Synthesis and biological evaluation of novel 4-(6-substituted quinolin-4-yl)-N-arylthiazol-2-amine derivatives as potential antimicrobial agents

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Abstract

Cyclocondensation reaction of 4-(2-bromoacetyl)quinolin-1-ium bromide (**4a-d**) with substituted arylthiourea, (**5a-g**) afforded 4-(6-substituted quinolin-4-yl)-N-aryl/pyridyl thiazol-2-amine (**6a-ab**). These newly synthesized derivatives were evaluated for *in vitro* antibacterial activity against *Escherichia coli* (NCIM 2574), *Proteus mirabilis* (NCIM 2388) (Gram negative strains) *Bacillus subtilis* (NCIM 2063), *Staphylococcus albus* (NCIM 2178) (Gram positive strains) and *in vitro* antifungal activity against *Aspergillus niger* (ATCC 504) and *Candida albicans* (NCIM 3100). Compounds **6a**, **6b**, **6d**, **6f**, **6k** and **6l** showed moderate to good antibacterial activity against *S. albus*. Ten derivatives **6c**, **6q**, **6r**, **6s**, **6t**, **6v**, **6w**, **6x**, **6y** and **6aa**, showed moderate to good activity against *A. niger*. N-[4-(Quinolin-4-yl)-1,3-thiazol-2-yl]pyridin-2-amine presented comparable activity against *A. niger* with respect to standard drug Rouconazole.

Keywords: Quinoline, 2-Amino Thiazole, Antibacterial activity, Antifungal activity

1 | INTRODUCTION

WHO has warned the misuse of antibiotics during the COVID-19 pandemic that could increase the antimicrobial drug resistance[1] which may become future public health emergencies.

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Accordingly, the prevention and treatment of infections will become more challenging.[2,3] Two or more bioactive pharmacophore tethered scaffolds plays a vital role in the search of new lead compounds.[4] Nitrogen and sulphur containing pharmacophores are the valuable sources that are utilized in the field of lead identification and development.[5,6]

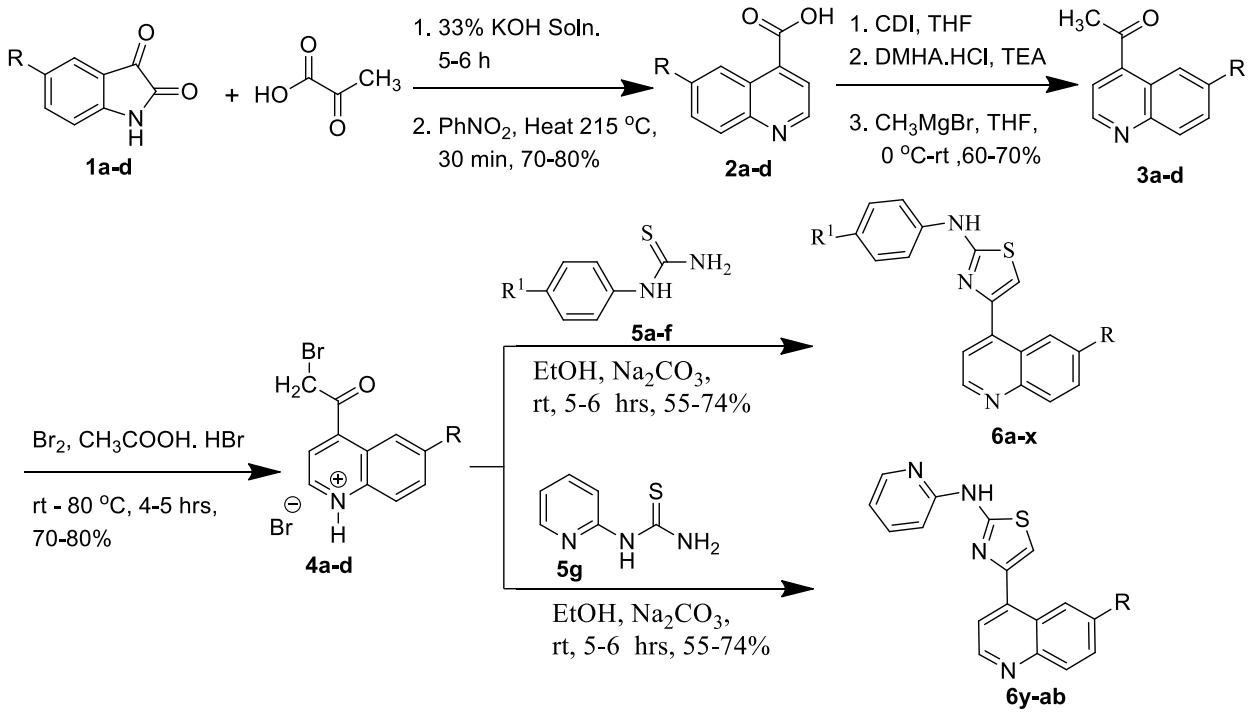
Natural and synthetic quinoline nucleus containing compounds endowed a broad spectrum of biological activities.[7,8] Quinoline derivatives displayed vital pharmacological activities such as antimalarial,[9,10] antimicrobial,[11,12] antifungal,[13,14] antitubercular,[15,16] anticancer,[17,18] antiviral,[19,20] anti-inflammatory and COX inhibitors,[21,22] carbonic anhydrase inhibitors,[23] antileishmanial,[24] PIM inhibitors,[25] anticonvulsant and antihypertensive[26] activities. Thiazole is the important scaffold of several bioactive natural products[27,28] and reported broad spectrum of biological activity such as antibacterial,[29,30] inflammatory,[31] antifungal,[32,33] antitubercular,[34,35] antimalarial,[36] anticancer,[37] antiviral,[38] and CNS active agents.[39] The quinoline tethered azoles are the significant architecture that has received attention due to their potential biological activity.[40-43] Clubbed thiazolyl-quinoline derivatives are known for antimicrobial,[44] antibacterial,[45] antiviral,[46] antifungal and anticancer[47] activities, that have made them prominent target for new antimicrobial agents.

Owing to the significant biological activities of quinoline and thiazole derivatives, we report herein the synthesis and antimicrobial evaluation of 4-(6-substitutedquinolin-4-yl)-N-arylthiazol-2-amine derivatives.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

The synthetic route for 4-(6-substitutedquinolin-4-yl)-N-arylthiazol-2-amine derivatives **6a-ab** is presented in Scheme 1. 1-(6-substituted quinolin-4-yl)ethanone[48] **3a-d** upon reaction with bromine in HBr in acetic acid (30% solution) gave 4-(2-bromoacetyl)-6-substituted quinolin-1-ium bromide **4a-d**. Bromo compounds **4a-d** upon cyclocondensation reaction with substituted arylthiourea, **5a-g** and sodium carbonate in ethanol gave 4-(6-substituted quinolin-4-yl)-N-arylthiazol-2-amine, **6a-ab**. The structure of newly synthesized quinolinyl-thiazole was confirmed by ^{1}H NMR, ^{13}C NMR and Mass spectral analysis. All the synthesized compounds were evaluated for antibacterial and antifungal activity.



