J = 8.6, 1.7 Hz, 1H), 7.64–7.51 (m, 2H), 7.47 (s, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.31–7.17 (m, 2H), 7.02 (td, J = 8.0, 2.2 Hz, 2H), 4.83 (q, J = 8.9 Hz, 2H). HRMS calcd for $[C_{17}H_{12}F_4N_2OS + H]^+$: 369.06792, Found: 369.06784.

4.6.53. N-(2-fluorophenyl)-4-(3-(trifluoromethyl)phenyl)thiazol-2-amine (53)

By following procedure 1, the title compound **53** was obtained from 1-(2-fluorophenyl)thiourea and -bromo-1-(3-(trifluoromethyl)phenyl)ethanone as a colorless solid in 57% yield (HPLC purity: 97.2%). TLC R_f = 0.45 (20% EtOAc in Hexanes). M. P. = 66–68 °C. ESI-MS m/z: 339.0. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.13 (s, 1H), 8.50 (td, J = 8.4, 1.6 Hz, 1H), 8.29–8.09 (m, 2H), 7.77–7.53 (m, 3H), 7.35–7.15 (m, 2H), 7.11–6.94 (m, 1H). HRMS calcd for $[C_{16}H_{10}F_4N_2S + H]^+$: 339.05736, Found: 339.05681.

4.6.54. N-(2-fluorophenyl)-4-(3-(3-methyl-1,2,4-oxadiazol-5-yl) phenyl)thiazol-2-amine (54)

To a rapidly stirring mixture of 3-(2-((2-fluorophenyl)amino) thiazol-4-yl)benzoic acid (60 mg, 0.191 mmol) in DMF (1909 μl) was added (*Z*)-*N*′-hydroxyacetimidamide (14.14 mg, 0.191 mmol)) followed by DIEA (100 μl, 0.573 mmol). After stirring for 10 min, HATU (80 mg, 0.210 mmol) was added, and the reaction mixture was stirred at room temperature for 24 h. DMF was removed, and the oily residue was reconstituted in AcOH (2 mL) and the reaction was heated to reflux for 3 h. Then the reaction mixture was cooled and added saturated $NaHCO_3$, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The filtrate was concentrated *in vacuo* and the crude product was purified on Teledyne Isco Combiflash® R_f purification machine to afford *N*-(2-fluorophenyl)-4-(3-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)thiazol-2-amine, **54** as an yellow solid in 7% yield (HPLC purity: 95.3%). M. P. = 131–133 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (td, J = 1.7, 0.5 Hz, 1H), 8.20 (td, J = 8.3, 1.6 Hz, 1H), 8.13 (ddd, J = 7.9, 1.8, 1.2 Hz, 1H), 8.07 (ddd, J = 7.8, 1.7, 1.2 Hz, 1H), 7.59 (td, J = 7.8, 0.6 Hz, 1H), 7.22 (dddd, J = 8.2, 7.4, 1.5, 0.9 Hz, 1H), 7.15 (ddd, J = 11.2, 8.2, 1.5 Hz, 1H), 7.06–6.98 (m, 2H), 2.50 (s, 3H). HRMS calcd for $[C_{18}H_{13}FN_4OS + H]^+$: 353.08669, Found: 353.08618.

4.6.55. 4-(3-(Aminomethyl)phenyl)-N-(2-fluorophenyl)thiazol-2-amine (55)

By following procedure 1, the intermediate 3-(2-((2-fluorophenyl)amino)thiazol-4-yl)benzonitrile was obtained from 1-(2-fluorophenyl)thiourea and 3-(2-bromoacetyl)benzonitrile as a colorless solid in 42% yield. ESI-MS m/z: 296.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.14 (s, 1H), 8.53 (td, J = 8.6, 1.7 Hz, 1H), 8.31 (td, J = 1.7, 0.6 Hz, 1H), 8.23 (ddd, J = 7.9, 1.8, 1.2 Hz, 1H), 7.75 (dt, J = 7.7, 1.3 Hz, 1H), 7.68–7.58 (m, 2H), 7.30–7.19 (m, 2H), 7.06–6.96 (m, 1H).

By following procedure 3, the title compound **55** was obtained from 3-(2-((2-fluorophenyl)amino)thiazol-4-yl)benzonitrile as a pale yellow solid in 78% yield (HPLC purity: 96.6%). TLC R_f = 0.20 (10% MeOH in CH_2Cl_2). M. P. = 118–120 °C. ESI-MS m/z: 300.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.59 (td, J = 8.6, 1.7 Hz, 1H), 7.85 (dt, J = 1.8, 0.9 Hz, 1H), 7.77–7.72 (m, 1H), 7.39–7.31 (m, 2H), 7.31–7.19 (m, 3H), 7.01 (dddd, J = 8.0, 7.5, 4.9, 1.7 Hz, 1H), 3.77 (s, 2H), 1.24 (s, 2H). HRMS calcd for $[C_{16}H_{14}FN_3S + H]^+$: 300.09652, Found: 300.09545.

4.6.56. 4-(3-(Aminomethyl)phenyl)-N-(3-fluorophenyl)thiazol-2-amine (56)

By following procedure 1, the intermediate 3-(2-((3-fluorophenyl)amino)thiazol-4-yl)benzonitrile was obtained from 1-(3-fluorophenyl)thiourea and 3-(2-bromoacetyl)benzonitrile as a colorless solid in 76% yield. ESI-MS m/z: 296.1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (td, J = 8.2, 1.8 Hz, 1H), 8.08–8.06 (m, 1H), 7.60–7.48 (m, 3H), 7.34–7.29 (m, 2H), 7.15–7.12 (m, 1H), 6.95 (s, 1H), 6.81–6.76 (m, 1H).

By following procedure 3, the title compound **56** was obtained from 3-(2-((3-fluorophenyl)amino)thiazol-4-yl)benzonitrile as a pale yellow solid in 79% yield (HPLC purity: 96.9%). TLC R_f = 0.20 (10% MeOH in CH_2Cl_2). M. P. = 112–114 °C. ESI-MS m/z: 300.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1H), 7.87 (s, 1H), 7.82–7.73 (m, 2H), 7.41–7.34 (m, 4H), 7.30 (d, J = 7.5 Hz, 1H), 6.77 (dtd, J = 9.1, 4.6, 2.5 Hz, 1H), 3.79 (s, 2H). HRMS calcd for $[C_{16}H_{14}FN_3S + H]^+$: 300.09652, Found: 300.09632.

4.6.57. 4-(3-(Aminomethyl)phenyl)-N-(4-fluorophenyl)thiazol-2-amine (57)

By following procedure 1, the intermediate 3-(2-((4-fluorophenyl)amino)thiazol-4-yl)benzonitrile was obtained from 1-(3-fluorophenyl)thiourea and 3-(2-bromoacetyl)benzonitrile as a colorless solid in 53% yield. M. P. = 135–137 °C. ESI-MS m/z: 296.1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (td, J = 8.3, 1.8 Hz, 1H), 8.05–8.02 (m, 1H), 7.59–7.40 (m, 5H), 7.11–7.06 (m, 2H), 6.88 (s, 1H).

