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Articles

Synthesis and Antibacterial Evaluation of Some Novel 2-Arylamino-4-phenyl-thiazolyl Derivatives

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A series of 2-aminothiazoles derivatives have been synthesized and tested for *in vitro* antibacterial activity on different microorganisms. Syntheses have been carried out following simple methodology in excellent isolated yields. The structure and purity of the original compounds were confirmed by IR, NMR, Mass spectroscopy, and elemental analysis. All compounds were tested for antibacterial activity against *S. aureus*, *S. pyogenes*, *E. coli*, *P. aeruginosa*, *S. typhi* and *V. parahaemolyticus*. These preliminary results indicate that some of compounds are exhibiting good activity.

Key Words: Thiazole, 2-Amino-4-phenyl-thiazolyl, Antibacterial activity, MIC

Introduction

The incidence of bacterial infections has increased dramatically in recent years.[1] The widespread use of antibacterial drugs and their resistance against bacterial infections has led to serious health hazards. The resistance of wide spectrum antibacterial agents has prompted discovery and modification towards new antifungal and antibacterial drugs.[2,3]

Thiazoles and their derivatives have attracted continuing interest over the years because of their varied biological activities.[4,5] Thiazole and in particular the 2-amino thiazole nucleus have been incorporated into a wide variety of therapeutically interesting candidates including antibacterial,[6-10] anti-HIV,[11] hypertension,[12] anti-inflamentory,[13] anti-viral[14,15] and anticancer,[16,17] agents. Recent studies have shown the synthesis of some new thiazole candidates as adenosine receptor antagonists[18] and Src family kinase inhibitors,[19] more recently 2-aminothiazole analogues reported as potential neuroprotective agents[20] for the treatment of neurological diseases and modulators of transcriptional repression for treatment of huntington's disease.[21]

Prompted by the observed biological activities of the above mentioned derivatives and in continuation of our ongoing studies on novel biologically active molecules, we have designed and synthesized some novel 2-aminothiazoles following Hantzsch's synthesis[22] as potential antibacterial agents.