Compd.	R	R^1	Compd.	R	R^1	Compd.	R	R^1	Compd.	R	R^1	Compd.	R
6a	H	H	**6g**	Br	H	**6m**	Cl	H	**6s**	F	H	**6y**	**H**
6b	H	CH_3	**6h**	Br	CH_3	**6n**	Cl	CH_3	**6t**	F	CH_3	**6z**	**Br**
6c	H	OCH_3	**6i**	Br	OCH_3	**6o**	Cl	OCH_3	**6u**	F	OCH_3	**6aa**	**Cl**
6d	H	Br	**6j**	Br	Br	**6p**	Cl	Br	**6v**	F	Br	**6ab**	**F**
6e	H	Cl	**6k**	Br	Cl	**6q**	Cl	Cl	**6w**	F	Cl		
6f	H	F	**6l**	Br	F	**6r**	Cl	F	**6x**	F	F		

Scheme 1: Synthetic route of 4-(6-substituted quinolin-4-yl)-N-arylthiazol-2-amine, **6a-ab**

The structure of 4-(6-substituted quinolin-4-yl)-N-aryl/pyridyl thiazol-2-amine, **6a-ab** was confirmed using spectral analysis. The structure of N-(4-methoxyphenyl)-4-(quinolin-4-yl)thiazol-2-amine, **6c** is presented in Figure 1. The ^{1}H NMR spectrum of **6c** revealed a singlet for methoxy proton attached to phenyl ring at δ 3.74. Two doublets at δ 7.63 and δ 6.96 (J = 9.1 Hz) integrated for two protons each are assigned to for C-2, C-6 and C-3,C-5 protons of phenyl ring, respectively. N-H and thiazole-H protons appeared at δ 10.46 and 7.96, respectively. The C-2 and C-3 protons of quinoline ring appeared as doublet with coupling constant J = 5.7 Hz at δ 9.29 and 8.29, respectively. The four quinoline ring protons of C-5, C-6, C-7 and C-8 resonated between δ 9.13-7.96. The ^{13}C NMR spectrum of compound **6c** displayed the methoxy carbon at δ 55.73. The four signals at δ 155.08, 134.18, 119.67 and 114.83 are assigned to C-4′, C-1′, C-2′ C-6′ and C-3′ C-5′ aromatic carbons, respectively. The three carbons of thiazole ring appeared at δ 165.10, 145.36 and 115.93 corresponds to thiazole-C-2″, C-4″ and C-5″ carbons, respectively.

The nine carbons of quinoline ring C-9, C-2, C-4, C-7, C-8, C-6, C-5, C-10 and C-3 resonated at δ 148.07, 146.31, 140.34, 134.58, 129.66, 128.01, 125.77, 122.70 and 120.94, respectively. Structure of compound **6c** was further confirmed by molecular ion peaks (HRMS) at *m/z* = 334.1013 $(M+H)^+$. Structure of all synthesized compounds was confirmed accordingly.

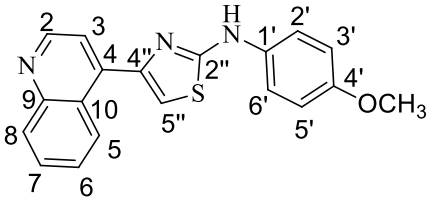


Figure 1: Structure of compound **6c**.

2.2 | Antimycobacterial activity

Newly synthesized 4-(6-substituted quinolin-4-yl)-N-aryl/pyridyl thiazol-2-amine, **6a-ab** were screened for antibacterial activity against Gram-negative bacteria *E. coli* and *P. mirabilis* and Gram-positive bacteria *B. subtilis* and *S. albus* using the well diffusion method.[49,50] Standard drug Streptomycin and DMSO were used as positive and negative control, respectively. The *in vitro* antifungal activity was performed against *A. niger* and *A. candida* using well diffusion method.[49,50] The antifungal drugs Fluconazole and Ravuconazole were used as reference. All the test solutions were prepared in DMSO at 1000 µg/mL concentrations and the wells were filled with 80 µL (80 µg) of the samples. The result of antimicrobial activity in zone of inhibition (mm) has been presented in **Table 1**.

The antimicrobial activity result analysis of 4-(6-substituted quinolin-4-yl)-N-aryl/pyridyl thiazol-2-amine, **6a-ab** revealed that, Against *E. coli* compound **6k** showed moderate activity whereas other compounds were found less active. Against *P. mirabilis* and *B. subtilis* all tested compounds were found less active. Against *S. albus*, compounds **6a**, **6f**, **6k** and **6l** showed moderate activity with MIC 125 µg/mL, whereas compounds **6b** and **6d** showed good activity with MIC 62.5 µg/mL.

The preliminary antifungal activity (**Table 1**) showed that, most of the 4-(6-substituted quinolin-4-yl)-N-aryl/pyridyl thiazol-2-amine derivatives presented moderate to good antifungal activity. The convincing antifungal activities against both fungal strains of compounds **6a-ab** lead us to determine the minimum inhibitory concentration (MIC). To further explore this class of lead molecules, we screened the compounds **6a-ab** for a dose dependent way with the concentrations

range from 500 to 3.90 μg/mL. The *in vitro* antifungal screening results MIC (μg/mL) of synthesized compounds **6a-ab** has been presented in **Table 2**.

Table 1: Antimicrobial activity in zone of inhibition (mm) of compounds **6a-ab**

Compd.	R	R^1	*E. coli*	*P. mirabilis*	*B. subtilis*	*S. albus*	*A. candida*	*A. niger*
6a	H	H	9.2	10.8	9.8	**14.5**	12.25	11.6
6b	H	4-CH_3	10.2	10.4	9.2	**19.75**	**13.4**	10.8
6c	H	4-OCH_3	9.2	11.2	9.8	10.4	**15.2**	**15.4**
6d	H	4-Br	10.4	10.2	11.25	**17.6**	10.4	10.2
6e	H	4-Cl	10.2	9.4	10	11.25	9.8	11.2
6 f	H	4-F	10	10	10.4	**16.6**	9.0	10.8
6g	Br	H	9.6	10.5	10.2	9.0	11.8	12
6h	Br	4-CH_3	9.6	10.2	9.8	9.0	8.8	10.2
6i	Br	4-OCH_3	8.5	10.5	10.6	12.5	10.6	9.8
6*J*	Br	4-Br	8.2	10.8	10.4	9.0	11.75	10.8
6k	Br	4-Cl	**13.8**	9.75	9.2	**14.8**	11	11.2
6l	Br	4-F	11	10.25	11.6	13	11.4	11
6m	Cl	H	9.8	9.6	9.5	10.75	9	10
6n	Cl	4-CH_3	9.4	9.0	9.8	11.75	9.8	11.6
6o	Cl	4-OCH_3	10.6	9.0	10	9.8	12.2	10.2
6p	Cl	4-Br	9.6	10.6	9	**14.6**	12.6	10.6
6q	Cl	4-Cl	8.8	10.4	9.75	9.8	12	**16.6**
6r	Cl	4-F	11.16	11.8	10.4	10.6	12	**14.2**
6s	F	H	9.6	11	10.6	9.8	**14.8**	**14**
6t	F	4-CH_3	10.4	10.6	10.2	10.5	**15.4**	**13.4**
6v	F	4-Br	8.8	10.8	10	**13.6**	12	**15.6**
6w	F	4-Cl	11.6	11.8	14.8	10.2	12.8	**14.2**
6x	F	4-F	9	12.4	10.6	10.6	10.8	**15.4**
6y	H	-	9.8	11	10.2	12.2	**20.2**	**23.4**
6z	Br	-	8.8	9	8.4	12.25	9.6	12
6aa	Cl	-	9.6	10.25	10	9.25	12	**14.8**
6ab	F	-	10	10.6	10.4	12.5	12.4	**16.2**
Streptomycin			25.0	18.52	21.6	21.6	NA	NA
Fluconazole			NA	NA	NA	NA	20.25	18.35
Ravuconazole			NA	NA	NA	NA	28.64	20.18

