18-Crown-6 Catalyzed Microwave-mediated Synthesis of Symmetric Bis-Heterocyclic Compounds under Solvent-free Condition

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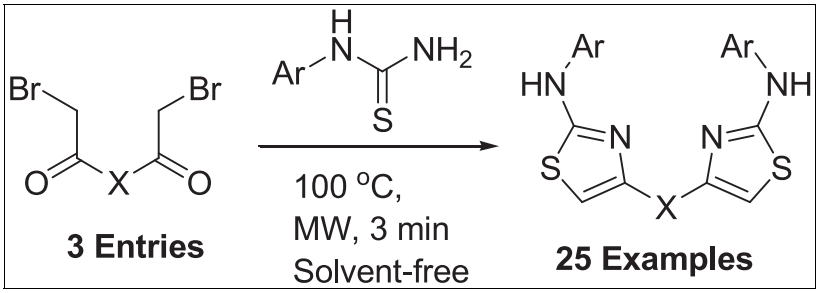

An efficient, solvent-free and 18-crown-6 catalyzed method for the synthesis of *N*-alkyl-4-(4-(5-(2-(alkyl-amino)thiazol-4-yl)pyridin-3-yl)phenyl)thiazol-2-amine, *N*-alkyl-4-(5-(2-alkyamino)thiazol-4-yl)pyridine-3-yl) thiazol-2-amine, and 4,4′-bis-{2-[amino]-4-thiazolyl}biphenyl bis-heterocyclic derivatives via microwave accelerated cyclization is presented.

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INTRODUCTION

Thiazole derivatives are prominent heterocyclic compounds in medicinal chemistry as well as in pharmaceutical research [1,2]. Typically, 2-aminothiazole heterocyclic compounds have shown a wide variety of pharmacological properties such as antibacterial [3], anti-inflammatory [4], antitumor [5], antimicrobial [6], antithrombotic activities [7], and have been used to treat conditions like HIV infections [8] and schizophrenia [9]. The structure activity studies on 2-aminothiazoles have proved their remarkable potential in counteracting tau-induced cytotoxicity in a human neuronal cell line model [10]. 2-aminothiazole derivatives have also shown high affinity for the neuropeptide Y5 (NPY5) receptor, useful for the treatment of eating disorders such as obesity and hyperphagia [11]. Besides, thiazoles are also synthetic intermediates and common substructures in numerous biologically active natural products [12]. Aminothiazole analogs are known to be ligands of estrogen receptors [13], adenosine receptor antagonists [14], and as schistosomicidal and anthelmintic drugs [15].

The pervasiveness and eminence of 2-aminothiazole moiety have led to the development of many synthetic approaches [16–21]. Generally, 2-aminothiazoles are prepared by Hantzsch's cyclocondensation of α-halo ketones with mono substituted thioureas [22], or by modified Hantzsch's methodologies via the reaction of *in situ* generated α-λ^3-iodanyl ketones with thioureas [23,24]. Aminothiazoles are also prepared by the reaction of α-thiocyanato carbonyl compounds with aromatic or aliphatic amine hydrochlorides [25]. The Kodomari's group has reported the synthesis of 2-aminothiazoles from α-bromo ketones using the supported reagents $KSCN/SiO_2$–RNH_3OAc/Al_2O_3 [26]. Recently, Meshram *et al*. have reported the synthesis of 2-aminothiazoles by the reaction of α-haloketone carbonyls with ammonium thiocyanate in the presence of *N*-methylimidazole [27]. Despite these procedures, novel and widely applicable green methodologies for the synthesis of 2-aminothiazole derivatives are still in demand.

Bis-heterocyclic compounds offer enhanced pharmacological utility especially when two pharmacologically active heterocyclic moieties are present in the same molecule. In this report, we describe solvent-free routes for the synthesis of bis-heterocyclic compounds containing 2-aminothiazole moiety. One of the key intermediates 3, 5-diacetyl pyridine was prepared using Stille coupling method. 3-acetyl-5-(4-acetylphenyl)pyridine was prepared using Mayura-Suzuki coupling. Consequently, three diacetyl derivatives were converted into the corresponding

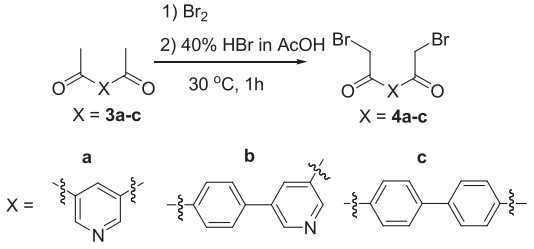
bis(α-bromo ketones) and utilized for the efficient synthesis of novel bis-heterocyclic compounds using 18-crown-6 phase transfer catalyst and microwave irradiation under solvent-free conditions [28].

RESULTS AND DISCUSSION

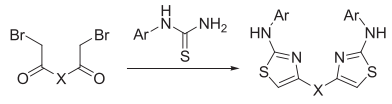
Considering the synthetic utility of α-bromo ketones in cross aldol condensations, enaminoketones, Favorskii rearrangements, and a variety of heterocyclic compounds, we set out to synthesize three bis(α-bromo ketones) bridged by a pyridine, pyridin-3-yl-phenyl or biphenyl system. In the first part of the study, the synthesis of one of the key substrates, 3,5-diacetyl pyridine, was prepared by Stille coupling [29–31] of 3-bromo-5-acetyl pyridine (**1a**) with ethoxyethene-tributyltin in 1,4-dioxane at 80°C. The resultant intermediate 1-(3-(1-ethoxyethyl)pyridyl) ethanone was quenched in *aq*. 1.5 *N* HCl to obtain 3,5-diacetyl pyridine (**3a**) in good yield as depicted in Scheme 1. The other diacetyl substrate 3-acetyl-5-(4-acetylphenyl)pyridine (**3b**) was prepared from 4-bromoacetophenone in two steps using Mayura-Suzuki coupling method [32,33] as depicted in Scheme 2. The first step was the preparation of 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone (**2b**) using 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane, $Pd(dppf)_2Cl_2$, and potassium acetate in 1,4-dioxane. In the second step, **2b** was coupled with 1-(5-bromopyridin-3-yl)ethanone (**1a**) using $Pd(PPh_3)_4$ catalyst and Na_2CO_3 in 1,4-dioxane/water 1:1 mixture to obtain the diacetyl compound **3b**. The 4,4-diacetylbiphenyl **3c** was purchased from Sigma-Aldrich, USA. The controlled α-bromination of the diketo compounds **3a–c** was achieved using Br_2 and 40% HBr in acetic acid, which afforded the corresponding bis(α-bromo ketones) **4a–c** in high yield (Scheme 3).

Having synthesized the bis(α-bromo ketone) intermediates **4a–c**, we then focused on their synthetic utility as building blocks for the construction of bis-heterocyclic compounds as outlined in Scheme 4. Various substituted arylthiourea derivatives, **5a–h** were chosen for cyclization with bis(α-bromo ketone) intermediates **4a–c** as the amino and mercapto groups in the thiourea moiety serve as nucleophilic centers [34]. In an attempt to minimize the

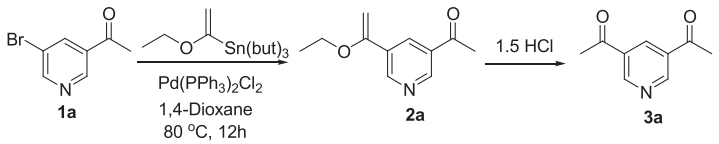
Scheme 3. Synthesis of Bis(α-bromo ketone) **4a–c**.