By following procedure 3, the title compound **57** was obtained from 3-(2-((4-fluorophenyl)amino)thiazol-4-yl)benzonitrile as a pale yellow solid in 64% yield (HPLC purity: 95.1%). TLC R_f = 0.20 (10% MeOH in CH_2Cl_2). M. P. = 145–147 °C. ESI-MS m/z: 300.2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.27 (s, 1H), 7.90–7.80 (m, 2H), 7.79–7.67 (m, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.32–7.12 (m, 3H), 3.75 (s, 2H). HRMS calcd for $[C_{16}H_{14}FN_3S + H]^+$: 300.09652, Found: 300.09637.

4.6.58. 4-(4-(Aminomethyl)phenyl)-N-(2-fluorophenyl)thiazol-2-amine (58)

By following procedure 1, the intermediate 4-(2-((2-fluorophenyl)amino)thiazol-4-yl)benzonitrile was obtained from 1-(2-fluorophenyl)thiourea and 4-(2-bromoacetyl)benzonitrile as a colorless solid in 99% yield. ESI-MS *m/z*: 296.0. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.17 (s, 1H), 8.56 (td, J = 8.5, 1.8 Hz, 1H), 8.10–8.07 (m, 2H), 7.90–7.87 (m, 2H), 7.69 (s, 1H), 7.29–7.22 (m, 2H), 7.06–7.02 (m, 1H).

By following procedure 3, the title compound **58** was obtained from 4-(2-((2-fluorophenyl)amino)thiazol-4-yl)benzonitrile as a pale yellow solid in 94% yield (HPLC purity: 96.2%). TLC R_f = 0.20 (10% MeOH in CH_2Cl_2). M. P. = 102–104 °C. ESI-MS *m/z*: 300.2. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (td, J = 8.3, 1.6 Hz, 1H), 7.87–7.79 (m, 2H), 7.39–7.33 (m, 2H), 7.23–7.06 (m, 2H), 6.99 (dddd, J = 8.2, 7.4, 5.1, 1.6 Hz, 1H), 6.87 (s, 1H), 3.91 (s, 2H). HRMS calcd for $[C_{16}H_{14}FN_3S + H]^+$: 300.09652, Found: 300.09618.

4.6.59. N-(3-(2-((2-fluorophenyl)amino)thiazol-4-yl)benzyl) acetamide (59)

Acetic anhydride (23.64 μL, 0.251 mmol) and DIEA (58.3 μL, 0.334 mmol) were added to a solution of 4-(3-(aminomethyl) phenyl)-*N*-(2-fluorophenyl)thiazol-2-amine, **55** (50 mg, 0.167 mmol) in dichloromethane (1 mL) 0 °C under argon. The solution was slowly warmed to room temperature and allowed to stir overnight. The mixture was diluted with 10 mL of DCM, and organic phase was washed with 1 N HCl (5 × 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and the filtrate was concentrated *in vacuo*. The crude residue was purified on Teledyne Isco Combiflash® R_f purification machine to afford *N*-(3-(2-((2-fluorophenyl)amino)thiazol-4-yl)benzyl)acetamide, **59** as a pale yellow solid in 7% yield (HPLC purity: 98.6%). M. P. = 123–125 °C. ESI-MS *m/z*: 342.1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (td, J = 8.3, 1.6 Hz, 1H), 7.83–7.73 (m, 2H), 7.38 (td, J = 7.5, 0.7 Hz, 1H), 7.25–7.09 (m, 3H), 7.04–6.95 (m, 1H), 6.89 (s, 1H), 5.75 (s, 1H), 4.49 (d, J = 5.7 Hz, 2H), 2.04 (s, 3H). HRMS calcd for $[C_{18}H_{16}FN_3OS + H]^+$: 342.10709, Found: 342.10730.

4.6.60. 3-(4-((2-Fluorophenyl)amino)thiazol-2-yl)benzoic acid (60)

A solution of 2-chloro-*N*-(2-fluorophenyl)acetamide (104 mg, 0.552 mmol) and 3-carbamothioylbenzoic acid (100 mg, 0.552 mmol) in DMF (2 ml) was heated at 80 °C for overnight. Solvent was removed and the crude residue was purified on Teledyne Isco Combiflash® R_f purification machine to afford 3-(4-((2-fluorophenyl)amino)thiazol-2-yl)benzoic acid, **60** as a pale yellow solid in 8% yield (HPLC purity: 100%). TLC R_f = 0.25 (30% EtOAc in Hexanes). M. P. = 191–193 °C. ESI-MS *m/z*: 315.0. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.25 (s, 1H), 8.67 (d, J = 2.0 Hz, 1H), 8.43 (t, J = 1.8 Hz, 1H), 8.13 (dt, J = 7.8, 1.5 Hz, 1H), 8.00 (dt, J = 7.8, 1.4 Hz, 1H), 7.78–7.57 (m, 2H), 7.24–7.04 (m, 2H), 6.90–6.83 (m, 1H), 6.73 (s, 1H). HRMS calcd for $[C_{16}H_{11}FN_2O_2S + H]^+$: 315.0598, Found: 315.06004.

4.6.61. 3-(2-((2-Fluorophenyl)amino)oxazol-5-yl)benzoic acid (61) and methyl 3-(2-((2-fluorophenyl)amino)oxazol-5-yl)benzoate (75)

By following procedure 4, the title compound **75** was obtained from methyl 3-(2-bromoacetyl)benzoate and 1-fluoro-2-*iso*-thiocyanatobenzene as a colorless solid in 62% yield (HPLC purity: 98.8%). TLC R_f = 0.35 (30% EtOAc in Hexanes). M. P. = 187–189 °C. ESI-MS *m/z*: 313.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.16 (s, 1H), 8.26–8.07 (m, 2H), 7.88–7.81 (m, 2H), 7.66–7.49 (m, 2H), 7.30–7.11 (m, 2H), 7.08–6.95 (m, 1H), 3.87 (s, 3H). HRMS calcd for $[C_{17}H_{13}FN_2O_3+H]^+$: 313.0983, Found: 313.09804.

Compound **75** was hydrolyzed by following procedure 2 to get compound **61** as a colorless solid in 45% yield (HPLC purity: 98.2%). TLC R_f = 0.25 (40% EtOAc in Hexanes). M. P. = 229–231 °C. ESI-MS *m/z*: 299.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.13 (s, 1H), 8.29–8.08 (m, 2H), 7.84–7.78 (m, 2H), 7.61–7.48 (m, 2H), 7.31–7.11 (m, 2H), 7.05–6.98 (m, 1H). HRMS calcd for $[C_{16}H_{11}FN_2O_3+H]^+$: 299.08265, Found: 299.08288.