Table 2: Antimicrobial activity in Minimum Inhibitory Concentration (μg/mL) of compounds **6a-ab**

Compd.	R	R^1	*E. coli*	*P. mirabilis*	*B. subtilis*	*S. albus*	*A. Candida*	*A. niger*
6a	H	H	>250	>250	>250	**125**	>250	>250
6b	H	4-CH_3	>250	>250	>250	**62.5**	**125**	>250
6c	H	4-OCH_3	>250	>250	>250	>250	**62.5**	**62.5**
6d	H	4-Br	>250	>250	>250	**62.5**	>250	>250
6e	H	4-Cl	>250	>250	>250	>250	>250	>250
6 f	H	4-F	>250	>250	>250	**125**	>250	>250
6g	Br	H	>250	>250	>250	>250	>250	>250
6h	Br	4-CH_3	>250	>250	>250	>250	>250	>250
6i	Br	4-OCH_3	>250	>250	>250	>250	>250	>250
6*J*	Br	4-Br	>250	250	250	>250	>250	>250
6k	Br	4-Cl	250	>250	>250	**125**	>250	>250
6l	Br	4-F	>250	>250	>250	**125**	>250	>250
6m	Cl	H	>250	>250	>250	>250	>250	>250
6n	Cl	4-CH_3	>250	>250	>250	>250	>250	>250
6o	Cl	4-OCH_3	>250	>250	>250	>250	>250	>250
6p	Cl	4-Br	>250	>250	>250	>250	>250	>250
6q	Cl	4-Cl	>250	>250	>250	>250	>250	**62.5**
6r	Cl	4-F	>250	>250	>250	>250	>250	**125**
6s	F	H	>250	>250	>250	>250	**125**	**125**
6t	F	4-CH_3	>250	>250	>250	>250	**125**	**125**
6v	F	4-Br	>250	>250	>250	>250	>250	**62.5**
6w	F	4-Cl	>250	>250	>250	>250	>250	**125**
6x	F	4-F	>250	>250	>250	>250	>250	**125**
6y	H	-	>250	>250	>250	>250	**31.25**	**31.25**
6z	Br	-	>250	>250	>250	>250	>250	>250
6aa	Cl	-	>250	>250	>250	>250	>250	**250**
6ab	F	-	>250	>250	>250	>250	>250	**125**
Streptomycin			7.81	7.81	7.81	7.81	NA	NA
Fluconazole			NA	NA	NA	NA	7.81	7.81
Ravuconazole			NA	NA	NA	NA	7.81	31.25

The result analysis of antifungal activity presented in **Table 2** provided some lead compounds that showed good activity against *A. niger*. It is notable that the compounds **6c**, **6q**, **6v** and **6y** recorded two-fold less activity against *A. niger* with respect to the standard drug Ravuconazole.

The structure activity relationship analysis revealed that, amongst the N-aryl-4-(quinolin-4-yl)thiazol-2-amine (**6a-f**), the compound **6b** (R = H, R^1 = CH_3) showed moderate activity against *A. candida* and was less active against *A. niger*. The compound **6c** (R = H, R^1 = OCH_3) showed good activity against both fungal strains with MIC 62.5 µg/mL. Compounds **6a**, **6d**, **6e**, **6f** found less active against both fungal strains. From compounds N-aryl-4-(6-bromoquinolin-4-yl)thiazol-2-amine (**6g-l)** all six derivatives were found less active against both fungal strains. Amongst N-aryl-4-(6-chloroquinolin-4-yl)thiazol-2-amine (**6m-r)**, compound **6q** (R = Cl, R^1 = Cl) reported good activity against *A. niger* with MIC 62.5 µg/mL which was twofold less than the standard drug Ravuconazole. Compound **6r** (R = Cl, R^1 = F) showed moderate activity against *A. niger*. From the compounds N-aryl-4-(6-bromoquinolin-4-yl)thiazol-2-amine (**6-x)**, compounds **6s** (R = F, R^1 = H) and **6t** (R = F, R^1 = CH_3) showed moderate activity against both fungal strains. Compounds **6v** (R = F, R^1 = Br) and **6x** (R = F, R^1 = F) showed good activity against *A. niger* with MIC 62.5 µg/mL however, were found less active against *A. candida*. Compound **6w** (R = F, R^1 = Cl) showed moderate activity against *A. niger* strain. Among the compounds 4-(6-substituted quinolin-4-yl)-N-(pyridin-2-yl)thiazol-2-amine, **6y-ab,** with respect to standard drug Ravuconazole, compound **6y** (R = H) reported comparable activity against *A. niger* and good activity against *A. candida* with MIC 31.25µg/mL. Compound **6ab** (R = F) showed moderate activity against *A. niger* strain with MIC 125 µg/mL.

It is worth mentioning that, amongst the twenty eight derivatives of 4-(6-substituted quinolin-4-yl)-N-aryl/pyridyl thiazol-2-amine, **6a-ab**, the 6-chloroquinoline-4-yl at 4-position and 4-chlorophenyl aniline at 2-position of thiazole (**6q**), 6-fluoroquinoline-4-yl at 4-position and 4-bromophenyl aniline at 2-position of thiazole (**6v**) reported good activity against *A. niger*. Similarly quinoline-4-yl at 4-position and 4-methoxyphenyl aniline (**6c**) or pyridin-4-yl amine (**6y**) at 2-position of thiazole showed good activity against *A. candida* and *A. niger* strains. Compound **6y** showed comparable activity against *A. niger* with respect to the standard drug Ravuconazole. It was noticed that when R substituent was fluoro, all the compounds reported moderate to good activity against *A. niger*.

3 | CONCLUSIONS

In conclusion, new derivatives of 4-(6-substituted quinolin-4-yl)-N-aryl/pyridyl thiazol-2-amine (**6a-ab**) have been synthesized and evaluated for antibacterial and antifungal activities. Ten thiazolyl quinoline derivatives reported good activity against *A. niger*, and five reported

moderate to good activity against *C. albicans* with MIC 31.25-125 µg/mL concentration. Six derivatives showed good antibacterial activity against *S. albus*. Compounds N-(4-methoxyphenyl)-4-(quinolin-4-yl)-1,3-thiazol-2-amine (**6c**) and N-[4-(quinolin-4-yl)-1,3-thiazol-2-yl]pyridin-2-amine, (**6y**) presented good activity against both fungal strains. It is concluded that, 6-fluoro substituted quinoline derivatives are more effective against fungal strains.