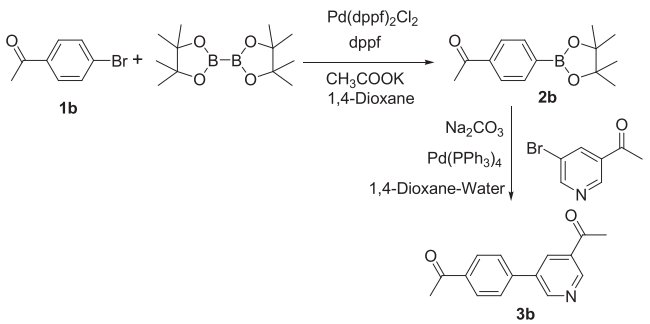
Scheme 4. Synthesis of Bis-heterocyclic compounds.



Scheme 1. Synthesis of 3,5-Diacetyl pyridine **3a**.



Scheme 2. Synthesis of 3-Acetyl-5-(4-acetylphenyl)pyridine, **3b**.



useof organic solvents, solvent-free microwave accelerated reaction conditions in the presence of a catalyst were optimized. For this purpose, the efficiency of different catalysts at room temperature was screened and the results are described in Table 1. The cyclization reaction in water or ethanol solvent without any catalyst showed a lower yield (Entries **1** and **2**, Table 1). As it is clear from Table 1, when ethanol is used as the solvent, the phase transfer catalysts TBAF and 18-crown-6 provide better yields under microwave irradiation (2–3 min) conditions.

Table 1

Cyclization of bromoethanones, **4**, with 1-(2-fluorophenyl)thiourea, **5**.[a]

Entry	Bis-α-bromo ketone	Catalyst 10 mol%	Solvent	LC–MS purity[b] (area %)
1	**4a**	No catalyst	water	61%
2	**4a**	No catalyst	Ethanol	67%
3	**4a**	Imidazole	Ethanol	65%
4	**4a**	DMAP	Ethanol	69%
5	**4a**	DABCO	Ethanol	66%
6	**4a**	Et_3N	Ethanol	64%
7	**4a**	DIPEA	Ethanol	62%
8	**4a**	TBAF	Ethanol	80%
9	**4a**	18-crown-6	Ethanol	83%
10	**4b**	18-crown-6	Ethanol	84%
11	**4c**	18-crown-6	Ethanol	89%

[a]Reaction condition: bis-α-bromo ketone, **4** (1 mmol), 1-(2-fluoro phenyl) thiourea, **5** (2 mmol), with or without catalyst in the solvent indicated and agitated at room temperature for 12 h.
[b]LC–MS purity.

Further optimization of the reaction conditions was carried out using 1-(2-fluorophenyl)thiourea **2** with and without solvent, and the results are summarized in Table 2. As seen in Table 2, the cyclization reaction proceeds in the presence and absence of solvents, and the best yields are obtained only under solvent-free condition and in the presence of the phase transfer catalyst 18-Crown-6.

Having optimized a solvent-free reaction condition, we set out to synthesize three different series of bis-heterocyclic compounds viz., *N*-alkyl-4-(5-(2-alkyamino)thiazol-4-yl)pyridine-3-yl)thiazol-2-amine (**6a–h**), *N*-alkyl-4-(4-(5-(2-(alkyl-amino) thiazol-4-yl)pyridin-3-yl)phenyl)thiazol-2-amine (**7a–e**), and 4,4′-bis-{2-[amino]-4-thiazolyl}biphenyl (**8a–l**) derivatives as depicted in Scheme 5. In almost all the

Scheme 5. Synthesis of *N*-Alkyl-4-(5-(2-alkyamino)thiazol-4-yl)pyridine-3-yl)thiazol-2-amine (**6a–h**), *N*-Alkyl-4-(4-(5-(2-(alkyl-amino)thiazol-4-yl) pyridin-3-yl)phenyl)thiazol-2-amine (**7a-e**), and 4,4′-Bis-{2-[amino]-4-thiazolyl}biphenyl (**8a–l**) derivatives.

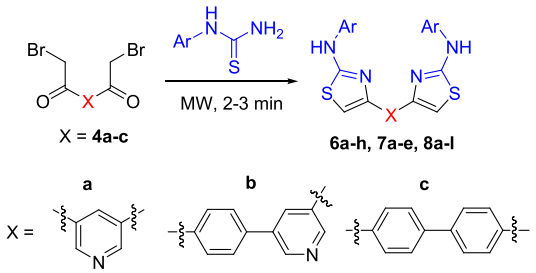


Table 2

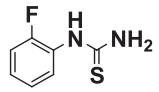
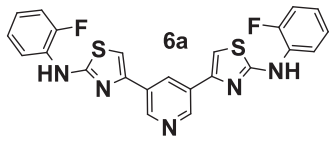
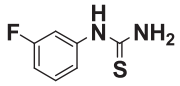
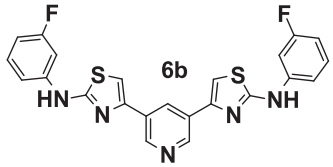
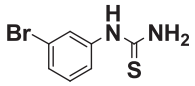
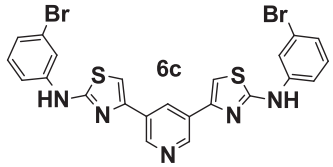
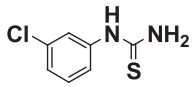
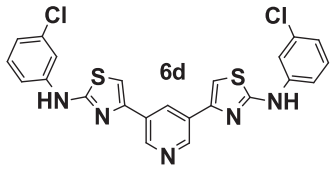
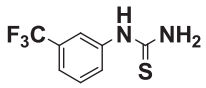
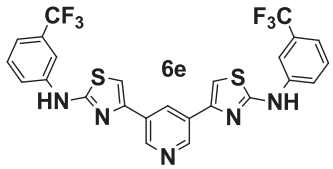
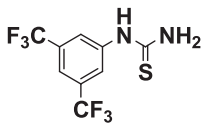
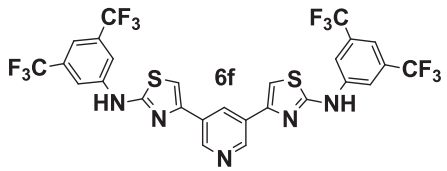
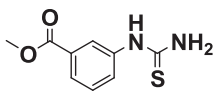
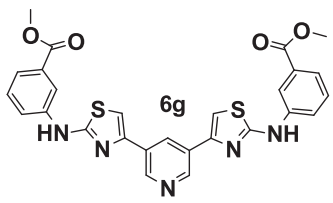
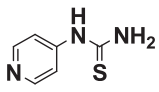
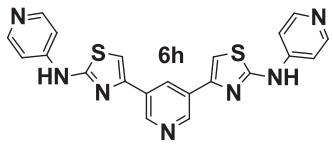
Cyclization of bromoethanones, **1**, with 1-(2-fluorophenyl)thiourea, **2**.[a]