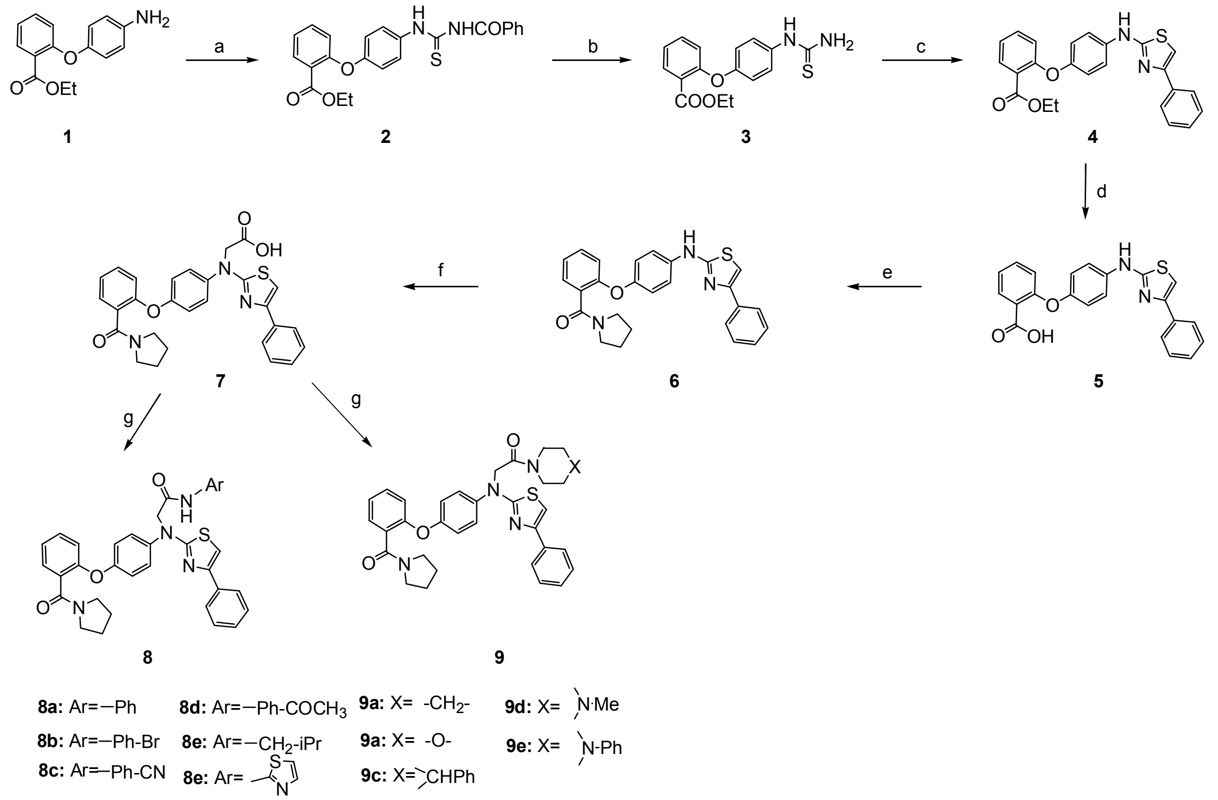
Results and Discussion

Chemistry. The synthetic routs of compounds **8a-f** and **9a-e** are outlined in Scheme 1. 2-(4-Amino-phenoxy)-benzoic acid ethyl ester **1** was prepared from 2-hydroxy-benzoic acid ethyl ester in accordance to the method described in the literature.[23]

The ethyl 2-(4-amino-phenoxy)-benzoate **1** was converted to thioureido derivative **2** by treatment with benzoyl chloride and ammonium thiocyanate and then was, hydrolyzed by sodium methoxide in methanol in good yield to give thiourea derivative **3**. Compound **3** underwent Hantzsch thioazole synthesis with phenacyl bromide to give thiazol **4** in good yield, which was further hydrolyzed to give acid **5** in presence of aqueous sodium hydroxide in methanol. Compound **5** was treated with pyrrolidin in presence of EDCI and DIPEA in THF to produce pyrrolidine derivative **6**. Compound **6** was alkylated using ethyl bromoacetate in presence of NaH in DMF to give ester derivative which was in-situ hydrolyzed to give acetic acid derivative **7**. Amide coupling of compound **7** with various aromatic amines, as well as, secondary aliphatic amines was carried out in presence of EDCI and DIPEA to give the final compounds **8a-f** and **9a-e**.

The structures of all compounds **8a-f** and **9a-e** were determined using IR, ^{1}H-NMR and EI-MS spectral data together with elemental analysis. IR spectra of compounds **8a-f** and **9a-e** showed absorption bands around 1637 - 1705 cm^{-1} regions resulting from C=O function of amide, while compound **8a-f** showed one additional absorption bands around 3431 - 3451 cm^{-1} regions resulting from N-H function of -CONH. ^{1}H NMR spectra of compound **8a-f** showed singlet proton at chemical shift around 10.38 - 10.64 ppm for PhNHCO- proton, while this proton was disappeared in compounds **9a-e**. In addition, the EI-MS spectra of **8a-f** and **9a-e** showed molecular ion peak (M+, 90%).

Biological Activities. The newly synthesized derivatives were evaluated for their *in vitro* antibacterial activity against *E. coli*, *P. aeruginosa*, *S. aureus*, *S. pyogenes*, *S. typhi* and *V. parahaemolyticus* by micro broth dilution methods.[24] The standard strains used for screening of antibacterial and antifungal activities were procured from Institute of Microbial Technology (IMTECH), Chandigarh, India. The MIC values are given in Table 1. The standard drug used for antibacterial activity was



Scheme 1. Reagents and conditions (a) Benzoyl chloride, ammonium thiocyanate, acetone, reflux, 0.5 h., yield 80%. (b) NaOMe, methanol, rt, 1 h., yield 73%. (c) Phenacyl chloride, $NaHCO_3$, acetonitrile, reflux, 2 h., yield 78%. (d) aq. NaOH, methanol-THF, rt, 10 h., yield 75% (e) Pyrrolidine, EDCI, DIPEA, THF, rt, 10 h., yield 72% (f) 1) Ethyl bromo acetate, NaH, DMF, rt, 3 h. 2) Methanol, water, rt, 5 h., yield 70%. (g) $ArNH_2$ or cyclic amine, EDCI, DIPEA, THF, rt, 4 - 7 h., yields 71 - 81%.