4 | EXPERIMENTAL

The solvents and chemicals used were laboratory grade and purified as per literature methods. All the reactions were monitored by thin-layer chromatography (TLC). TLC was performed on Merck 60 F-254 silica gel plates with visualization by UV light. Compounds were purified by column chromatography was performed on silica gel (100–200 mesh) supplied by Acme Chemical Co. (Mumbai, Maharashtra, India). Melting points were determined in capillary tubes in silicon oil bath using a Veego melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on BRUKER ADVANCE II 500 NMR spectrometer (Bruker Instruments Inc., Billerica, MA, USA) at either 500-MHz (^{1}H NMR) and 126-MHz (^{13}C NMR) spectrometer instruments. HRMS spectra were recorded on Bruker Compass Data Analysis 4.2 and the theoretical HRMS was calculated for M+H.

4.1 | General procedure for synthesis of 2-bromo-1-(6-substituted quinolin-4-yl)ethanone, (**4a-d**)

To the ice cold solution of 1-(6-substitutes quinolin-4-yl) ethanone (**3a-d**)[43] in 35% hydrobromic acid in acetic acid bromine was added slowly for 10-15 minutes. After addition was over reaction mixture was stirred at room temperature for 10-15 min followed by the reaction was stirred at 45 °C for 1-2 h and at 80 °C for 2 h. Progress of reaction was monitored by TLC. After complete conversion, reaction mixture was cooled to the room temperature and poured in diethyl ether. The solid product obtained was filtered and washed with diethyl ether furnished 2-bromo-1-(6-substituted quinolin-4-yl)ethanone (**4a-d**) as pure product with good yields.

4.2 | General procedure for synthesis of 4-(6-substituted quinolin-4-yl)-N-aryl/pyridyl thiazol-2-amine (**6a-ab**)

A solution of 2-bromo-1-(6-substituted quinolin-4-yl)ethanone (**4a-d**) and aryl / 2-pyridyl thiourea (**5a-g**) in ethanol was stirred at 25-30 °C for 5-6 h (TLC). After completion of reaction, the product was filtered and washed with chilled ethanol and dried in oven at 50-60 °C for 2-4 h gave 4-(6-substituted quinolin-4-yl)-N-aryl/pyridyl thiazol-2-amine, **6a-ab**.

4.2.1 | N-Phenyl-4-(quinolin-4-yl)-1,3-thiazol-2-amine (6a)

MF: $C_{18}H_{13}N_3S$; Color: Orange solid; Yield: 68%; Mp. >240 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.68 (s, 1H), 9.31 (d, *J* = 5.7 Hz, 1H), 9.11 (d, *J* = 8.2 Hz, 1H), 8.32-8.30 (m, 2H), 8.18-8.15 (m, 1H), 8.03 (s, 1H), 7.99-7.96 (m, 1H), 7.73 (dd, *J* = 8.6, 0.9 Hz, 2H), 7.40 – 7.32 (m, 2H), 7.02 (t, *J* = 7.3 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.42, 148.12, 146.22, 145.36, 141.17, 140.23, 134.26, 129.72, 129.61, 127.96, 125.78, 122.64, 122.37, 121.06, 117.67, 116.61; HRMS calculated for $C_{18}H_{14}N_3S$: 304.0908, found *m/z* = 304.0908 $(M+H)^+$.

4.2.2 | N-(4-Methylphenyl)-4-(quinolin-4-yl)-1,3-thiazol-2-amine (**6b**)

MF: $C_{19}H_{15}N_3S$; Color: Brown solid; Yield: 70%; Mp. >240 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.57 (s, 1H), 9.30 (d, *J* = 5.7 Hz, 1H), 9.13 (d, *J* = 8.6 Hz, 1H), 8.34 – 8.26 (m, 2H), 8.18-8.14 (m, 1H), 8.03 – 7.93 (m, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.17 (d, *J* = 8.2 Hz, 2H), 2.27 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.63, 148.19, 146.27, 145.26, 140.16, 138.75, 134.28, 131.36, 129.99, 129.68, 128.02, 125.77, 122.54, 120.97, 117.86, 116.38, 20.86; HRMS calculated for $C_{19}H_{16}N_3S$: 318.1065; found *m/z* = 318.1064 $(M+H)^+$.

4.2.3 | N-(4-Methoxyphenyl)-4-(quinolin-4-yl)-1,3-thiazol-2-amine (**6c**)

MF: $C_{19}H_{15}N_3OS$; Color: Orange solid; Yield: 74%; Mp. >240 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.46 (s, 1H), 9.29 (d, *J* = 5.7 Hz, 1H), 9.13 (d, *J* = 8.2 Hz, 1H), 8.29 (d, *J* = 5.8 Hz, 2H), 8.15 (ddd, *J* = 8.4, 7.0, 1.2 Hz, 1H), 8.00 – 7.93 (m, 2H), 7.63 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 3.74 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.10, 155.08, 148.07, 146.31, 145.36, 140.34, 134.58, 134.18, 129.66, 128.01, 125.77, 122.70, 120.94, 119.67, 115.93, 114.83, 55.73; HRMS calculated for $C_{19}H_{16}N_3OS$: 334.1014; found *m/z* = 334.1013 $(M+H)^+$.

4.2.4 | N-(4-Bromophenyl)-4-(quinolin-4-yl)-1,3-thiazol-2-amine (**6d**)

MF: $C_{18}H_{12}BrN_3S$; Color: Orange solid; Yield: 65%; Mp. >240 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.75 (s, 1H), 9.22 (d, *J* = 5.7 Hz, 1H), 8.97 (d, *J* = 8.3 Hz, 1H), 8.22 (d, *J* = 5.9 Hz, 2H), 8.07 (ddd, *J* = 8.4, 7.0, 1.2 Hz, 1H), 7.96 (s, 1H), 7.90 (ddd, *J* = 8.3, 7.0, 1.1 Hz, 1H), 7.63 (m, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.02, 147.91, 146.22, 145.46, 140.47, 140.34, 134.20, 132.29, 129.80, 127.85, 125.78, 122.77, 121.14, 119.52, 116.90, 113.52; HRMS calculated for $C_{18}H_{13}BrN_3S$: 382.0014; found *m/z* = 382.0018 $(M+H)^+$, 383.9998 $(M+2+H)^+$.

4.2.5 | N-(4-Chlorophenyl)-4-(quinolin-4-yl)-1,3-thiazol-2-amine (6e)

MF: $C_{18}H_{12}ClN_3S$; Color: Brown solid; Yield: 70%; Mp. >240 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.84 (s, 1H), 9.31 (d, *J* = 5.7 Hz, 1H), 9.10 – 9.01 (m, 1H), 8.31 (d, *J* = 5.9 Hz, 2H), 8.16 (ddd, *J* = 8.4, 7.0, 1.2 Hz, 1H), 8.05 (s, 1H), 7.98 (ddd, *J* = 8.3, 7.0, 1.1 Hz, 1H), 7.76 (d, *J* = 9.0 Hz, 2H), 7.40 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.07, 147.99, 146.17, 145.39, 140.25, 140.07, 134.24, 129.81, 129.41, 127.86, 125.78, 125.66, 122.69, 121.13, 119.10, 116.93; HRMS calculated for $C_{18}H_{13}ClN_3S$: 338.0519; found *m/z* = 338.0522 $(M+H)^+$, 340.0497 $(M+2+H)^+$.