Entry	Bis-α-bromo ketone	Catalyst	Solvent	Time (in min)	LC–MS purity[b] (area %)
1	**4a**	No catalyst	Water	2	81%
2	**4a**	No catalyst	Ethanol	1	79%
3	**4a**	No catalyst	Ethanol	2	81%
4	**4a**	Imidazole	Ethanol	2	74%
5	**4a**	DMAP	Ethanol	2	83%
6	**4a**	DABCO	Ethanol	2	89%
7	**4a**	Et_3N	Ethanol	2	75%
8	**4a**	DIPEA	Ethanol	2	78%
9	**4a**	TBAF	Ethanol	2	85%
10	**4a**	Basic alumina	Ethanol	3	85%
11	**4a**	18-crown-6	Ethanol	2	90%
12	**4a**	Imidazole	Water	2	81%
13	**4a**	DMAP	Water	2	78%
14	**4a**	DABCO	Water	2	86%
15	**4a**	Et_3N	Water	2	79%
16	**4a**	DIPEA	Water	2	83%
17	**4a**	TBAF	Water	2	90%
18	**4a**	Basic alumina	Water	3	82%
19	**4a**	18-crown-6	Water	2	80%
20	**4a**	18-crown-6	Solvent-free	2	99%
21	**4b**	18-crown-6	Solvent-free	2	99%
22	**4c**	18-crown-6	Solvent-free	2	98%

[a]Reaction condition: bis-α-bromo ketone, **4** (1 mmol), 1-(2-fluoro phenyl) thiourea, **5** (2 mmol), with or without catalyst and/or solvent. Microwave irradiation (120 W) at100°C for 3 min.
[b]LC–MS purity.

Table 3

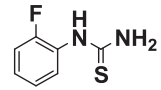
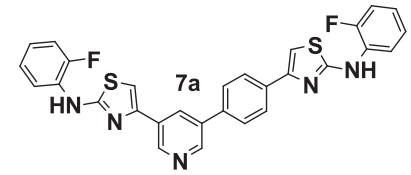
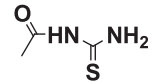
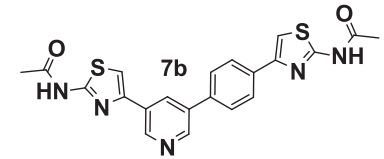
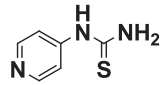
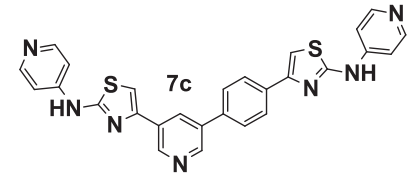
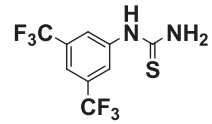
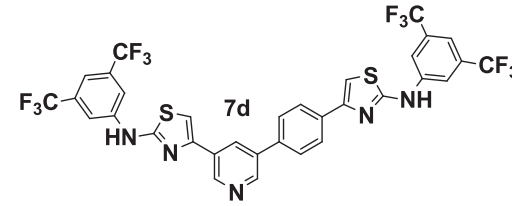
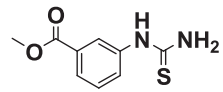
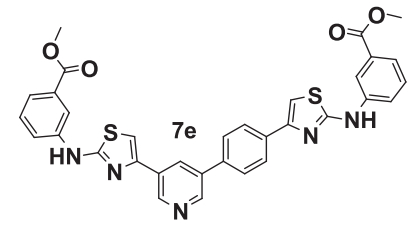
Condensation reaction of **4a** with various aryl thioureas, **5**.[a]

Entry	Substituted thiourea **5**	Product, **6**	Yield[b] (%)
1			82
2			84
3			88
4			80
5			91
6			90
7			92
8			83

[a]Reaction condition: bis-α-bromo ketone, **4**a (1 mmol), substituted thiourea, **5** (2 mmol), 18-crown-6 (10 mol%), microwave irradiation (120 W) at100°C for 3 min; [b]Isolated yield.

Table 4

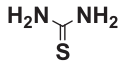
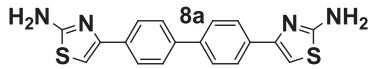
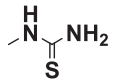
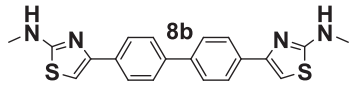
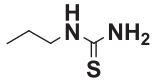
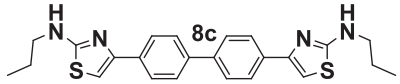
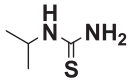
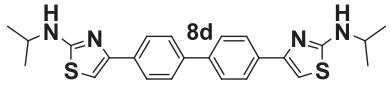
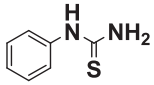
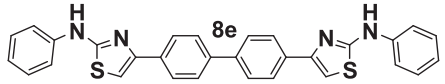
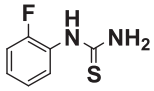
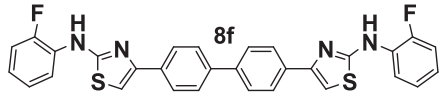
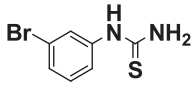
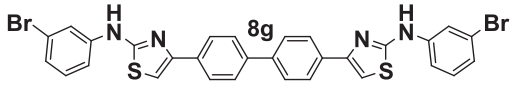
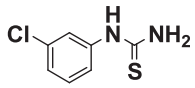
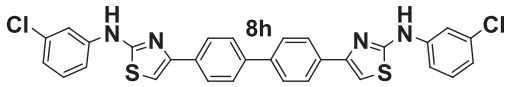
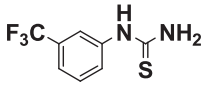
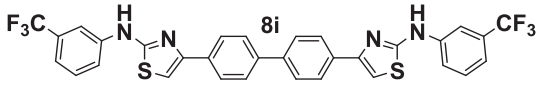
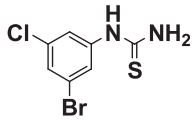
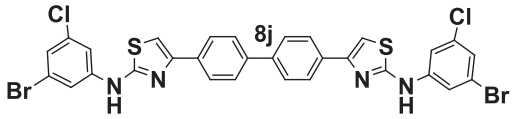
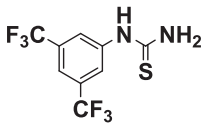
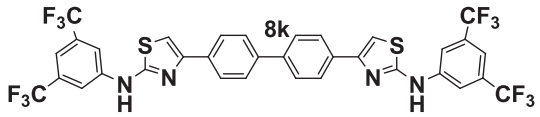
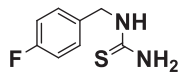
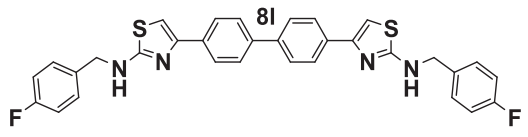
Condensation reaction of **4b** with various substituted thioureas, **5**.[a]

Entry	Substituted thiourea **5**	Product, **7**	Yield[b] (%)
1			86
2			82
3			84
4			90
5			91

[a]Reaction condition: bis-α-bromo ketone, **4b** (1 mmol), substituted thiourea, **5** (2 mmol), 18-crown-6 (10 mol%) Microwave irradiation (120 W) at100°C for 3 min.
[b]Isolated yield.