Table 1. Antibacterial activity data of newly synthesized compounds **8a-f** and **9a-e**

Compounds	Antibacterial MIC in μg/mL					
	E.coli MTCC 443	*P. aeruginosa* MTCC 1688	*S. aureus* MTCC 96	*S. pyogenes* MTCC 442	*S. typhi* TCC98	*V. parahaemolyticus* MTCC 82
8a	62.5	62.5	200	125	100	500
8b	62.5	50	62.5	62.5	500	100
8c	125	125	62.5	500	500	500
8d	100	50	125	250	500	200
8e	1000	1000	500	100	50	100
8f	1000	500	500	1000	100	100
9a	50	100	50	125	1000	500
9b	125	200	100	250	500	500
9c	125	500	500	250	500	500
9d	100	50	50	125	500	1000
9e	500	125	50	500	200	200
Ciprofloxacin	25	25	50	50	-	-

ciprofloxacin. Mueller Hinton Broth was used as nutrient medium for bacteria and sabouraud dextrose broth for fungal to grow. Inoculums size for test strain was adjusted to 108 CFU/mL by comparing the turbidity. The serial dilutions were prepared in primary and secondary screening. The target compounds and standard drugs were dissolved in DMSO-water (1:1 v/v) at a concentration of 2.0 mg/mL. In primary screening, 500 μg/mL, 250 μg/mL and 125 μg/mL concentrations of the synthesized drugs were taken. Data were not taken for the initial solution because of the high DMSO concentration (10%). The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms. In secondary screening, the drugs found active in primary screening were similarly diluted to obtain 100 μg/mL, 50 μg/mL, 25 μg/mL, 12.5 μg/mL and 6.25 μg/mL concentrations. The inoculated wells were incubated overnight at 37 °C in a humid atmosphere. The highest dilution showing at least 99% inhibition zone is taken as MIC.

The investigation of antibacterial screening revealed that all the newly synthesized compounds showed moderate to excellent inhibition. Compound **8a** shows very good activity against *E. coli* and *P. aeruginosa* while moderate activity against *S. typhi*. Compounds **8b** exhibit very good activity against all tested microorganism except *S. typhi*, while compound **8c** shows very good activity against *S. aureus* only. Compound **8d** and **8e** exhibit excellent activity against *P. aeruginosa* and *S. typhi* respectively only. Compound **9a** shows excellent activity against *E. coli* and *S. aureus*, while compound **9d** exhibits excellent activity against *P. aeruginosa* and *S. aureus*. Compound **9e** exhibits excellent activity against *S. aureus* only, while compounds **9b** and **9c** show moderate activity against one bacteria strain only.

Conclusion

Present study reports synthesis of novel of ((4-phenyl-thiazol-2-yl)-{4-[2-(pyrrolidine-1-carbonyl)-phenoxy]-phenyl}-amino)-acetic acid and successively amide coupling with different amines. The antibacterial screening of newly synthesize compounds was carried out against six different organism, and some of compounds exhibits moderate to excellent activity. Many known drugs posses 2-amino thiazole nucleus as active core and it well known to shows the potential pharmacological activities. The presence of diphenyl ether moiety is also instrumental in contributing to the net biological activity of a system. The antibacterial screening suggests that the newly synthesized compound **8b** having bromo substitution on phenyl ring exhibited good to excellent activity against all the tested microorganisms except *S. typhi*. Compound **8a** having phenyl ring only also exhibit very good activity against some organism. On the contrary to expectation replacement of phenyl ring with thiazole moiety to the structure in compound **8f** not caused substantial enhancement in antibacterial activity.

Experimental

Melting points were determined with Buchi B-545 melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer PE-1600 FTIR spectrometer in KBr disc. ^{1}H NMR spectra were recorded on a Varian spectrometer using TMS as an internal standard. Mass spectra were performed on a Waters mass spectrometer (Waters LC/MS-3100 Mass Detector API). Progress of the reaction was checked by thin layer chromatography (TLC) on silica gel coated aluminum sheets (silica gel 60 F254) using a mixture of ethyl acetate and hexane (1:1 v/v). All of the solvents and materials were reagent grade and purified as required.