4.2.6 | N-(4-Fluorophenyl)-4-(quinolin-4-yl)-1,3-thiazol-2-amine (6f)

MF: $C_{18}H_{12}FN_3S$; Color: Orange solid; Yield: 75%; Mp. >240 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.64 (s, 1H), 9.23 (d, *J* = 5.7 Hz, 1H), 9.00 (d, *J* = 8.6 Hz, 1H), 8.26 – 8.20 (m, 2H), 8.08 (ddd, *J* = 8.4, 7.0, 1.2 Hz, 1H), 7.94 (s, 1H), 7.91 – 7.88 (m, 1H), 7.67 (dd, *J* = 9.1, 4.8 Hz, 2H), 7.13 (t, *J* = 8.9 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.51, 158.64 and 156.74 (^1J = 239.4 Hz), 148.16, 146.09, 145.28, 140.11, 137.68 and 137.67 (^4J = 1.26 Hz), 134.29, 129.80, 127.92, 125.77, 122.54, 121.06, 119.35 and 119.28 (^3J = 8.82 Hz), 116.67, 116.23 and 116.05 (^2J = 22.68 Hz); HRMS calculated for $C_{18}H_{13}FN_3S$: 322.0814; found *m/z* = 322.0807 $(M+H)^+$.

4.2.7 | 4-(6-Bromoquinolin-4-yl)-N-phenyl-1,3-thiazol-2-amine (6g)

MF: $C_{18}H_{12}BrN_3S$; Color: ; Yield: 60%; Mp. >240 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.70 (s, 1H), 9.64 (d, *J* = 2.0 Hz, 1H), 9.24 (d, *J* = 5.6 Hz, 1H), 8.30 (d, *J* = 5.5 Hz, 1H), 8.22 – 8.10 (m, 3H), 7.73 (dd, *J* = 8.5, 0.9 Hz, 2H), 7.39 (dd, *J* = 8.4, 7.6 Hz, 2H), 7.02 (t, *J* = 7.3 Hz, 1H); ^{13}C NMR (126 MHz DMSO-d_6) δ 164.35, 146.62, 146.47, 144.92, 141.08, 136.16, 130.33,

129.66, 126.65, 126.02, 122.37, 122.28, 121.28, 117.74, 117.54, 116.74; HRMS calculated for $C_{18}H_{13}BrN_3S$: 382.0014; found *m/z* = 382.0018 $(M+H)^+$, 383.9998 $(M+2+H)^+$.

4.2.8 | 4-(6-Bromoquinolin-4-yl)-N-(4-methylphenyl)-1,3-thiazol-2-amine (6h)

MF: $C_{19}H_{14}BrN_3S$; Color: Brown solid; Yield: 68%; Mp. >240 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.47 (s, 1H), 9.52 (d, *J* = 1.9 Hz, 1H), 9.12 (d, *J* = 5.4 Hz, 1H), 8.15 (d, *J* = 5.4 Hz, 1H), 8.10 (dd, *J* = 9.0, 2.1 Hz, 1H), 8.06 (d, *J* = 9.0 Hz, 1H), 7.96 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.52, 146.80, 146.55, 144.57, 141.20, 140.12, 135.97, 130.20, 129.33, 126.66, 126.39, 122.38, 122.23, 121.32, 120.08, 116.78, 20.88; HRMS calculated for $C_{19}H_{15}BrN_3S$: 396.0170; found *m/z* = 396.0168 $(M+H)^+$, 398.0147 $(M+2+H)^+$.

4.2.9 | 4-(6-Bromoquinolin-4-yl)-N-(4-methoxyphenyl)-1,3-thiazol-2-amine (6i)

MF: $C_{19}H_{14}BrN_3OS$; Color: brown solid; Yield: 65%; Mp. >240 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.56 (s, 1H), 9.68 (d, *J* = 1.9 Hz, 1H), 9.30 (d, *J* = 5.4 Hz, 1H), 8.33 (d, *J* = 5.4 Hz, 1H), 8.30-8.24 (m, 1H), 8.11 (s, 1H), 7.74 (d, *J* = 9.1 Hz, 2H), 7.07 (d, *J* = 9.1 Hz, 2H), 3.85 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.02, 155.10, 146.79, 146.54, 144.47, 141.19, 134.60, 133.11, 132.36, 129.95, 126.78, 126.52, 122.30, 119.71, 116.71, 114.85, 55.68; HRMS calculated for $C_{19}H_{15}BrN_3OS$: 412.0119; found *m/z* = 412.0118 $(M+H)^+$, 414.0097 $(M+2+H)^+$.

4.2.10 | N-(4-Bromophenyl)-4-(6-bromoquinolin-4-yl)-1,3-thiazol-2-amine (6*j*)

MF: $C_{18}H_{11}Br_2N_3S$; Color: Orange solid; Yield: 65%; Mp. >240 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.88 (s, 1H), 9.55 (d, *J* = 1.9 Hz, 1H), 9.28 (d, *J* = 5.5 Hz, 1H), 8.31 (d, *J* = 5.5 Hz, 1H), 8.25-8.20 (m, 2H), 8.17 (s, 1H), 7.75 (d, *J* = 8.9 Hz, 2H), 7.57 (d, *J* = 8.9 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.97, 146.85, 146.60, 144.52, 141.25, 140.40, 135.95, 132.26, 130.10, 126.64, 126.43, 122.25, 121.41, 119.39, 116.66, 113.52; HRMS calculated for $C_{18}H_{12}Br_2N_3S$: 459.9119; found *m/z* = 459.9113 $(M+H)^+$, 461.9096 $(M+2+H)^+$, 463.9075 $(M+4+H)^+$.

4.2.11 | 4-(6-Bromoquinolin-4-yl)-N-(4-chlorophenyl)-1,3-thiazol-2-amine (6k)

MF: $C_{18}H_{11}BrClN_3S$; Color: Orange solid; Yield: 68%; Mp. >240 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.82 (s, 1H), 9.51 (d, J = 1.9 Hz, 1H), 9.22 (d, J = 5.5 Hz, 1H), 8.26 (d, J = 5.5 Hz, 1H), 8.20-8.14 (m, 2H), 8.11 (s, 1H), 7.74 (d, J = 8.9 Hz, 2H), 7.39 (d, J = 8.9 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.50, 146.74, 146.52, 144.55, 141.24, 135.97, 134.24, 130.20, 129.55, 128.08, 126.66, 126.39, 122.23, 121.32, 119.78,116.70; HRMS calculated for $C_{18}H_{12}BrClN_3S$: 415.9624; found *m/z* = 415.9624 $(M+H)^+$, 417.9600 $(M+2+H)^+$, 419.9776 $(M+4+H)^+$.