4.6.62. 3-(2-((3-Fluorophenyl)amino)oxazol-5-yl)benzoic acid (62) and methyl 3-(2-((3-fluorophenyl)amino)oxazol-5-yl)benzoate (76)

By following procedure 4, the title compound **76** was obtained from methyl 3-(2-bromoacetyl)benzoate and 1-fluoro-3-*iso*-thiocyanatobenzene as a colorless solid in 70% yield (HPLC purity: 98.8%). TLC R_f = 0.35 (30% EtOAc in Hexanes). M. P. = 171–173 °C. ESI-MS *m/z*: 313.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.70 (s, 1H), 8.13 (t, J = 1.8 Hz, 1H), 7.90–7.80 (m, 2H), 7.72–7.51 (m, 3H), 7.42–7.25 (m, 2H), 6.79–6.73 (m, 1H), 3.87 (s, 3H). HRMS calcd for $[C_{17}H_{13}FN_2O_3+H]^+$: 313.0983, Found: 313.09819.

Compound **76** was hydrolyzed by following procedure 2 to get compound **62** as a colorless solid in 24% yield (HPLC purity: 95.6%). TLC R_f = 0.25 (40% EtOAc in Hexanes). M. P. = 230–232 °C. ESI-MS *m/z*: 299.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.16 (s, 1H), 10.66 (s, 1H), 8.14 (t, J = 1.7 Hz, 1H), 7.85–7.78 (m, 2H), 7.67–7.51 (m, 3H), 7.36–7.28 (m, 2H), 6.80–6.72 (m, 1H). HRMS calcd for $[C_{16}H_{11}FN_2O_3+H]^+$: 299.08265, Found: 299.08199.

4.6.63. 3-(2-((4-Fluorophenyl)amino)oxazol-5-yl)benzoic acid (63) and methyl 3-(2-((4-fluorophenyl)amino)oxazol-5-yl)benzoate (77)

By following procedure 4, the title compound **77** was obtained from methyl 3-(2-bromoacetyl)benzoate and 1-fluoro-4-*iso*-thiocyanatobenzene as a colorless solid in 66% yield (HPLC purity: 100%). TLC R_f = 0.35 (30% EtOAc in Hexanes). M. P. = 188–190 °C. ESI-MS *m/z*: 313.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.45 (s, 1H), 8.11 (t, J = 1.7 Hz, 1H), 7.88–7.79 (m, 2H), 7.69–7.53 (m, 4H), 7.19–7.10 (m, 2H), 3.87 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.9, 157.3 (d, $J_{C\text{-}F}$ = 259.8 Hz), 156.7 (2C), 142.6 (2C), 135.7 (d, $J_{C\text{-}F}$ = 2.5 Hz), 130.4, 129.6, 128.5, 127.4, 127.0, 123.7, 122.6, 118.1 (d, $J_{C\text{-}F}$ = 7.8 Hz), 115.5 (d, $J_{C\text{-}F}$ = 22.5 Hz), 52.3. HRMS calcd for $[C_{17}H_{13}FN_2O_3+H]^+$: 313.0983, Found: 313.09843.

Compound **77** was hydrolyzed by following procedure 2 to get compound **63** as a colorless solid in 75% yield (HPLC purity: 96.5%). TLC R_f = 0.25 (40% EtOAc in Hexanes). M. P. = 236–238 °C. ESI-MS *m/z*: 299.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.15 (s, 1H), 10.42 (s, 1H), 8.12 (t, J = 1.8 Hz, 1H), 7.83–7.78 (m, 2H), 7.67–7.60 (m, 2H), 7.59–7.51 (m, 2H), 7.21–7.11 (m, 2H). HRMS calcd for $[C_{16}H_{11}FN_2O_3+H]^+$: 299.08265, Found: 299.08281.

4.6.64. 3-(2-(Phenylamino)oxazol-5-yl)benzoic acid (64) and methyl 3-(2-(phenylamino)oxazol-5-yl)benzoate (78)

By following procedure 4, the title compound **78** was obtained from methyl 3-(2-bromoacetyl)benzoate and *iso*-thiocyanatobenzene as a colorless solid in 66% yield (HPLC purity: 98.4%). TLC R_f = 0.35 (30% EtOAc in Hexanes). M. P. = 170–172 °C. ESI-MS *m/z*: 295.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.40 (s, 1H), 8.12 (t, J = 1.7 Hz, 1H), 7.90–7.79 (m, 2H), 7.67–7.54 (m, 4H), 7.35–7.26 (m, 2H), 6.95 (td, J = 7.3, 1.1 Hz, 1H), 3.87 (s, 3H). HRMS calcd for $[C_{17}H_{14}N_2O_3+H]^+$: 295.10772, Found: 295.10742.

Compound **78** was hydrolyzed by following procedure 2 to get compound **64** as a colorless solid in 85% yield (HPLC purity: 97.7%). TLC R_f = 0.25 (40% EtOAc in Hexanes). M. P. = 233–235 °C. ESI-MS *m/z*: 281.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.15 (s, 1H), 10.37 (s, 1H), 8.14–8.12 (m, 1H), 7.87–7.76 (m, 2H), 7.67–7.50 (m, 4H), 7.35–7.25 (m, 2H), 6.94 (tt, J = 7.4, 1.1 Hz, 1H). HRMS calcd for $[C_{16}H_{12}N_2O_3+H]^+$: 281.09207, Found: 281.09152.

4.6.65. 3-(2-((2,6-Difluorophenyl)amino)oxazol-5-yl)benzoic acid (65) and methyl 3-(2-((2,6-difluorophenyl)amino)oxazol-5-yl) benzoate (79)

By following procedure 4, the title compound **79** was obtained from methyl 3-(2-bromoacetyl)benzoate and 1,3-difluoro-2-*iso*-thiocyanatobenzene as a colorless solid in 56% yield (HPLC purity: 98.9%). TLC $R_f = 0.35$ (30% EtOAc in Hexanes). M. P. = 188–190 °C. ESI-MS *m/z*: 331.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.80 (s, 1H), 8.03 (t, $J = 1.8$ Hz, 1H), 7.84–7.73 (m, 2H), 7.59–7.50 (m, 1H), 7.47 (s, 1H), 7.31 (q, $J = 7.1$, 6.5 Hz, 1H), 7.20 (t, $J = 8.0$ Hz, 2H), 3.86 (s, 3H). HRMS calcd for $[C_{17}H_{12}F_2N_2O_3+H]^+$: 331.0884, Found: 331.0884.

Compound **79** was hydrolyzed by following procedure 2 to get compound **65** as a colorless solid in 19% yield (HPLC purity: 95.1%). TLC $R_f = 0.25$ (40% EtOAc in Hexanes). M. P. = 242–244 °C. ESI-MS *m/z*: 317.0. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.78 (s, 1H), 8.02 (t, $J = 1.7$ Hz, 1H), 7.76 (ddt, $J = 22.6$, 7.8, 1.5 Hz, 2H), 7.56–7.42 (m, 2H), 7.37–7.27 (m, 1H), 7.25–7.13 (m, 2H). HRMS calcd for $[C_{16}H_{10}F_2N_2O_3+H]^+$: 317.07323, Found: 317.07389.