Synthesis of 2-(4-amino-phenoxy)-benzoic acid ethyl ester (1). Compound **1** was synthesized following a literature method,[23] starting from 2-hydroxy benzoic acid ethyl ester and 4-fluoro nitrobenzene to give title compound **1** (yield 73%) as reddish oil. Anal. Calcd. for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.24; H, 6.08; N, 5.21. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.29 (t, 3H, J = 7.1 Hz, CH_3), 4.26 (q, 2H, J = 7.1, CH_2), 4.98 (bs, 2H, NH_2), 6.42-6.44 (dd, 2H, ArH), 6.71-6.73 (dd, 2H, ArH), 7.11-7.63 (m, 4H, ArH). Mass spectrum (ES) *m*/*z* 258 (M+1).

Synthesis 2-[4-(3-benzoyl-thioureido)-phenoxy]-benzoic acid ethyl ester (2). To a suspension of NH_4SCN (1.06 g, 0.014 mol) in acetone (50 mL) was added slowly benzoylchloride (1.47 mL, 0.0127 mol) under dry condition within 10 min. After completion of addition, reaction mixture was refluxed for 15 min. A solution of compound **1** (3.0 g, 0.011 mol) in acetone (20 mL) was added to above stirred suspension at such a rate that refluxes gently. After completion of addition reaction mixture was refluxed for 30 min. Reaction mixture was cooled and poured in water, resulting solid was filtered and washed with water. Solid was recrystalized in ethanol to give pure compound **2** as off-white solid, Yield 80%, mp 173 - 175 °C. Anal. Calcd. for $C_{23}H_{20}N_2O_4S$: C, 65.70; H, 4.79; N, 6.66. Found: C, 65.58; H, 4.92; N, 6.43. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.32 (t, 3H, J = 7.1 Hz, CH_3), 4.28 (q, 2H, J = 7.1 Hz, CH_2), 6.40-6.43 (d, 2H, ArH), 6.73-6.76 (d, 2H, ArH), 7.15-7.21 (d, 3H, ArH), 7.25-7.37 (m, 4H, ArH), 7.41-7.61 (m, 2H, ArH), 10.21 (s, 1H, NHCS), 12.83 (s, 1H, CONHCS). Mass spectrum (ES) *m*/*z* 419 (M-1).

Synthesis of 2-(4-thioureido-phenoxy)-benzoic acid ethyl ester (3). To a suspension of compound 2 (3.8 g, 0.009 mol) in methanol (50 mL) was added sodium methoxide (0.732 g, 0.0135 mol), and stirred at room temperature for 1 h. Reaction mixture was poured in 5% aq. HCl and stirred for 10 min. Resulting solid was filtered, washed with water and suck dried. Solid was recrystallized from ethanol giving pure compound **3** as white solid, Yield 73%, mp 182 - 184 °C. Anal. Calcd. for $C_{16}H_{16}N_2O_3S$: C, 60.74; H, 5.10; N, 8.85. Found: C, 61.03; H, 5.34; N, 8.75. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.29 (t, 3H, J = 7.1 Hz, CH_3), 4.26 (q, 2H, J = 7.1 Hz, CH_2), 6.41-6.46 (d, 2H, ArH), 6.71-6.77 (d, 2H, ArH), 7.09-7.21 (m, 2H, ArH), 7.25-7.31 (m, 2H, ArH), 8.23 (s, 2H, NH_2), 10.11 (s, 1H, NHCS). Mass spectrum (ES) *m*/*z* 317 (M+1).

Synthesis of 2-[4-(4-phenyl-thiazol-2-ylamino)-phenoxy]-benzoic acid ethyl ester (4). A mixture of compound **3** (2.0 g, 0.0063 mol), phenacyl chloride (0.942 g, 0.0066 mole) and sodium bicarbonate (1.1 g, 0.0132 mol) in acetonitrile (30 mL) was heated at 60 - 62 °C with stirring for 2 h. Reaction mixture was carefully poured in ice water (100 mL) and stirred for 15 min. Resulting solid was filtered and washed with water (50 mL) and hexane (20 mL). Solid was dried to give compound **4** as off-white solid, Yield 78%, mp 202 - 204 °C. Anal. Calcd. for $C_{24}H_{20}N_2O_3S$: C, 69.21; H, 4.84; N, 6.73. Found: C, 69.09; H, 4.52; N, 6.23. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.28 (t, 3H, J = 7.1 Hz, CH_3), 4.25 (q, 2H, J = 7.1 Hz, CH_2), 6.43-6.48 (d, 2H, ArH), 6.73-6.81 (d, 2H, ArH), 7.13-7.22 (m, 3H, ArH), 7.38-7.48 (m, 5H, ArH), 7.51-7.73 (m, 2H, ArH), 10.07 (s, 1H, NH). Mass spectrum (ES) *m*/*z* 417 (M+1).