Table 5

Condensation reaction of **4c** with various substituted thiourea, **5**.[a]

Entry	Substituted thiourea **5**	Product, **8**	Yield[b] (%)
1			86
2			80
3			82
4			80
5			86
6			82
7			90
8			84
9			92
10			88
11			90
12			86

[a]Reaction condition: bis-α-bromo ketone, **4c** (1 mmol), substituted thiourea, **5** (2 mmol), 18-crown-6 (10 mol%) microwave irradiation (120 W) at100°C for 3 min.
[b]Isolated yield.

cases, very good yields were obtained in less than 3 min under solvent-free microwave irradiation condition as summarized in Tables 3, 4, and 5. All the compounds were characterized using NMR, mass, and elemental analyses.

CONCLUSION

In conclusion, we have presented 18-crown-6 catalyzed, microwave-mediated solvent-free reaction condition for the efficient synthesis of three classes of bis-heterocyclic compounds viz. *N*-alkyl-4-(4-(5-(2-(alkyl-amino)thiazol-4-yl)pyridin-3-yl)phenyl)thiazol-2-amine, *N*-alkyl-4-(5-(2-alkyamino)thiazol-4-yl)pyridine-3-yl)thiazol-2-amine, and 4,4′-bis-{2-[amino]-4-thiazolyl}biphenyl derivatives. In addition, a three-step protocol for the preparation of symmetric bis(α-bromo ketones) bridged by a pyridine or pyridin-3-yl-phenyl system, is also presented. The biological and photophysical properties of these compounds are being explored.

EXPERIMENTAL

All the reagents were purchased from Sigma-Aldrich and used without further purification. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Spectrospin Avance DPX400 spectrometer. Mass spectra were obtained using Agilent mass spectrometry 1200 series. Microwave irradiation was performed in a Biotage microwave oven operating at 20 kHz with the output power set at 120 W. The China Health and Nutrition Survey analysis was done on a Vario Micro elemental analyser.

General procedure for the synthesis of 2-Aminothiazole derivatives. A mixture of bis-α-bromo ketone (**4a** or **4b** or **4c**, 1.0 mmol), *N*-substituted thiourea **5** (2.0 mmol), and 18-crown-6 (catalyst, 10 mol%) was taken in 8 mL vials and irradiated in a Biotage Microwave Oven at 100°C for 2–3 min. The reaction progress was monitored by TLC. Upon completion of the reaction, the reaction mixture was cooled to ambient temperature and quenched with water, and the solid obtained was filtered off, dried under reduced pressure, and then crystallized in methanol or methanol-DMSO mixture to obtain pure bis-2-aminothiazole derivatives (**6a–h**, **7a–e**, **8a–l**). All the compounds were characterized using ^{1}H-NMR, ^{13}C-NMR, LC–MS, and elemental analysis techniques, and the analytical data are given below.

N-(2-Fluorophenyl)-4-(5-(2-(2-fluorophenylamino)thiazol-4-yl)pyridin-3-yl)thiazol-2-amine (6a). Yellow solid; yield: 82%; ^{1}H-NMR (DMSO-d_6): δ = 7.43–7.47 (t, 2H, 2-fluoro-phenyl), 7.57–7.59 (m, 2H, 2-fluoro-phenyl), 7.94 (s, 2H, thiazole), 7.97–7.99 (m, 2H, phenyl), 8.49 (s, 2H, pyridyl), 9.20–9.21 (bs, 3H, pyridyl, phenyl), 10.74 (s, 2H, NH-proton). ^{13}C-NMR (DMSO-d_6): δ = 109.15, 118.17, 121.65, 122.86, 129.78, 132.03, 133.00, 134.96, 139.64, 141.43, 144.96, 164.28, 167.79. LC–MS (ESI) *m/z*: 464.0 (M + 1) for $C_{23}H_{15}F_2N_5S_2$ requires 463.53. Elemental analysis, calculated for $C_{23}H_{15}F_2N_5S_2$: C, 59.60; H, 3.26; F, 8.20; N, 15.11; S, 13.84%. Found: C, 59.84; H, 3.33; N, 15.30; S, 13.94%.

N-(3-Fluorophenyl)-4-(5-(2-(3-fluorophenylamino)thiazol-4-yl)pyridin-3-yl)thiazol-2-amine (6b). Yellowish brown solid; yield: 84%; ^{1}H-NMR (DMSO-d_6): δ = 6.78–6.82 (m, 2H, phenyl), 7.32–7.38 (m, 2H, phenyl), 7.43–7.45 (d, 2H, *J* = 8.4 Hz, phenyl), 7.77–7.80 (d, 2H, 3.6 Hz, phenyl), 7.98 (s, 2H, thiazole), 9.21 (m, 3H, pyridyl), 10.75 (s, 2H, NH-proton). ^{13}C-NMR (DMSO-d_6): δ = 104.17, 104.44, 108.25, 108.46, 109.50, 113.46, 131.01, 131.11, 133.00, 135.38, 139.94, 142.81, 142.93, 145.15, 161.85, 164.14, 164.25. LC–MS (ESI) *m/z*: 464.0 (M + 1) for $C_{23}H_{15}F_2N_5S_2$ requires 463.53. Elemental analysis, calculated for $C_{23}H_{15}F_2N_5S_2$: C, 59.60; H, 3.26; F, 8.20; N, 15.11; S, 13.84%. Found: C, 59.86; H, 3.31; N, 15.28; S, 13.94%.

N-(3-Bromo-5-fluorophenyl)-4-(5-(2-(3-bromo-5-fluorophenylamino)thiazol-4-yl)pyridin-3-yl)thiazol-2-amine (6c). Yellowish brown solid; yield: 88%; ^{1}H-NMR (DMSO-d_6): δ = 7.14–7.17 (m, 2H, 3-bromo-phenyl), 7.26–7.30 (t, 2H, *J* = 8.0 Hz 3-bromo-phenyl), 7.70–7.73 (m, 2H, 3-bromo-phenyl), 7.98 (s, 2H, thiazole), 8.06–8.07 (s, 2H, pyridyl), 9.18–9.21 (m, 3H, pyridyl, phenyl), 10.73 (s, 2H, NH-proton). ^{13}C-NMR (DMSO-d_6): δ = 109.72, 116.39, 119.84, 122.39, 124.53, 131.45, 133.12, 135.69, 139.40, 142.69, 144.92, 164.04. LC–MS (ESI) *m/z*: 583.9 (M-1) for $C_{23}H_{15}Br_2N_5S_2$ requires 585.34. Elemental analysis, calculated for $C_{23}H_{15}Br_2N_5S_2$: C, 47.19; H, 2.58; Br, 27.30; N, 11.96; S, 10.96%. Found: C, 47.28; H, 2.65; N, 12.00; S, 11.07%.