4.2.12 | 4-(6-Bromoquinolin-4-yl)-N-(4-fluorophenyl)-1,3-thiazol-2-amine (**6l**)

MF: $C_{18}H_{11}BrFN_3S$; Color: Brown solid; Yield: 65%; Mp. >240 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.62 (s, 1H), 9.47 (d, J = 1.9 Hz, 1H), 9.14 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 5.5 Hz, 1H), 8.12-8.06 (m, 2H), 8.01 (s, 1H), 7.66 (dd, J = 9.1, 4.8 Hz, 2H), 7.13 (t, J = 8.8 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.46, 158.61 and 156.72 (^1J = 238.16 Hz), 146.79, 146.56, 144.60, 141.24, 137.63 and 137.62 (^4J = 1.26 Hz), 135.97, 130.20, 126.66, 126.39, 122.23, 121.32, 119.24 and 119.18 (^3J = 7.56 Hz), 116.26 and 116.08 (^2J = 22.68 Hz); HRMS calculated for $C_{18}H_{12}BrFN_3S$: 399.9919; found *m/z* = 399.9920 $(M+H)^+$, 401.9899 $(M+2+H)^+$.

4.2.13 | 4-(6-Chloroquinolin-4-yl)-N-phenyl-1,3-thiazol-2-amine (**6m**)

MF: $C_{18}H_{12}ClN_3S$; Color: Orange solid; Yield: 72%; Mp. >240 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.67 (s, 1H), 9.42 (d, J = 2.2 Hz, 1H), 9.21 (d, J = 5.4 Hz, 1H), 8.27 (d, J = 5.4 Hz, 1H), 8.24 (d, J = 9.0 Hz, 1H), 8.10-8.08 (m, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.38 (dd, J = 8.4, 7.6 Hz, 2H), 7.03 (t, J = 7.3 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.40, 147.01, 146.65, 144.55, 141.14, 133.44, 133.32, 129.60, 126.94, 126.72, 126.32, 122.41, 121.37, 117.76, 117.62, 116.01; HRMS calculated for $C_{18}H_{13}ClN_3S$: 338.0519; found *m/z* = 338.0521 $(M+H)^+$, 340.0496 $(M+2+H)^+$.

4.2.14 | 4-(6-Chloroquinolin-4-yl)-N-(4-methylphenyl)-1,3-thiazol-2-amine (**6n**)

MF: $C_{19}H_{14}ClN_3S$; Color: Brown solid; Yield: 65%; Mp. >240 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.47 (s, 1H), 9.34 (d, J = 2.2 Hz, 1H), 9.13 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 5.5 Hz, 1H), 8.15 (d, J = 9.0 Hz, 1H), 8.01 (dd, J = 9.1, 2.3 Hz, 1H), 7.97 (s, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.2 Hz, 2H), 2.19 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.58, 146.77, 146.64,

144.80, 141.13, 138.70, 133.47, 133.44, 131.39, 129.98, 127.01, 126.45, 126.32, 121.31, 117.77, 115.94, 20.88; HRMS calculated for $C_{19}H_{15}ClN_3S$: 352.0675; found *m/z* = 352.0678 $(M+H)^+$, 354.0653 $(M+2+H)^+$.

4.2.15 | 4-(6-Chloroquinolin-4-yl)-N-(4-methoxyphenyl)-1,3-thiazol-2-amine (6o)

MF: $C_{19}H_{14}ClN_3OS$; Color: Brown solid; Yield: 66%; Mp. >240 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.46 (s, 1H), 9.39 (d, *J* = 2.2 Hz, 1H), 9.20 (d, *J* = 5.5 Hz, 1H), 8.25-8.22 (m, 2H), 8.08 (dd, *J* = 9.1, 2.3 Hz, 1H), 8.00 (s, 1H), 7.63 (d, *J* = 9.1 Hz, 2H), 6.95 (d, *J* = 9.1 Hz, 2H), 3.74 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.07, 155.06, 146.94, 146.63, 144.62, 141.38, 134.56, 133.39, 133.31, 126.98, 126.68, 126.33, 121.29, 119.64, 115.36, 114.80, 55.72; HRMS calculated for $C_{19}H_{15}ClN_3OS$: 368.0624; found *m/z* = 368.0624 $(M+H)^+$; 370.0600 $(M+2+H)^+$.

4.2.16 | N-(4-Bromophenyl)-4-(6-chloroquinolin-4-yl)-1,3-thiazol-2-amine (6p)

MF: $C_{18}H_{11}BrClN_3S$; Color: Orange solid; Yield: 62%; Mp. >240 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.90 (s, 1H), 9.36 (d, *J* = 2.2 Hz, 1H), 9.30 (d, *J* = 5.4 Hz, 1H), 8.37 – 8.30 (m, 2H), 8.20 – 8.15 (m, 2H), 7.79 (d, *J* = 8.9 Hz, 2H), 7.60 (d, *J* = 8.9 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.00, 147.24, 146.59, 144.33, 142.49, 140.46, 133.46, 133.21, 132.23, 126.98, 126.73, 126.31, 121.51, 119.47, 116.14, 113.52; HRMS calculated for $C_{18}H_{12}BrClN_3S$: 415.9624; found *m/z* = 415.9623 $(M+H)^+$, 417.9600 $(M+2+H)^+$, 419.9776 $(M+4+H)^+$.

4.2.17 | N-(4-Chlorophenyl)-4-(6-chloroquinolin-4-yl)-1,3-thiazol-2-amine (6q)

MF: $C_{19}H_{14}ClN_3OS$; Color: Orange solid; Yield: 72%; Mp. >240 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.79 (s, 1H), 9.26 (d, *J* = 2.3 Hz, 1H), 9.20 (d, *J* = 5.3 Hz, 1H), 8.24-8.21 (m, 2H), 8.08 (ddd, *J* = 9.1, 2.3 Hz, 1H), 8.04 (s, 1H), 7.75 (d, *J* = 8.9 Hz, 2H), 7.39 (d, *J* = 8.9 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.07, 146.94, 146.63, 144.62, 141.38, 138.58, 133.39, 132.78, 130.00, 129.36, 127.03, 126.30, 125.28, 123.68, 121.29, 115.45; HRMS calculated for $C_{19}H_{15}ClN_3OS$: 372.0129; found *m/z* = 372.0132 $(M+H)^+$, 374.0105 $(M+2+H)^+$.

4.2.18 | 4-(6-Chloroquinolin-4-yl)-N-(4-fluorophenyl)-1,3-thiazol-2-amine (6r)

MF: $C_{18}H_{11}ClFN_3S$; Color: Yellow solid; Yield: 68%; Mp. >240 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.61 (s, 1H), 9.26 (d, *J* = 2.2 Hz, 1H), 9.13 (d, *J* = 5.5 Hz, 1H), 8.18 (d, *J* = 5.5

Hz, 1H), 8.15 (d, *J* = 9.1 Hz, 1H), 8.00 (dd, *J* = 9.1, 2.3 Hz, 1H), 7.99 (s, 1H), 7.66 (dd, *J* = 9.1, 4.8 Hz, 2H), 7.12 (t, *J* = 8.8 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 164.52, 158.64, 156.74 (^1J = 238.16 Hz), 146.90, 146.47, 144.67, 141.19, 137.66 and 137.65 (^4J = 1.26 Hz), 133.53, 133.39, 126.87, 126.57, 126.30, 121.40, 119.35 and 119.28 (^3J = 8.82 Hz), 116.20 and 116.02 (^2J = 22.68 Hz); HRMS calculated for $C_{18}H_{12}ClFN_3S$: 356.0424; found *m/z* = 356.0428 $(M+H)^+$, 356.0402 $(M+H)^+$.