4.6.66. 3-(2-((2,4-Difluorophenyl)amino)oxazol-5-yl)benzoic acid (66) and methyl 3-(2-((2,4-difluorophenyl)amino)oxazol-5-yl) benzoate (80)

By following procedure 4, the title compound **80** was obtained from methyl 3-(2-bromoacetyl)benzoate and 2,4-difluoro-1-*iso*-thiocyanatobenzene as a colorless solid in 52% yield (HPLC purity: 100%). TLC $R_f = 0.35$ (30% EtOAc in Hexanes). M. P. = 193–195 °C. ESI-MS *m/z*: 331.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.14 (s, 1H), 8.22–8.06 (m, 2H), 7.84 (dddd, J = 10.6, 7.8, 1.8, 1.2 Hz, 2H), 7.65–7.51 (m, 2H), 7.32 (ddd, $J = 11.6$, 8.9, 2.9 Hz, 1H), 7.15–7.00 (m, 1H), 3.87 (s, 3H). HRMS calcd for $[C_{17}H_{12}F_2N_2O_3+H]^+$: 331.0884, Found: 331.0883.

Compound **80** was hydrolyzed by following procedure 2 to get compound **66** as a colorless solid in 33% yield (HPLC purity: 95.4%). TLC $R_f = 0.25$ (40% EtOAc in Hexanes). M. P. = 262–264 °C. ESI-MS *m/z*: 317.0. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.12 (s, 1H), 8.21–8.08 (m, 2H), 7.81 (dd, $J = 7.7$, 1.8 Hz, 2H), 7.59–7.47 (m, 2H), 7.32 (ddd, J = 11.6, 8.9, 2.9 Hz, 1H), 7.12–7.05 (m, 1H). HRMS calcd for $[C_{16}H_{10}F_2N_2O_3+H]^+$: 317.07323, Found: 317.07366.

4.6.67. 3-(2-((2,5-Difluorophenyl)amino)oxazol-5-yl)benzoic acid (67) and methyl 3-(2-((2,5-difluorophenyl)amino)oxazol-5-yl) benzoate (81)

By following procedure 4, the title compound **81** was obtained from methyl 3-(2-bromoacetyl)benzoate and 2,5-difluoro-1-*iso*-thiocyanatobenzene as a colorless solid in 51% yield (HPLC purity: 99.1%). TLC $R_f = 0.35$ (30% EtOAc in Hexanes). M. P. = 175–177 °C. ESI-MS *m/z*: 331.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.51 (s, 1H), 8.25–8.10 (m, 2H), 7.87 (dddd, J = 16.0, 7.8, 1.8, 1.2 Hz, 2H), 7.68–7.63 (m, 1H), 7.63–7.56 (m, 1H), 7.29 (ddd, $J = 10.9$, 9.0, 5.1 Hz, 1H), 6.87–6.75 (m, 1H), 3.88 (s, 3H). HRMS calcd for $[C_{17}H_{12}F_2N_2O_3+H]^+$: 331.0884, Found: 331.0882.

Compound **81** was hydrolyzed by following procedure 2 to get compound **67** as a colorless solid in 39% yield (HPLC purity: 99.6%). TLC $R_f = 0.25$ (40% EtOAc in Hexanes). M. P. = 290–292 °C. ESI-MS *m/z*: 317.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.49 (s, 1H), 8.24–8.12 (m, 2H), 7.84 (tt, $J = 7.8$, 1.4 Hz, 2H), 7.64 (s, 1H), 7.55 (t, $J = 7.8$ Hz, 1H), 7.28 (ddd, $J = 11.0$, 9.0, 5.2 Hz, 1H), 6.85–6.77 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.0, 158.1 (dd, $J_{C\text{-}F} = 238.4$, 2.1 Hz), 156.0, 147.8 (dd, $J_{C\text{-}F}$ = 240.4, 2.5 Hz), 143.6, 131.7, 129.4, 128.3 (dd, $J_{C\text{-}F}$ = 26.1, 13.0 Hz), 128.1, 128.0, 126.8, 123.3, 123.2, 116.1 (dd, $J_{C\text{-}F}$ = 21.3, 10.2 Hz), 107.8 (dd, $J_{C\text{-}F}$ = 24.5, 7.5 Hz), 105.9 (d, $J_{C\text{-}F}$ = 30.3 Hz). HRMS calcd for $[C_{16}H_{10}F_2N_2O_3+H]^+$: 317.07323, Found: 317.07387.

4.6.68. 3-(2-((2,3-Difluorophenyl)amino)oxazol-5-yl)benzoic acid (68) and methyl 3-(2-((2,3-difluorophenyl)amino)oxazol-5-yl) benzoate (82)

By following procedure 4, the title compound **82** was obtained from methyl 3-(2-bromoacetyl)benzoate and 2,3-difluoro-1-*iso*-thiocyanatobenzene as a colorless solid in 58% yield (HPLC purity: 96.5%). TLC $R_f = 0.35$ (30% EtOAc in Hexanes). M. P. = 179–181 °C. ESI-MS *m/z*: 331.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.44 (s, 1H), 8.14 (dt, J = 1.8, 0.9 Hz, 1H), 8.03 (t, J = 7.8 Hz, 1H), 7.86 (dddd, $J = 13.7$, 7.8, 1.8, 1.1 Hz, 2H), 7.63–7.57 (m, 2H), 7.18 (tdd, $J = 8.4$, 6.0, 2.1 Hz, 1H), 7.04 (dddd, J = 10.2, 8.6, 7.2, 1.5 Hz, 1H), 3.87 (s, 3H). HRMS calcd for $[C_{17}H_{12}F_2N_2O_3+H]^+$: 331.0884, Found: 331.0889.

Compound **82** was hydrolyzed by following procedure 2 to get compound **68** as a colorless solid in 63% yield (HPLC purity: 99.7%). TLC $R_f = 0.25$ (40% EtOAc in Hexanes). M. P. = 281–283 °C. ESI-MS *m/z*: 317.0. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.44 (s, 1H), 8.16 (td, $J = 1.8$, 0.5 Hz, 1H), 8.03 (ddt, $J = 8.7$, 7.3, 1.6 Hz, 1H), 7.85–7.75 (m 2H), 7.60 (s, 1H), 7.54 (t, $J = 8.4$ Hz, 1H), 7.21–7.13 (m, 1H), 7.07–6.99 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.0, 156.3, 150.1 (dd, $J_{C\text{-}F}$ = 244.2, 10.5 Hz), 143.6, 140.3 (dd, $J_{C\text{-}F}$ = 247.2, 15.0 Hz), 131.7, 129.4, 129.1 (dd, $J_{C\text{-}F} = 8.2$, 2.3 Hz), 128.2, 127.9, 126.8, 124.4 (dd, $J_{C\text{-}F}$ = 8.6, 4.8 Hz), 123.3, 123.2, 115.1 (d, $J_{C\text{-}F} = 2.9$ Hz), 110.0 (d, $J_{C\text{-}F} = 17.1$ Hz). HRMS calcd for $[C_{16}H_{10}F_2N_2O_3+H]^+$: 317.07323, Found: 317.07346.