N-(3-Chlorophenyl)-4-(5-(2-(3-chlorophenylamino)thiazol-4-yl)pyridin-3-yl)thiazol-2-amine (6d). Yellow solid; yield: 80%; ^{1}H-NMR (DMSO-d_6): δ = 7.31–7.35 (m, 2H, 3-Chloro-phenyl), 7.70–7.73 (m, 2H, 3-chloro-phenyl), 7.89 (s, 2H, thiazole), 7.99–8.04 (m, 3H, 3-Chloro-phenyl, pyridyl), 8.79–8.84 (m, 2H, 3-Chloro-phenyl), 9.29 (s, 2H, pyridyl), 10.69 (s, 2H, NH-proton). ^{13}C-NMR (DMSO-d_6): δ = 108.84, 116.59, 119.84, 122.39, 124.53, 131.45, 133.12, 135.69, 139.41, 142.69, 144.93, 164.04. LC–MS (ESI) *m/z*: 498.0 (M + 2) for $C_{23}H_{15}Cl_2N_5S_2$ requires 496.43. Elemental analysis, calculated for $C_{23}H_{15}Cl_2N_5S_2$: C, 55.65; H, 3.05; Cl, 14.28; N, 14.11; S, 12.92%. Found: C, 55.73; H, 3.12; N, 14.20; S, 13.00%.

N-(3-(Trifluoromethyl)phenyl)-4-(5-(2-(3-(trifluoromethyl)phenylamino)thiazol-4-yl)pyridin-3-yl)thiazol-2-amine (6e). Yellow solid; yield: 91%; ^{1}H-NMR (DMSO-d_6): δ = 7.30–7.32 (d, 2H, *J* = 7.6 Hz, 3-CF_3- phenyl), 7.55–7.59 (t, 2H, *J* = 8.0 Hz, phenyl), 7.77 (s, 2H, 3-CF_3-phenyl), 7.89–7.91 (d, 2H, *J* = 9.6 Hz, phenyl), 8.36 (s, 2H, thiazole), 8.88 (s, 1H, pyridyl), 9.122–9.12 (d, 2H, *J* = 2.0 Hz, pyridyl), 10.81 (s, 2H, NH-proton). ^{13}C-NMR (DMSO-d_6): δ = 104.44, 108.25, 108.46, 109.36, 109.62, 113.46, 118.13, 121.03, 123.31, 126.02, 130.37, 130.67, 131.09, 132.78, 133.08, 139.70, 140.27, 141.84, 142.80, 145.07, 145.25, 164.02, 164.14. LC–MS (ESI) *m/z*: 564.0 (M + 1) for $C_{23}H_{15}F_6N_5S_2$ requires 563.54. Elemental analysis, calculated for $C_{23}H_{15}F_6N_5S_2$: C, 53.28; H, 2.68; F, 20.23; N, 12.43; S, 11.38%. Found: C, 53.35; H, 2.73; N, 12.42; S, 11.45%.

N-(3,5-Bis(trifluoromethyl)phenyl)-4-(5-(2-(3,5-bis(trifluoromethyl)phenylamino)thiazol-4-yl)pyridin-3-yl)thiazol-2-amine (6f). Yellow solid; yield: 90%; ^{1}H-NMR (DMSO-d_6): δ = 7.57 (s, 2H), 7.85 (s, 2H), 8.43 (s, 4H), 8.94 (s, 1H), 9.11–9.12 (m, 2H, pyridyl), 11.18 (s, 2H, NH-proton). ^{13}C-NMR (DMSO-d_6): δ = 104.44, 113.46, 118.14, 121.04, 123.31, 126.02, 130.37, 130.67, 131.09, 132.78, 133.08, 139.70, 140.27, 141.84, 142.81, 145.07, 145.25, 164.02, 164.14. LC–MS (ESI) *m/z*: 700.0 (M + 1) for $C_{27}H_{13}F_{12}N_5S_2$ requires 699.54. Elemental analysis, calculated for $C_{27}H_{13}F_{12}N_5S_2$: C, 46.36; H, 1.87; F, 32.59; N, 10.01; S, 9.17%. Found: C, 46.35; H, 1.94; N, 10.08; S, 9.20%.

N-(Methylbenzoate)-4-(5-(2-((methylbenzoate)amino)thiazol-4-yl)pyridin-3-yl)thiazol-2-amine (6g). Brown solid; yield: 92%; ^{1}H-NMR (DMSO-d_6): δ = 3.82 (s, 6H, methyl ester), 7.42–7.46 (t, 2H, phenyl), 7.54–7.56 (d, 2H, *J* = 8.0 Hz, phenyl), 7.91–7.94 (m, 2H, phenyl), 7.98 (s, 2H, thiazole), 8.61-8.62 (d, 2H, *J* = 1.6 Hz, pyridyl), 9.18–9.22 (m, 3H, pyridyl, phenyl), 10.77 (s, 2H, NH-proton). ^{13}C-NMR (DMSO-d_6): δ = 52.62, 109.20, 117.95, 121.87, 122.49, 129.87, 130.82, 132.95, 135.07, 139.78, 141.54, 145.07, 164.06, 166.66. LC–MS (ESI) *m/z*: 544.0 (M + 1) for $C_{27}H_{21}N_5O_4S_2$ requires 543.62. Elemental analysis, calculated for $C_{27}H_{21}N_5O_4S_2$: C, 59.65; H, 3.89; N, 12.88; O, 11.77; S, 11.80%. Found: C, 59.71; H, 3.90; N, 12.89; S, 11.87%.

N-(4-(5-(2-(Pyridin-4-ylamino)thiazol-4-yl)pyridin-3-yl)thiazol-2-yl)pyridin-4-amine (6h). Yellowish brown solid; yield: 83%; ^{1}H-NMR (DMSO-d_6): δ = 7.43–7.47 (t, 2H, *J* = 8.0 Hz, phenyl), 7.57–7.60 (m, 2H, phenyl), 7.94 (s, 2H, thiazole), 7.97–8.00 (m, 2H, phenyl), 8.49–8.50 (bs, 2H, phenyl), 9.20–9.21 (3H, pyridyl, phenyl), 10.75 (s, 2H, NH-proton). ^{13}C-NMR (DMSO-d_6) δ: 109.15, 118.17, 121.65, 122.87, 129.78, 132.03, 133.00, 134.97, 139.64, 141.44, 144.96, 164.27, 167.79. LC–MS (ESI) *m/z*: 430.0 (M + 1) for $C_{21}H_{15}N_7S_2$ requires 429.52. Elemental analysis, calculated for $C_{21}H_{15}N_7S_2$: C, 58.72; H, 3.52; N, 22.83; S, 14.93%. Found: C, 58.71; H, 3.57; N, 22.89; S, 15.00%.