4.2.19 | 4-(6-Fluoroquinolin-4-yl)-N-phenyl-1,3-thiazol-2-amine (6s)

MF: $C_{18}H_{12}FN_3S$; Color: Yellow solid; Yield: 74%; Mp. >240 °C; ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 10.73 (s, 1H), 9.29 (d, *J* = 5.5 Hz, 1H), 9.03 (dd, *J* = 11.0, 2.8 Hz, 1H), 8.39 (dd, *J* = 9.3, 5.3 Hz, 1H), 8.35 (d, *J* = 5.5 Hz, 1H), 8.12 (s, 1H), 8.11 – 8.07 (m, 1H), 7.80 – 7.73 (m, 2H), 7.42 (dd, *J* = 8.5, 7.5 Hz, 2H), 7.08 (t, *J* = 7.3 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 164.47, 162.04 and 160.07 (^1J = 248.22 Hz), 146.40, 145.84, 145.74 and 145.70 (^4J = 5.04 Hz), 141.16, 139.21, 129.57, 127.05 and 126.97 (^3J = 10.08 Hz), 126.82 and 126.73 (^3J = 11.34 Hz), 123.56 and 123.35 (^2J = 26.46 Hz), 122.45, 121.30, 117.75, 117.72, 115.97, 111.94 and 111.74 (^2J = 25.2 Hz); HRMS calculated for $C_{18}H_{13}FN_3S$: 322.0814 ; found *m/z* = 322.0807 $(M+H)^+$.

4.2.20 | 4-(6-Fluoroquinolin-4-yl)-N-(4-methylphenyl)-1,3-thiazol-2-amine (6t)

MF: $C_{19}H_{14}FN_3S$; Color: Pink solid; Yield: 65%; Mp. >240 °C; ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 10.55 (s, 1H), 9.23 (d, *J* = 5.4 Hz, 1H), 8.99 (d, *J* = 11.0 Hz, 1H), 8.33 (dd, *J* = 9.3, 5.2 Hz, 1H), 8.28 (d, *J* = 5.4 Hz, 1H), 8.08 – 8.00 (m, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 2.27 (s, 3H); ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 164.55, 162.06 and 160.09 (^1J = 248.22 Hz), 146.43, 145.87, 145.74 and 145.70 (^4J = 5.04 Hz), 141.16, 139.21, 133.50, 130.49, 127.18 and 127.10 (^3J = 10.08 Hz), 126.85 and 126.76 (^3J = 11.34 Hz), 123.61 and 123.40 (^2J = 26.46 Hz), 121.32, 117.75, 115.95, 111.92 and 111.72 (^2J = 25.2 Hz), 20.85; HRMS calculated for $C_{19}H_{15}FN_3S$: 336.0971; found *m/z* = 336.0973 $(M+H)^+$.

4.2.21 | 4-(6-Fluoroquinolin-4-yl)-N-(4-methoxyphenyl)-1,3-thiazol-2-amine (6u)

MF: $C_{19}H_{14}FN_3OS$; Color: Brown solid; Yield: 55%; Mp. >240 °C; ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 10.49 (s, 1H), 9.26 (t, *J* = 5.7 Hz, 1H), 9.04 – 8.94 (m, 1H), 8.43 – 8.33 (m, 1H), 8.31 (t, *J* = 7.1 Hz, 1H), 8.08 (s, 1H), 8.05 – 7.99 (m, 1H), 7.66 (d, *J* = 9.0 Hz, 2H), 7.00 (d, *J* = 9.0 Hz, 2H),

3.80 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.24, 161.96 and 159.99 (^1J = 248.22 Hz), 155.15, 146.51 and 146.46 (^4J = 6.3 Hz), 146.07, 138.40 and 139.35 (^4J = 6.3 Hz), 134.57, 130.28, 127.32 and 127.14 (^2J = 22.68 Hz), 126.81 and 126.72 (^3J = 11.34 Hz), 123.36 and123.27 (^3J = 11.34 Hz), 121.21, 119.88, 119.82, 114.79, 111.92 and 111.75 (^2J = 21.42 Hz), 55.73; HRMS calculated for $C_{19}H_{15}FN_3OS$: 352.0920; found *m/z* = 352.0923 $(M+H)^+$.

4.2.22 | N-(4-Bromophenyl)-4-(6-fluoroquinolin-4-yl)-1,3-thiazol-2-amine (**6v**)

MF: $C_{18}H_{11}BrFN_3S$; Color: Orange solid; Yield: 70%; Mp. >240 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.85 (s, 1H), 9.26 (d, *J* = 5.3 Hz, 1H), 8.86 (dd, *J* = 10.9, 2.7 Hz, 1H), 8.37 (dd, *J* = 9.3, 5.4 Hz, 1H), 8.29 (d, *J* = 5.3 Hz, 1H), 8.11 – 8.03 (m, 2H), 7.75 (d, *J* = 8.9 Hz, 2H), 7.57 (d, *J* = 8.9 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.06, 162.02 and 160.05 (^1J = 248.22 Hz), 146.48, 145.07 and 145.03 (^4J = 5.04 Hz), 140.51, 140.13 and 140.09 (^4J = 5.04 Hz), 132.25, 127.84 and 127.77 (^3J = 8.82 Hz), 126.79 and 126.71 (^3J = 10.08 Hz), 123.17 and 122.95 (^2J = 27.72 Hz), 121.48, 119.54, 115.59, 113.53, 111.60 and 111.40 (^2J = 25.2 Hz); HRMS calculated for $C_{18}H_{12}BrFN_3S$: 399.9919; found *m/z* = 399.9921 $(M+H)^+$, 401.9899 $(M+2+H)^+$.

4.2.23 | N-(4-Chlorophenyl)-4-(6-fluoroquinolin-4-yl)-1,3-thiazol-2-amine (**6w**)

MF: $C_{18}H_{11}ClFN_3S$; Color: Orange solid; Yield: 75%; Mp. >240 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.81 (s, 1H), 9.22 (d, *J* = 5.4 Hz, 1H), 8.83 (dd, *J* = 10.9, 2.8 Hz, 1H), 8.33 (dd, *J* = 9.3, 5.4 Hz, 1H), 8.26 (d, *J* = 5.4 Hz, 1H), 8.05 – 8.01 (m, 2H), 7.74 (d, *J* = 8.9 Hz, 2H), 7.38 (d, *J* = 8.9 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.12, 162.06 and 160.09 (^1J = 248.22 Hz), 146.36, 146.16, 145.43 and 145.39 (^4J = 5.04 Hz), 140.10, 139.60 and 139.58 (^4J = 2.26 Hz), 129.36, 127.44 and 127.36 (^3J = 10.08 Hz), 126.81 and 126.72 (^3J = 11.34 Hz), 125.70, 123.38 and 123.17 (^2J = 26.46 Hz), 121.45, 119.13, 115.93, 111.71 and 111.51 (^2J = 25.2 Hz); HRMS calculated for $C_{18}H_{12}ClFN_3S$: 356.0424; found *m/z* = 356.0428 $(M+H)^+$, 358.0402 $(M+2+H)^+$.