4.6.69. 4-(2-((2-Fluorophenyl)amino)oxazol-5-yl)benzoic acid (69) and methyl 4-(2-((2-fluorophenyl)amino)oxazol-5-yl)benzoate (83)

By following procedure 4, the title compound **83** was obtained from methyl 4-(2-bromoacetyl)benzoate and 1-fluoro-2-*iso*-thiocyanatobenzene as a colorless solid in 36% yield (HPLC purity: 95%). TLC $R_f = 0.35$ (30% EtOAc in Hexanes). M. P. = 217–219 °C. ESI-MS *m/z*: 313.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.23 (s, 1H), 8.15 (td, J = 8.4, 1.7 Hz, 1H), 8.04–7.98 (m, 2H), 7.73–7.67 (m, 3H), 7.30–7.17 (m, 2H), 7.09–7.02 (m, 1H), 3.86 (s, 3H). HRMS calcd for $[C_{17}H_{13}FN_2O_3+H]^+$: 313.0983, Found: 313.0992.

Compound **83** was hydrolyzed by following procedure 2 to get compound **69** as a colorless solid in 17% yield (HPLC purity: 96.3%). TLC $R_f = 0.25$ (40% EtOAc in Hexanes). M. P. = 267–269 °C. ESI-MS *m/z*: 299.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (s, 1H), 8.15 (td, $J = 8.3$, 1.7 Hz, 1H), 8.03–7.96 (m, 2H), 7.71–7.64 (m, 3H), 7.30–7.17 (m, 2H), 7.10–7.03 (m, 1H). HRMS calcd for $[C_{16}H_{11}FN_2O_3+H]^+$: 299.08265, Found: 299.0827.

4.6.70. 4-(2-((3-Fluorophenyl)amino)oxazol-5-yl)benzoic acid (70) and methyl 4-(2-((3-fluorophenyl)amino)oxazol-5-yl)benzoate (84)

By following procedure 4, the title compound **84** was obtained from methyl 4-(2-bromoacetyl)benzoate and 1-fluoro-3-*iso*-thiocyanatobenzene as an off-white solid in 39% yield (HPLC purity: 99%). TLC $R_f = 0.35$ (30% EtOAc in Hexanes). M. P. = 216–218 °C. ESI-MS *m/z*: 313.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.77 (s, 1H), 8.04–7.99 (m, 2H), 7.74–7.69 (m, 3H), 7.66–7.60 (m, 1H), 7.38–7.32 (m, 2H), 6.82–6.75 (m, 1H), 3.86 (s, 3H). HRMS calcd for $[C_{17}H_{13}FN_2O_3+H]^+$: 313.0983, Found: 313.0990.

Compound **84** was hydrolyzed by following procedure 2 to get compound **70** as a colorless solid in 16% yield (HPLC purity: 96.2%). TLC $R_f = 0.25$ (40% EtOAc in Hexanes). M. P. = 282–284 °C. ESI-MS *m/z*: 299.0. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.75 (s, 1H), 8.01–7.97 (m, 2H), 7.71–7.61 (m, 4H), 7.39–7.31 (m, 2H), 6.79 (ddt, $J = 8.8$, 5.6, 2.8 Hz, 1H). HRMS calcd for $[C_{16}H_{11}FN_2O_3+H]^+$: 299.08265, Found: 299.0829.

4.6.71. 4-(2-((4-Fluorophenyl)amino)oxazol-5-yl)benzoic acid (71) and methyl 4-(2-((4-fluorophenyl)amino)oxazol-5-yl)benzoate (85)

By following procedure 4, the title compound **85** was obtained from methyl 4-(2-bromoacetyl)benzoate and 1-fluoro-4-

*iso*thiocyanatobenzene as a light yellow solid in 28% yield (HPLC purity: 96.7%). TLC R_f = 0.35 (30% EtOAc in Hexanes). M. P. = 229–231 °C. ESI-MS *m/z*: 313.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.52 (s, 1H), 8.03–7.99 (m, 2H), 7.73–7.62 (m, 5H), 7.21–7.14 (m, 2H), 3.86 (s, 3H). HRMS calcd for $[C_{17}H_{13}FN_2O_3+H]^+$: 313.0983, Found: 313.0985.

Compound **85** was hydrolyzed by following procedure 2 to get compound **71** as a colorless solid in 51% yield (HPLC purity: 99.4%). TLC R_f = 0.25 (40% EtOAc in Hexanes). M. P. = 293–295 °C. ESI-MS *m/z*: 299.0. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.53 (s, 1H), 8.01–7.96 (m, 2H), 7.71–7.63 (m, 5H), 7.21–7.14 (m, 2H). HRMS calcd for $[C_{16}H_{11}FN_2O_3+H]^+$: 299.08265, Found: 299.0831.

4.6.72. 4-(2-((2,6-Difluorophenyl)amino)oxazol-5-yl)benzoic acid (72) and methyl 4-(2-((2,6-difluorophenyl)amino)oxazol-5-yl) benzoate (86)

By following procedure 4, the title compound **86** was obtained from methyl 4-(2-bromoacetyl)benzoate and 1,3-difluoro-2-*iso*-thiocyanatobenzene as a colorless solid in 29% yield (HPLC purity: 98.9%). TLC R_f = 0.35 (30% EtOAc in Hexanes). M. P. = 210–212 °C. ESI-MS *m/z*: 331.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.92 (s, 1H), 8.01–7.94 (m, 2H), 7.64–7.59 (m, 2H), 7.56 (s, 1H), 7.34 (q, J = 7.2 Hz, 1H), 7.22 (t, J = 8.2 Hz, 2H), 3.85 (s, 3H). HRMS calcd for $[C_{17}H_{12}F_2N_2O_3+H]^+$: 331.0889, Found: 331.0888.

Compound **86** was hydrolyzed by following procedure 2 to get compound **72** as a colorless solid in 32% yield (HPLC purity: 98.5%). TLC R_f = 0.25 (40% EtOAc in Hexanes). M. P. = 300–302 °C. ESI-MS *m/z*: 317.0. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.89 (s, 1H), 7.98–7.92 (m, 2H), 7.61–7.56 (m, 2H), 7.53 (s, 1H), 7.39–7.30 (m, 1H), 7.26–7.18 (m, 2H). HRMS calcd for $[C_{16}H_{10}F_2N_2O_3+H]^+$: 317.0732, Found: 317.0730.

4.6.73. 4-(2-((2,5-Difluorophenyl)amino)oxazol-5-yl)benzoic acid (73) and methyl 4-(2-((2,5-difluorophenyl)amino)oxazol-5-yl) benzoate (87)

By following procedure 4, the title compound **87** was obtained from methyl 4-(2-bromoacetyl)benzoate and 1,4-difluoro-2-*iso*-thiocyanatobenzene as a colorless solid in 44% yield (HPLC purity: 99.2%). TLC R_f = 0.35 (30% EtOAc in Hexanes). M. P. = 222–224 °C. ESI-MS *m/z*: 331.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.58 (s, 1H), 8.16 (ddd, J = 10.9, 6.7, 3.2 Hz, 1H), 8.05–7.99 (m, 2H), 7.76–7.70 (m, 3H), 7.31 (ddd, J = 10.9, 9.0, 5.2 Hz, 1H), 6.85 (ddt, J = 9.0, 7.9, 3.3 Hz, 1H), 3.86 (s, 3H). HRMS calcd for $[C_{17}H_{12}F_2N_2O_3+H]^+$: 331.0889, Found: 331.0889.