N-(2-Fluorophenyl)-4-(5-(4-(2-(2-fluorophenylamino)thiazol-4-yl)phenyl)pyridin-3-yl)thiazol-2-amine (7a). Yellowish brown solid; yield: 86%; ^{1}H-NMR (DMSO-d_6): δ = 6.94–6.98 (m, 2H, phenyl), 7.44–7.50 (m, 4H, phenyl), 7.66 (s, 1H, thiazole), 8.04–8.06 (m, 2H, phenyl), 8.12–8.13 (m, 3H, phenyl, thiazole), 8.16–8.26 (m, 2H, phenyl), 9.17–9.25 (m, 3H, pyridyl), 10.73 (s, 1H, NH-proton), 10.90 (s, 1H, NH-proton).^{13}C-NMR (DMSO-d_6) δ: 105.79, 117.82, 117.94, 126.85, 128.34, 129.86, 129.96, 130.85, 133.52, 136.15, 141.56, 141.91, 149.56, 163.32, 164.23, 166.66. LC–MS (ESI) *m/z*: 540.0 (M + 1) for $C_{29}H_{19}F_2N_5S_2$ requires 539.62. Elemental analysis, calculated for $C_{29}H_{19}F_2N_5S_2$: C, 64.55; H, 3.55; F, 7.04; N, 12.98; S, 11.88%. Found: C, 64.66; H, 3.59; N, 13.02; S, 12.00%.

N-(Acetyl)-4-(5-(4-(2-(acetylamino)thiazol-4-yl)phenyl)pyridin-3-yl)thiazol-2-amine (7b). Yellowish brown solid; yield: 82%; ^{1}H-NMR (DMSO-d_6): δ = 2.19–2.21 (bs, 6H, acetyl), 7.82 (s, 1H, thiazole), 7.99–8.14 (m, 4H, phenyl), 8.31 (s, 1H, thiazole), 9.18–9.25 (m, 3H, pyridyl), 12.28 (s, 1H, NH-proton), 12.43 (s, 1H, NH-proton). ^{13}C-NMR (DMSO-d_6): δ = 24.08, 113.42, 116.36, 116.59, 119.67, 120.15, 120.23, 121.90, 121.96, 122.23, 126.70, 127.00, 130.58, 132.09, 132.34, 133.23, 141.44, 144.38, 148.41, 156.98, 159.39, 162.48, 162.52. LC–MS (ESI) *m/z*: 436.2 (M + 1) for $C_{21}H_{17}N_5O_2S_2$ requires 435.52. Elemental analysis, calculated for $C_{21}H_{17}N_5O_2S_2$: C, 57.91; H, 3.93; N, 16.08; O, 7.35; S, 14.72%. Found: C, 58.00; H, 4.00; N, 16.10; S, 14.80%.

N-(4-(5-(4-(2-(Pyridin-4-ylamino)thiazol-4-yl)phenyl)pyridin-3-yl)thiazol-2-yl)pyridin-4-amine (7c). Yellow solid; yield: 84%; ^{1}H-NMR (DMSO-d_6): δ = 7.48–7.52 (m, 2H, phenyl), 7.56–7.61 (m, 3H, phenyl, thiazole), 7.96–8.11 (m, 5H, phenyl, thiazole), 8.18–8.20 (m, 2H, phenyl), 8.41–8.50 (m, 2H, phenyl), 9.23–9.26 (m, 3H, pyridyl), 10.57 (s, 1H, NH-proton), 10.76 (s, 1H, NH-proton). ^{13}C-NMR (DMSO-d_6): δ = 110.42, 113.36, 113.59, 116.67, 117.15, 117.23, 130.58, 132.09, 132.34, 133.23, 141.44, 144.38, 148.41, 156.88, 159.39, 162.48, 162.58. LC–MS (ESI) *m/z*: 506.5 (M + 1) for $C_{27}H_{19}N_7S_2$ requires 505.62. Elemental analysis, calculated for $C_{27}H_{19}N_7S_2$: C, 64.14; H, 3.79; N, 19.39; S, 12.68%. Found: C, 64.07; H, 3.81; N, 19.40; S, 12.77%.

N-(3,5-Bis(trifluoromethyl)phenyl)-4-(5-(4-(2-(3,5-bis(trifluoromethyl)phenylamino)thiazol-4-yl)phenyl) pyridin-3-yl)thiazol-2-amine (7d). Yellowish brown solid; yield: 90%; ^{1}H-NMR (DMSO-d_6): δ = 7.64–7.65 (m, 2H, phenyl), 7.74 (s, 1H, thiazole), 7.98–8.03 (m, 3H, phenyl, thiazole), 8.10–8.12 (m, 2H, phenyl), 8.50 (m, 4H, phenyl), 8.87 (s, 1H, pyridyl), 9.10–9.11 (m, 1H, pyridyl), 9.20 (s, 1H, pyridyl), 11.13 (s, 1H, NH-proton), 11.24 (s, 1H, NH-proton).^{13}C-NMR (DMSO-d_6): δ = 102.20, 109.21, 117.91, 121.88, 122.46, 129.87, 130.88, 132.95, 135.07, 139.78, 141.55, 145.07, 164.16, 166.66. LC–MS (ESI) *m/z*: 776.0 (M + 1) for $C_{33}H_{17}F_{12}N_5S_2$ requires 775.63. Elemental analysis, calculated for $C_{33}H_{17}F_{12}N_5S_2$: C, 51.10; H, 2.21; F, 29.39; N, 9.03; S, 8.27%. Found: C, 51.24; H, 2.27; N, 9.10; S, 8.35%.

N-(3(Methybenzoate))-4-(4-(5-(2-(phenylamino)thiazol-4-yl) pyridin-3-yl)methybenzoate) thiazol-2-amine (7e). White solid; yield: 91%; ^{1}H-NMR (DMSO-d_6): δ = 3.85 (s, 3H, methyl ester), 3.91 (s, 3H, methyl ester), 7.50–7.63 (m, 5H, phenyl, thiazole), 7.86–7.93 (m, 2H, phenyl), 8.05–8.10 (m, 3H, phenyl, thiazole), 8.19–8.21 (m, 2H, phenyl), 8.70–8.75 (m, 2H, phenyl), 9.12 (s, 1H, pyridyl), 9.19 (s, 1H, pyridyl), 9.25 (s, 1H, pyridyl), 10.61 (s, 1H, NH-proton), 10.77 (s, 1H, NH-proton). ^{13}C-NMR (DMSO-d_6): δ = 52.73, 105.79, 117.82, 121.68, 122.03, 122.24, 122.62, 128.34, 129.86, 129.96, 130.85, 133.52, 136.15, 141.91, 149.52, 163.32, 164.13, 166.76. LC–MS (ESI) *m/z*: 620.0 (M + 1) for $C_{33}H_{25}N_5O_4S_2$ requires 619.71. Elemental analysis, calculated for $C_{33}H_{25}N_5O_4S_2$: C, 63.96; H, 4.07; N, 11.30; O, 10.33; S, 10.35%. Found: C, 64.07; H, 4.07; N, 11.37; S, 10.37%.

4,4′-Bis-{2-[amino]-4-thiazolyl}biphenyl (8a). White solid; yield: 86 %; ^{1}H-NMR (DMSO-d_6) δ: 5.56 (s, 2H, –NH_2 proton, exchanged with water), 7.09 (s, 1H, thiazole), 7.96–7.98 (d, 2H, *J* = 8.4 Hz, biphenyl), 8.12–8.14 (d, 2H, *J* = 8.4 Hz, biphenyl); ^{13}C-NMR (DMSO-d_6) δ: 103.57, 126.85, 126.95, 127.62, 127.77, 127.96, 128.08, 128.26, 128.69, 128.84, 129.05, 129.90, 134.60, 139.24, 140.02, 140.50, 167.84, 170.77; LC–MS (ESI) *m/z*: 351.0 (M + 1) for $C_{18}H_{14}N_4S_2$ requires 350.46. Elemental analysis, calculated for $C_{18}H_{14}N_4S_2$: C, 61.69; H, 4.03; N, 15.99; S, 18.30%. Found: C, 61.73; H, 3.97; N, 16.05; S, 18.25%.