4.2.24 | N-(4-Fluorophenyl)-4-(6-fluoroquinolin-4-yl)-1,3-thiazol-2-amine (**6x**)

MF: $C_{18}H_{11}F_2N_3S$; Color: Orange solid; Yield: 70%; Mp. >240 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.59 (s, 1H), 9.14 (d, *J* = 5.4 Hz, 1H), 8.78 (dd, *J* = 11.0, 2.8 Hz, 1H), 8.24 (dd, *J* = 9.3, 5.4 Hz, 1H), 8.18 (d, *J* = 5.4 Hz, 1H), 8.00 – 7.88 (m, 2H), 7.65 (dd, *J* = 9.1, 4.8 Hz, 2H), 7.11 (t,

J = 8.9 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.62, 162.03 and 160.06 (^{1}J = 248.22 Hz), 158.68 and 156.78 (^{1}J = 239.4 Hz), 146.34, 146.13, 145.48 and 145.44 (^{4}J = 5.04 Hz), 139.60 and 139.57 (^{4}J = 3.78 Hz), 137.71 and 137.69 (^{4}J = 2.52 Hz), 127.41 and 127.33 (^{3}J = 10.8 Hz), 126.81 and 126.72 (^{3}J = 11.34 Hz), 123.38 and 123.17 (^{2}J = 26.46 Hz), 121.38, 119.45 and, 119.39 (^{3}J = 7.56 Hz), 116.20 and 116.02 (^{2}J = 22.68 Hz), 115.56, 111.77 and 111.57 (^{2}J = 25.2 Hz); HRMS calculated for $C_{18}H_{12}F_2N_3S$: 340.0720; found *m/z* = 340.0723 $(M+H)^+$.

4.2.25 | N-[4-(Quinolin-4-yl)-1,3-thiazol-2-yl]pyridin-2-amine (**6y**)

MF: $C_{17}H_{12}N_4S$; Color: Brown solid; Yield: 55%; Mp. >240 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.70 (s, 1H), 9.23 (d, *J* = 5.5 Hz, 1H), 9.12 (d, *J* = 1.5 Hz, 1H), 8.37 (d, *J* = 4.9 Hz, 1H), 8.31 -8.27 (m, 3H), 8.20 (d, *J* = 5.4 Hz, 1H), 8.11 – 8.01 (m, 1H), 7.85 – 7.75 (m, 1H), 7.15 (d, *J* = 8.3 Hz, 1H), 7.05 – 7.00 (m, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.85, 151.82, 146.90, 146.74, 145.30, 145.28, 141.20, 138.80, 132.98, 131.56, 128.90, 127.12, 126.67, 121.36, 118.66, 117.06, 111.56; HRMS calculated for $C_{17}H_{13}N_4S$: 305.0861; found *m/z* = 305.0865 $(M+H)^+$.

4.2.26 | N-[4-(6-Bromoquinolin-4-yl)-1,3-thiazol-2-yl]pyridin-2-amine (**6z**)

MF: $C_{17}H_{11}BrN_4S$; Color: Brown solid; Yield: 58%; Mp. >240 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.77 (s, 1H), 9.36 (d, *J* = 1.5 Hz, 1H), 9.25 (d, *J* = 5.4 Hz, 1H), 8.38 (d, *J* = 4.1 Hz, 1H), 8.22-8.16 (m, 3H), 8.07 (s, 1H), 7.81 – 7.77 (m, 1H), 7.18 (d, *J* = 8.3 Hz, 1H), 7.02 (dd, *J* = 6.8, 5.5 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.97, 151.86, 147.00, 146.81, 145.42, 145.38, 141.27, 138.83, 136.09, 130.10, 126.88, 126.49, 122.38, 121.86, 118.32, 117.07, 111.59; HRMS calculated for $C_{17}H_{12}BrN_4S$: 382.9966; found *m/z* = 382.9969 $(M+H)^+$, 384.9946 $(M+2+H)^+$.

4.2.27 | N-[4-(6-Chloroquinolin-4-yl)-1,3-thiazol-2-yl]pyridin-2-amine (**6aa**)

MF: $C_{17}H_{11}ClN_4S$; Color: Brown solid; Yield: 65%; Mp. >240 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.75 (s, 1H), 9.26 – 9.19 (m, 2H), 8.37 (dd, *J* = 4.9, 0.9 Hz, 1H), 8.25 (d, *J* = 9.1 Hz, 1H), 8.22 (d, *J* = 5.4 Hz, 1H), 8.11 – 8.04 (m, 2H), 7.82 – 7.75 (m, 1H), 7.17 (d, *J* = 8.3 Hz, 1H), 7.01 (dd, *J* = 6.8, 5.4 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.92, 151.85, 147.01, 146.80, 145.42, 145.36, 141.19, 138.83, 133.60, 133.47, 126.92, 126.61, 126.46, 121.82, 118.26, 117.07, 111.58; HRMS calculated for $C_{17}H_{12}ClN_4S$: 339.0471; found *m/z* = 339.0473 $(M+H)^+$, 341.0446 $(M+2+H)^+$.

4.2.28 | N-[4-(6-Fluoroquinolin-4-yl)-1,3-thiazol-2-yl]pyridin-2-amine (**6ab**)

MF: $C_{17}H_{11}FN_4S$; Color: Brown solid; Yield: 62%; Mp. >240 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.74 (s, 1H), 9.25 (d, J = 5.5 Hz, 1H), 9.08 (dd, J = 10.9, 2.7 Hz, 1H), 8.37 (d, J = 4.9 Hz, 1H), 8.33 (dd, J = 9.3, 5.3 Hz, 1H), 8.30 (d, J = 5.5 Hz, 1H), 8.16 (s, 1H), 8.11 – 8.01 (m, 1H), 7.85 – 7.75 (m, 1H), 7.16 (d, J = 8.3 Hz, 1H), 7.04 – 6.99 (m, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.03 and 160.06 (^1J = 248.22 Hz), 160.80, 151.84, 146.82, 146.19 and 146.15 (^4J = 5.04 Hz), 145.67, 145.27, 139.09 and 139.06 (^4J = 3.78 Hz), 138.83, 126.85 and 126.77 (^3J = 10.8 Hz), 123.65 and 123.44 (^2J = 26.46 Hz), 121.36, 118.66, 117.06, 112.35 and 112.15 (^2J = 25.2 Hz), 111.56; HRMS calculated for $C_{17}H_{12}FN_4S$: 323.0767; found m/z = 323.0770 $(M+H)^+$.

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Conflict of interest

The authors declare that they have no conflict of interest.

Supporting Information: Additional supporting information may be found online in the Supporting Information section.

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