Compound **87** was hydrolyzed by following procedure 2 to get compound **73** as a colorless solid in 31% yield (HPLC purity: 96.4%). TLC R_f = 0.25 (40% EtOAc in Hexanes). M. P. = 292–294 °C. ESI-MS *m/z*: 317.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.56 (s, 1H), 8.16 (ddd, J = 11.0, 6.7, 3.2 Hz, 1H), 8.03–7.96 (m, 2H), 7.73–7.67 (m, 3H), 7.31 (ddd, J = 10.9, 9.0, 5.2 Hz, 1H), 6.90–6.81 (m, 1H). HRMS calcd for $[C_{16}H_{10}F_2N_2O_3+H]^+$: 317.0732, Found: 317.0736.

4.6.74. 2-(2-((2-Fluorophenyl)amino)oxazol-5-yl)benzoic acid (74) and methyl 2-(2-((2-fluorophenyl)amino)oxazol-5-yl)benzoate (88)

By following procedure 4, the title compound **88** was obtained from methyl 2-(2-bromoacetyl)benzoate and 1-fluoro-2-*iso*-thiocyanatobenzene as a colorless solid in 28% yield (HPLC purity: 99.8%). TLC R_f = 0.35 (30% EtOAc in Hexanes). M. P. = 120–122 °C. ESI-MS *m/z*: 313.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.08 (s, 1H), 8.10 (td, J = 8.3, 1.6 Hz, 1H), 7.68–7.59 (m, 3H), 7.46–7.40 (m, 1H), 7.28–7.16 (m, 3H), 7.05 (dddd, J = 8.1, 7.4, 4.9, 1.7 Hz, 1H), 3.79 (s, 3H). HRMS calcd for $[C_{17}H_{13}FN_2O_3+H]^+$: 313.0983, Found: 313.0976.

Compound **88** was hydrolyzed by following procedure 2 to get compound **74** as a colorless solid in 26% yield (HPLC purity: 99.8%). TLC R_f = 0.25 (40% EtOAc in Hexanes). M. P. = 213–215 °C. ESI-MS *m/z*: 299.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.17 (s, 1H), 10.01 (s, 1H), 8.13 (td, J = 8.4, 1.7 Hz, 1H), 7.71–7.65 (m, 1H), 7.64–7.55 (m, 2H), 7.45–7.38 (m, 1H), 7.27–7.15 (m, 3H), 7.07–7.00 (m, 1H). HRMS calcd for $[C_{16}H_{11}FN_2O_3+H]^+$: 299.08265, Found: 299.0825.

4.6.75. Methyl 3-(2-((4-fluorophenyl)(methyl)amino)oxazol-5-yl) benzoate (89)

By following procedure 5, the title compound **89** was obtained from methyl 3-(2-((4-fluorophenyl)amino)oxazol-5-yl)benzoate, **77** as a pale yellow solid in 70% yield (HPLC purity: 99.7%). TLC R_f = 0.30 (25% EtOAc in Hexanes). M. P. = 96–98 °C. ESI-MS *m/z*: 327.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.02–7.98 (m, 1H), 7.80–7.72 (m, 2H), 7.62–7.48 (m, 4H), 7.30–7.21 (m, 2H), 3.85 (s, 3H), 3.48 (s, 3H). HRMS calcd for $[C_{18}H_{15}FN_2O_3+H]^+$: 327.11395, Found: 327.11489.

4.6.76. 3-(2-((4-Fluorophenyl)(methyl)amino)oxazol-5-yl)benzoic acid (90)

By following procedure 2, the title compound **90** was obtained from methyl 3-(2-((4-fluorophenyl)(methyl)amino)oxazol-5-yl) benzoate, **89** as a colorless solid in 49% yield (HPLC purity: 99.0%). TLC R_f = 0.35 (40% EtOAc in Hexanes). M. P. = 215–217 °C. ESI-MS *m/z*: 313.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.00 (t, J = 1.7 Hz, 1H), 7.77 (dt, J = 7.7, 1.4 Hz, 1H), 7.71 (d, J = 7.9 Hz, 1H), 7.59–7.54 (m, 2H), 7.54–7.46 (m, 2H), 7.30–7.23 (m, 2H), 3.50 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.2, 159.3 (d, $J_{C\text{-}F}$ = 242.9 Hz), 159.5 (2C), 144.1 (2C), 139.7 (d, $J_{C\text{-}F}$ = 2.7 Hz), 131.8, 129.5, 128.7, 127.7, 126.6, 125.2 (d, $J_{C\text{-}F}$ = 8.4 Hz), 124.2 (d, $J_{C\text{-}F}$ = 1.9 Hz), 122.9, 115.9 (d, $J_{C\text{-}F}$ = 22.6 Hz), 38.4. HRMS calcd for $[C_{17}H_{13}FN_2O_3+H]^+$: 313.0983, Found: 313.0980.

4.6.77. 3-(2-((4-Fluorophenyl)(isopropyl)amino)oxazol-5-yl) benzoic acid (91)

By following procedure 5, the intermediate compound **91A** was obtained from methyl 3-(2-((4-fluorophenyl)amino)oxazol-5-yl) benzoate, **77** as a yellow viscous liquid in 52% yield (HPLC purity: 97.0%). ESI-MS *m/z*: 355.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.88 (t, J = 1.6 Hz, 1H), 7.75 (dt, J = 7.7, 1.4 Hz, 1H), 7.62–7.58 (m, 1H), 7.51–7.46 (m, 2H), 7.41–7.28 (m, 4H), 4.56 (m, 1H), 3.84 (s, 3H), 1.21 (d, J = 6.7 Hz, 6H).

By following procedure 2, the title compound **91** was obtained from **91A** as a colorless solid in 39% yield (HPLC purity: 98.0%). TLC R_f = 0.30 (30% EtOAc in Hexanes). M. P. = 220–222 °C. ESI-MS *m/z*: 341.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.86 (t, J = 1.7 Hz, 1H), 7.73 (dt, J = 7.7, 1.4 Hz, 1H), 7.58 (ddd, J = 7.8, 1.9, 1.2 Hz, 1H), 7.49–7.44 (m, 2H), 7.41–7.36 (m, 2H), 7.35–7.28 (m, 2H), 4.55 (m, 1H), 1.21 (d, J = 6.7 Hz, 6H). HRMS calcd for $[C_{19}H_{17}FN_2O_3+H]^+$: 341.1296, Found: 341.1293.