4,4′-Bis-{2-[Methyl-amino]-4-thiazolyl}biphenyl (8b). White solid; yield: 80%; ^{1}H-NMR (DMSO-d_6) δ: 3.02 (s, 6H, methyl), 7.28 (s, 2H, thiazole), 7.84–7.86 (dd, 4H, *J* = 8.8 Hz, biphenyl), 7.89–7.91 (dd, 4H, *J* = 8.4 Hz, biphenyl), 8.82 (s, 2H, –NH); ^{13}C-NMR (DMSO-d_6) δ: 27.37, 101.36, 121.02, 125.30, 126.17, 128.03, 129.12, 142.74, 153.77, 165.39; LC–MS (ESI) *m/z*: 379.4 (M + 1) for $C_{20}H_{18}N_4S_2$ requires 378.51. Elemental analysis, calculated for $C_{20}H_{18}N_4S_2$: C, 63.46; H, 4.79; N, 14.80; S, 16.94%. Found: C, 63.51; H, 4.74; N, 14.85; S, 16.89%.

4,4′-Bis-{2-[propyl-amino]-4-thiazolyl}biphenyl (8c). White solid; yield: 82%; ^{1}H-NMR (DMSO-d_6) δ: 0.93 (t, 3H, *J* = 7.6 Hz, *n*-propyl), 1.62 (m, 2H, *n*-propyl), 3.22 (q, 2H, *J* = 6.8 Hz, *n*-propyl), 7.11 (s, 1H, thiazole), 7.68–7.71 (t, 1H, *J* = 8.0 Hz, –NH), 7.71–7.73 (dd, 2H, *J* = 8.4 Hz, biphenyl), 7.91–7.93 (dd, 2H, *J* = 8.4 Hz, biphenyl); ^{13}C-NMR (DMSO-d_6) δ: 11.59, 25.37, 51.03, 101.36, 121.02, 125.30, 126.17, 128.03, 129.12, 142.74, 153.77, 165.39; LC–MS (ESI) *m/z*: 435.2 (M + 1) for $C_{24}H_{26}N_4S_2$ requires 434.62. Elemental analysis, calculated for $C_{24}H_{26}N_4S_2$: C, 66.32; H, 6.03; N, 12.89; S, 14.76%. Found: C, 66.37; H, 5.97; N, 12.84; S, 14.81%.

4,4′-Bis-{2-[isopropyl-amino]-4-thiazolyl}biphenyl (8d). White solid; yield: 80%; ^{1}H-NMR (DMSO-d_6) δ: 1.24–1.25 (d, 12H, J = 6.4 Hz, isopropyl) 3.9 (m, 2H, isopropyl), 7.17 (s, 2H, thiazole), 7.78–7.80 (d, 4H, J = 8.4 Hz, biphenyl), 7.88–7.90 (d, 4H, J = 8.4 Hz, biphenyl); ^{13}C-NMR (DMSO-d_6) δ: 24.59, 50.99, 101.01, 120.48, 124.89, 134.87, 142.10, 153.98, 166.41; LC–MS (ESI) *m/z*: 435.2 (M + 1) for $C_{24}H_{26}N_4S_2$ requires 434.62. Elemental analysis, calculated for $C_{24}H_{26}N_4S_2$: C, 66.32; H, 6.03; N, 12.89; S, 14.76%. Found: C, 66.36; H, 5.97; N, 12.85; S, 14.82%.

4,4′-Bis-{2-[phenyl-amino]-4-thiazolyl}biphenyl (8e). White solid; yield: 86%; ^{1}H-NMR (DMSO-d_6) δ: 6.97–7.01 (m, 2H, phenyl), 7.36–7.38 (m, 4H, phenyl), 7.40–7.43 (s, 2H, thiazole), 7.76–7.78 (d, 4H, J = 8.4 Hz, phenyl), 7.82–7.84 (dd, 4H, J = 8.4 Hz, biphenyl), 8.03–8.05 (dd, 4H, J = 8.4 Hz, biphenyl), 10.32 (s, 2H, –NH); ^{13}C-NMR (DMSO-d_6) δ: 103.67, 117.37, 117.70, 121.74, 122.32, 126.74, 126.88, 127.06, 127.16, 127.32, 127.92, 128.94, 129.50, 129.58, 139.08, 141.05, 141.68, 150.13, 162.40, 163.66; LC–MS (ESI) *m/z*: 503.0 (M + 1) for $C_{30}H_{22}N_4S_2$ requires 502.65. Elemental analysis, calculated for $C_{30}H_{22}N_4S_2$: C, 71.68; H, 4.41; N, 11.15; S, 12.76%. Found: C, 71.73; H, 4.36; N, 11.11; S, 12.80%.

4,4′-Bis-{2-[2-fluorophenylamino]-4-thiazolyl}biphenyl (8f). White solid; yield: 82%; ^{1}H-NMR (DMSO-d_6) δ: 6.44–6.49 (m, 2H, fluorophenyl), 7.01–7.31 (m, 4H, fluorophenyl), 7.47 (s, 2H, thiazole), 7.81–7.83 (d, 4H, J = 8.4 Hz, biphenyl), 8.01–8.04 (d, 4H, J = 8.4 Hz, biphenyl), 8.63–8.67 (t, 2H, J = 8.4 Hz, fluorophenyl), 10.13 (s, 2H, –NH); ^{13}C-NMR (DMSO-d_6) δ: 104.90, 105.04, 115.51, 115.69, 120.35, 122.69, 125.20, 122.70, 126.88, 127.15, 127.32, 128.90, 129.47, 129.58, 132.97, 134.01, 139.07, 139.76, 149.78, 150.98, 153.41, 162.48, 163.79; LC–MS (ESI) *m/z*: 539.0 (M + 1) for $C_{30}H_{20}F_2N_4S_2$ requires 538.63. Elemental analysis, calculated for $C_{30}H_{20}F_2N_4S_2$: C, 66.90; H, 3.74; F, 7.05; N, 10.40; S, 11.91%. Found: C, 66.97; H, 3.70; N, 10.39; S, 11.95%.