4.6.78. 3-(2-((4-Fluorophenyl)amino)oxazol-5-yl)-*N*-methylbenzamide (92)

A solution of methyl 3-(2-((4-fluorophenyl)amino)oxazol-5-yl) benzoate, **77** (80 mg, 0.26 mmol) and 2 M solution of methylamine (1.2 ml, 2.56 mmol) in methanol was heated in s sealed tube at 60 °C for 24 h, Then reaction mixture was concentrated *in vacuo* and the crude product was purified on Teledyne Isco Combiflash® R_f purification machine to afford 3-(2-((4-fluorophenyl)amino)oxazol-5-yl)-*N*-methylbenzamide, **92** as a colorless solid in 53% yield (HPLC purity: 100%). M. P. = 231–233 °C. ESI-MS *m/z*: 312.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.43 (s, 1H), 8.52 (d, J = 4.8 Hz, 1H), 8.06–8.03 (m, 1H), 7.73–7.63 (m, 4H), 7.54–7.48 (m, 2H), 7.21–7.13 (m, 2H), 2.81 (d, J = 4.5 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.3, 157.0 (d, $J_{C\text{-}F}$ = 238.5 Hz), 156.6 (2C), 143.2 (2C), 135.7 (d, $J_{C\text{-}F}$ = 2.2 Hz), 135.3, 129.0, 128.1, 125.3, 124.8, 123.2 (d, $J_{C\text{-}$

$_F$ = 2.2 Hz), 121.4, 118.1 (d, J_{C-F} = 7.7 Hz), 115.5 (d, J_{C-F} = 22.4 Hz), 26.3. HRMS calcd for $[C_{17}H_{14}FN_3O_2+H]^+$: 312.11428, found: 312.11382.

4.6.79. N-(4-fluorophenyl)-5-(3-(3-methyl-1,2,4-oxadiazol-5-yl) phenyl)oxazol-2-amine (93)

3-(2-((4-Fluorophenyl)amino)oxazol-5-yl)benzoic acid, **63** (52 mg, 0.17 mmol) and (E)-*N'*-hydroxyacetimidamide (12.9 mg, 0.17 mmol) were dissolved in anhydrous DMF (2 mL) at room temperature under nitrogen atmosphere. Triethylamine (53 mg, 0.52 mmol) was added to reaction mixture followed by the dropwise addition of propylphosphonic anhydride (139 mg, 0.44 mmol). Then the reaction mixture was heated at 80 °C for 5 h. The reaction mixture was allowed to cool to room temperature and poured onto ice water and extracted with EtOAc (3x). The combined organic layer was washed with saturated solution of $NaHCO_3$ (twice), brine and dried over Na_2SO_4. The filtrate was concentrated *in vacuo* and the crude product was purified on Teledyne Isco Combiflash® R_f purification machine to afford *N*-(4-fluorophenyl)-5-(3-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)oxazol-2-amine, **93** as a white solid in 17% yield (HPLC purity: 99%). M. P. = 237–239 °C. ESI-MS *m/z*: 337.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.50 (s, 1H), 8.27 (t, J = 1.7 Hz, 1H), 7.96 (ddd, J = 7.7, 1.7, 1.1 Hz, 1H), 7.90 (ddd, J = 7.9, 1.9, 1.1 Hz, 1H), 7.71–7.63 (m, 4H), 7.21–7.14 (m, 2H), 2.44 (s, 3H). HRMS calcd for $[C_{18}H_{13}FN_4O_2+H]^+$: 337.10953, found: 337.10869.

4.6.80. 3-[2-(4-Fluoroanilino)oxazol-5-yl]benzonitrile (94)

By following procedure 4, the title compound **94** was obtained from 3-(2-bromoacetyl)benzonitrile and 1-fluoro-4-*iso*-thiocyanatobenzene as a light yellow solid in 36% yield (HPLC purity: 96%). M. P. = 237–239 °C. ESI-MS *m/z*: 280.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.46 (s, 1H), 8.04 (td, J = 1.7, 0.6 Hz, 1H), 7.85 (ddd, J = 7.8, 1.8, 1.3 Hz, 1H), 7.71 (dt, J = 7.7, 1.4 Hz, 1H), 7.68–7.61 (m, 4H), 7.21–7.14 (m, 2H). HRMS calcd for $[C_{16}H_{10}FN_3O + H]^+$: 280. 08807, found: 280. 08798.

4.6.81. N-(4-fluorophenyl)-5-[3-(1H-tetrazol-5-yl)phenyl]oxazol-2-amine (95)

A solution of 3-[2-(4-fluoroanilino)oxazol-5-yl]benzonitrile, **94** (90 mg, 0.33 mmol), sodium azide (63.5 mg, 0.97 mmol) and ammonium chloride (52.3 mg, 0.97 mmol) in DMF (2 mL) was heated at 120 °C under nitrogen atmosphere overnight. The reaction mixture was cooled to room temperature, water was added and it was extracted with EtOAc (3 x). Combined organic layer was washed with brine and dried over Na_2SO_4. Drying agent was filtered off and the filtrate was concentrated under *vacuum* to obtain the crude product. Crude product was purified using Teledyne Isco Combiflash® R_f purification machine to afford *N*-(4-fluorophenyl)-5-[3-(1H-tetrazol-5-yl)phenyl]oxazol-2-amine, **95** as an off-white sticky solid in 25% yield (HPLC purity: 99.2%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.45 (s, 1H), 8.27 (t, J = 1.6 Hz, 1H), 7.92–7.88 (m, 1H), 7.77 (ddd, J = 7.9, 1.9, 1.2 Hz, 1H), 7.70–7.62 (m, 3H), 7.59 (s, 1H), 7.21–7.14 (m, 2H). HRMS calcd for $[C_{16}H_{11}FN_6O + H]^+$: 323.10511, found: 323.10537.

4.6.82. 5-[3-(Aminomethyl)phenyl]-N-(4-fluorophenyl)oxazol-2-amine (96)

By following procedure 3, the title compound **96** was obtained from 3-[2-(4-Fluoroanilino)oxazol-5-yl]benzonitrile (**94**) as a light yellow solid in 52% yield (HPLC purity: 99.2%). M. P. = 194–196 °C. ESI-MS *m/z*: 284.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.35 (s, 1H), 7.69–7.62 (m, 2H), 7.58 (s, 1H), 7.44–7.39 (m, 2H), 7.35 (t, J = 7.6 Hz, 1H), 7.23 (dt, J = 7.7, 1.4 Hz, 1H), 7.19–7.13 (m, 2H), 3.75 (s, 2H), 1.95 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.9 (d, J_{C-F} = 238.4 Hz), 156.4 (2C), 145.1, 144.0 (2C), 135.9 (d, J_{C-F} = 2.2 Hz), 128.7, 127.8, 125.9, 122.2 (d, J_{C-F} = 3.1 Hz), 121.2, 120.5, 118.0 (d, J_{C-F} = 7.7 Hz), 115.4 (d, J_{C-F} = 22.4 Hz), 45.5. HRMS calcd for $[C_{16}H_{14}FN_3O + H]^+$: 284. 11937, found: 284. 11889.

4.6.83. N-[[3-[2-(4-fluoroanilino)oxazol-5-yl]phenyl]methyl] acetamide (97)

A solution of 5-[3-(aminomethyl)phenyl]-*N*-(4-fluorophenyl) oxazol-2-amine, **96** (56 mg, 0.20 mmol) and DMAP (26.6 mg, 0.22 mmol) in anhydrous CH_2Cl_2 (4 mL) under nitrogen atmosphere was cooled to −15 °C and acetic anhydride (0.021 mL, 0.22 mmol) was added dropwise. After stirring at −15 °C for 3 h, the reaction mixture was concentrated *in vacuo* and taken up in EtOAc. The organic layer was washed with water (3x), brine and dried over Na_2SO_4. The filtrate was concentrated *in vacuo* and the crude product was purified on Teledyne Isco Combiflash® R_f purification machine to afford *N*-[[3-[2-(4-fluoroanilino)oxazol-5-yl]phenyl] methyl]acetamide, **97** as a white solid in 52% yield (HPLC purity: 99.7%). M. P. = 226–228 °C. ESI-MS *m/z*: 326.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.36 (s, 1H), 8.37 (t, J = 5.9 Hz, 1H), 7.68–7.62 (m, 2H), 7.49–7.42 (m, 3H), 7.38 (td, J = 7.5, 0.9 Hz, 1H), 7.20–7.12 (m, 3H), 4.28 (d, J = 5.9 Hz, 2H), 1.89 (s, 3H). HRMS calcd for $[C_{18}H_{16}FN_3O_2+H]^+$: 326.12993, found: 326.12964.

4.6.84. N-[3-[2-(4-fluoroanilino)oxazol-5-yl]phenyl]acetamide (98)

By following procedure 4, the title compound **98** was obtained from *N*-[3-(2-bromoacetyl)phenyl]acetamide and 1-fluoro-4-*iso*-thiocyanatobenzene as colorless solid in 54% yield (HPLC purity: 99.8%). M. P. = 235–237 °C. ESI-MS *m/z*: 312.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.38 (s, 1H), 10.02 (s, 1H), 7.98–7.94 (m, 1H), 7.69–7.62 (m, 2H), 7.38–7.25 (m, 4H), 7.19–7.12 (m, 2H), 2.06 (s, 3H). HRMS calcd for $[C_{17}H_{14}FN_3O_2+H]^+$: 312.11428, found: 312.11376.

4.6.85. 5-(3-Aminophenyl)-N-(4-fluorophenyl)oxazol-2-amine (99)

4N Hydrochloric acid (0.65 mL, 2.58 mmol) was added to a solution of *N*-[3-[2-(4-fluoroanilino)oxazol-5-yl]phenyl]acetamide, **98** (134 mg, 0.43 mmol) in ethanol (5 mL) and the reaction mixture was allowed to reflux for 4 h. Then the reaction mixture was allowed to reach room temperature and 1N NaOH was added till the solution attained pH = 12, then aqueous layer was extracted with EtOAc (thrice). The combined organic layer was washed with water, brine and dried over Na_2SO_4. The filtrate was concentrated *in vacuo* and the crude product was purified on Teledyne Isco Combiflash® R_f purification machine to obtain 5-(3-aminophenyl)-*N*-(4-fluorophenyl)oxazol-2-amine, **99** as an off-white solid in 38% yield (HPLC purity: 99.4%). M. P. = 188–190 °C. ESI-MS *m/z*: 270.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.26 (s, 1H), 7.67–7.61 (m, 2H), 7.24 (s, 1H), 7.19–7.11 (m, 2H), 7.05 (t, J = 7.9 Hz, 1H), 6.77–6.72 (m, 2H), 6.48 (ddd, J = 8.0, 2.1, 1.0 Hz, 1H), 5.19 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.9 (d, J_{C-F} = 238.2 Hz), 156.1 (2C), 149.0, 144.5 (2C), 135.9 (d, J_{C-F} = 2.2 Hz), 129.5, 128.5, 121.4 (d, J_{C-F} = 3.7 Hz), 118.0 (d, J_{C-F} = 7.7 Hz), 115.4 (d, J_{C-F} = 22.5 Hz), 113.1, 110.5, 107.7. HRMS calcd for $[C_{15}H_{12}FN_3O + H]^+$: 270.10372, found: 270.10373.

4.6.86. N-(4-fluorophenyl)-N-methyl-5-(3-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)oxazol-2-amine (100)

By following the same procedure as **93**, the title compound **100** was obtained from 3-(2-((4-fluorophenyl)(methyl)amino)oxazol-5-yl)benzoic acid (**90**) as an off-white solid in 60% yield (HPLC purity: 99.5%). M. P. = 103–105 °C. ESI-MS *m/z*: 351.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.15 (td, J = 1.8, 0.5 Hz, 1H), 7.92 (ddd, J = 7.7, 1.7, 1.1 Hz, 1H), 7.79 (ddd, J = 7.9, 1.8, 1.2 Hz, 1H), 7.67–7.61 (m, 2H), 7.61–7.55 (m, 2H), 7.31–7.24 (m, 2H), 3.52 (s, 3H), 2.43 (s, 3H). HRMS calcd for $[C_{19}H_{15}FN_4O_2+H]^+$: 351.12518, found:

351.12518.

4.6.87. 3-[2-(4-Fluoro-N-methyl-anilino)oxazol-5-yl]-N-methyl-benzamide (101)

By following the same procedure as **92**, the title compound **101** was obtained from methyl 3-(2-((4-fluorophenyl)(methyl)amino) oxazol-5-yl)benzoate (**89)** as a light brown solid in 62% yield (HPLC purity: 99.9%). M. P. = 135–137 °C. ESI-MS *m/z*: 326.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.48 (d, J = 4.7 Hz, 1H), 7.94 (t, J = 1.7 Hz, 1H), 7.69–7.54 (m, 4H), 7.50–7.44 (m, 2H), 7.30–7.22 (m, 2H), 3.51 (s, 3H), 2.79 (d, J = 4.5 Hz, 3H). HRMS calcd for $[C_{18}H_{16}FN_3O_2+H]^+$: 326.12993, found: 326.12962.

4.6.88. 3-(2-(2-Fluorophenyl)oxazol-5-yl)benzoic acid (102)

Iodine (313 mg, 1.23 mmol) was added to a microwave vessel containing a solution of 3-(2-bromoacetyl)benzoic acid (150 mg, 0.62 mmol), 2-fluorobenzylamine (93 mg, 0.74 mmol) and potassium carbonate (341 mg, 2.48 mmol) in DMF (2 mL) at room temperature under argon atmosphere. The resulted reaction mixture was heated at 80 °C for 2 h under microwave conditions. The reaction mixture was washed with aq. sodium thiosulfate and extracted with CH_2Cl_2 (thrice). The combined organic layer was dried over anhydrous Na_2SO_4 and the solid was filtered off. Solvent was removed from the filtrate *in vacuuo* and the crude product was purified on Teledyne Isco Combiflash® R_f purification machine to afford 3-(2-(2-fluorophenyl)oxazol-5-yl)benzoic acid (**102**) as an off-white solid in 4% yield (HPLC purity: 97.8%). TLC R_f = 0.15 (60% EtOAc in Hexanes). M. P. = 220–222 °C. ESI-MS *m/z*: 284.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 (t, J = 1.8 Hz, 1H), 8.13 (td, J = 7.7, 1.8 Hz, 1H), 8.05–7.99 (m, 2H), 7.94 (dt, J = 7.7, 1.4 Hz, 1H), 7.67–7.56 (m, 2H), 7.48–7.36 (m, 2H).

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Notes

Animal research conducted only after appropriate ethical consideration and reviewed by Pharmaron's IACUC (Institutional Animal Care and Use Committee). This review, identical to the procedures used in the US and Europe, ensures that a high level of care is provided to all animals used, and that a scientifically appropriate and validated alternative to the use of animals is not available.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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