4,4′-Bis-{2-[3-bromo-phenyl-amino]-4-thiazolyl}biphenyl (8g). White solid; yield: 90%; ^{1}H-NMR (DMSO-d_6) δ: 7.15–7.17 (m, 2H, phenyl), 7.31–7.35 (m, 2H, phenyl), 7.51 (s, 2H, thiazole), 7.66–7.68 (m, 2H, phenyl), 7.84–7.87 (dd, 4H, J = 8.4 Hz, biphenyl), 8.02–8.04 (dd, 4H, J = 8.4 Hz, biphenyl), 8.14–8.15 (m, 2H, phenyl), 10.53 (s, 2H, –NH); ^{13}C-NMR (DMSO-d_6) δ: 104.44, 104.58, 116.11, 116.41, 119.59, 119.88, 122.37, 124.08, 124.66, 126.67, 126.89, 127.07, 127.19, 127.36, 128.87, 131.38, 132.92, 133.97, 134.18, 138.89, 139.10, 139.74, 142.48, 143.12, 147.19, 150.15, 161.85, 163.08; LC–MS (ESI) *m/z*: 661.0 (M + 1) for $C_{30}H_{20}Br_2N_4S_2$ requires 660.44. Elemental analysis, calculated for $C_{30}H_{20}Br_2N_4S_2$: C, 54.56; H, 3.05; Br, 24.20; N, 8.48; S, 9.71%. Found: C, 54.61; H, 3.00; N, 8.45; S, 9.74%.

4,4′-Bis-{2-[3-chloro-phenyl-amino]-4-thiazolyl}biphenyl (8h). White solid; yield: 84%; ^{1}H-NMR (DMSO-d_6) δ: 7.02–7.04 (m, 2H, phenyl), 7.37–7.41 (m, 2H, phenyl), 7.51 (s, 2H, thiazole), 7.61–7.63 (m, 2H, phenyl), 7.84–7.86 (dd, 4H, J = 8.4 Hz, biphenyl), 8.01–8.02 (dd, 4H, J = 8.4 Hz, biphenyl), 10.55 (s, 2H, –NH); ^{13}C-NMR (DMSO-d_6) δ: 104.46, 115.77, 116.71, 121.19, 126.67, 127.19, 131.07, 133.84, 133.95, 139.08, 142.99, 150.10, 163.13; LC–MS (ESI) *m/z*: 572.0 (M + 1) for $C_{30}H_{20}Cl_2N_4S_2$ requires 571.54. Elemental analysis, calculated for $C_{30}H_{20}Cl_2N_4S_2$: C, 63.04; H, 3.53; Cl, 12.41; N, 9.80; S, 11.22%. Found: C, 63.10; H, 3.48; N, 9.76; S, 11.26%.

4,4′-Bis-{2-[3-(trifluoromethyl)-phenyl-amino]-4-thiazolyl} biphenyl (8i). White solid; yield: 92%; ^{1}H-NMR (DMSO-d_6) δ: 7.31–7.33 (d, 2H, J = 8 Hz, phenyl), 7.54 (s, 2H, thiazole), 7.59–7.62 (t, 2H, J = 8.0 Hz, phenyl), 7.85–7.90 (m, 6H, biphenyl and phenyl), 8.03–8.05 (dd, 4H, J = 8.4 Hz, biphenyl), 8.41(s, 2H, phenyl) 10.71 (s, 2H, –NH); ^{13}C-NMR (DMSO-d_6) δ: 105.13, 105.49, 108.30, 109.63, 113.54, 127.42, 131.02, 131.12, 133.24, 140.56, 140.95, 141.84, 142.79, 142.90, 144.73, 161.83, 164.25; LC–MS (ESI) *m/z*: 638.9 (M + 1) for $C_{32}H_{20}F_6N_4S_2$ requires 638.65. Elemental analysis, calculated for $C_{32}H_{20}F_6N_4S_2$: C, 60.18; H, 3.16; F, 17.85; N, 8.77; S, 10.04%. Found: C, 60.25; H, 3.14; N, 8.74; S, 10.09%.

4,4′-Bis-{2-[5-bromo-3-fluoro-phenyl-amino]-4-thiazolyl} biphenyl (8j). White solid; yield: 88%; ^{1}H-NMR (DMSO-d_6) δ: 7.47–7.51 (4H, phenyl, thiazole), 7.58–7.62 (m, 2H, phenyl), 7.80–7.82 (dd, 4H, J = 2.4 Hz, phenyl), 8.02–8.04 (dd, 4H, J = 8.4 Hz, biphenyl), 8.66–8.70 (m, 2H, phenyl), 10.26–10.27 (s, 2H, -NH); ^{13}C-NMR (DMSO-d_6) δ: 92.96, 112.85, 112.94, 118.74, 118.96, 121.40, 126.86, 127.03, 127.30, 128.13, 128.43, 133.10, 139.55, 146.85, 150.64, 153.11, 161.97; LC–MS (ESI) *m/z*: 730.2 (M + 1) for $C_{30}H_{18}Br_2Cl_2N_4S_2$ requires 729.33. Elemental analysis, calculated for $C_{30}H_{18}Br_2Cl_2N_4S_2$: C, 49.40; H, 2.49; Br, 21.91; Cl, 9.72; N, 7.68; S, 8.79%. Found: C, 49.51; H, 2.46; N, 7.66; S, 8.84%.

4,4′-Bis-{2-[3,5-Bis(trifluoromethyl)phenyl-amino]-4-thiazolyl} biphenyl (8k). White solid; yield: 90%; ^{1}H-NMR (DMSO-d_6) δ: 7.63–7.64 (m, 4H, phenyl, thiazole), 7.88–8.15 (m, 8H, biphenyl), 8.49 (s, 4H, phenyl), 11.08 (s, 2H, –NH); ^{13}C-NMR (DMSO-d_6) δ: 104.16, 104.43, 108.28, 108.49, 109.65, 113.52, 127.41, 131.02, 131.12, 133.23, 140.55, 140.95, 141.83, 142.79, 142.90, 144.71, 161.82, 164.15; LC–MS (ESI) *m/z*: 775.0 (M + 1) for $C_{34}H_{18}F_{12}N_4S_2$ requires 774.64. Elemental analysis, calculated for $C_{34}H_{18}F_{12}N_4S_2$: C, 52.72; H, 2.34; F, 29.43; N, 7.23; S, 8.28%. Found: C, 52.79; H, 2.30; N, 7.21; S, 8.26%.

4,4′-Bis-{2-[4-Fluoro-benzylamino]-4-thiazolyl}biphenyl (8l). White solid; yield: 86%; ^{1}H-NMR (DMSO-d_6) δ: 4.57 (s, 4H, benzylic), 7.19–7.23 (m, 6H, fluorophenyl, thiazole), 7.46–7.50 (m, 4H, fluoro phenyl), 7.77–7.80 (dd, 4H, J = 8.4 Hz, biphenyl), 7.89–7.91 (dd, 4H, J = 8.4 Hz, biphenyl), 8.72–8.85 (bs, 2H, –NH); ^{13}C-NMR (DMSO-d_6) δ: 48.25, 103.05, 115.48, 115.64, 115.85, 126.80, 127.11, 127.24, 127.78, 128.93, 130.04, 130.12, 130.24, 130.32, 131.40, 134.07, 135.36, 139.56, 146.70, 160.82, 163.23, 166.90, 169.34; LC–MS (ESI) *m/z*: 567.0 (M + 1) for $C_{32}H_{24}F_2N_4S_2$ requires 566.69. Elemental analysis, calculated for $C_{32}H_{24}F_2N_4S_2$: C, 67.82; H, 4.27; F, 6.71; N, 9.89; S, 11.32%. Found: C, 67.88; H, 4.25; N, 9.91; S, 11.36%.

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