Synthesis of [2-[4-(4-phenyl-thiazol-2-ylamino)-phenoxy]-benzoic acid (5). A mixture of compound **4** (2.0 g, 0.0048 mol), 20% aquous NaOH (1.92 mL, 0.0096 mol) in methanol (20 mL) and THF (20 mL) was stirred at room temperature for 10 h. Solvent was evaporated completely under vacuum and water (50 mL) was added to residue. Aqueous solution was acidified by addition of 10% aq. HCl to pH-4. Solid separated was filtered, washed with water (50 mL) and suck dried. Solid was recrystalized from ethanol to give compound **5** as white solid, Yield 75%, mp 245 - 247 °C. Anal. Calcd. for $C_{22}H_{16}N_2O_3S$: C, 68.02; H, 4.15; N, 7.21. Found: C, 68.30; H, 4.29; N, 7.39. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 6.42-6.46 (d, 2H, ArH), 6.69-6.78 (d, 2H, ArH), 7.15-7.23 (m, 3H, ArH), 7.35-7.49 (m, 5H, ArH), 7.68-7.78 (m, 2H, ArH), 10.10 (s, 1H, NH), 12.31 (s, 1H, COOH). Mass spectrum (ES) *m*/*z* 387 (M-1).

Synthesis of {2-[4-(4-phenyl-thiazol-2-ylamino)-phenoxy]-phenyl}-pyrrolidin-1-yl-methanone (6). A mixture of compound **5** (1.3 g, 0.0033 mol), pyrolidine (0.302 mL, 0.0036 mol), diisopropyl ethyl amine (DIPEA) (1.14 mL, 0.0066 mol) and dimethyl amino pyridine (40.0 mg, 0.33 mmol) in THF (30 mL) was stirred at 10 °C. 1-Ethyl-3-(3'-dimethylaminopropyl) carbodiimide (EDCI) (0.753 g, 0.0039 mol) was added portion wise to above reaction mixture and stirred at room temperature for 10 h. Solvent was evaporated under vacuum, water was added to residue and acidified to pH-6 by addition of 10% aq. HCl. Solid was filtered, washed with water and suck dried to give compound **6** as white solid, Yield 72%, mp 173 - 175 °C. Anal. Calcd. for $C_{26}H_{23}N_3O_2S$: C, 70.72; H, 5.25; N, 9.52. Found: C, 70.58; H, 5.39; N, 9.31. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.16 (t, 4H, J = 6.6 Hz, 2CH$_2$), 3.14 (t, 4H, J = 6.6 Hz, 2CH$_2$), 6.87-6.91 (d, 2H, ArH), 7.10-7.17 (d, 3H, ArH), 7.20-7.31 (m, 2H, ArH), 7.36-7.56 (m, 4H, ArH), 7.61-7.89 (m, 3H, ArH), 10.12 (s, 1H, NH). Mass spectrum (ES) *m*/*z* 442 (M+1).

Synthesis of {((4-phenyl-thiazol-2-yl)-{4-[2-(pyrrolidine-1-carbonyl)-phenoxy]-phenyl}-amino)-acetic acid (7). A suspension of 60% NaH (0.136 g, 0.0034 mol) and DMF (10 mL) was stirred at 10 °C. Solution of compound **6** (1.0 g, 0.0022 mol) in DMF (10 mL) was added and stirred for 30 min. Ethyl bromoacetate (0.275 mL, 0.0024 mol) was added to above reaction mixture and stirred for 3 h at room temperature. Methanol (10 mL) and water (10 mL) was added successively to reaction mixture and stirred at room temperature for 5 h. Reaction mixture was poured in ice water (50 mL) and washed with ethyl acetate (30 mL). Aqueous layer was acidified to pH-4 by addition of dil HCl and solid separated was filtered. Solid was washed with water (20), hexane (20) and suck dried to give compound **7** as white solid, Yield 70%, mp 246 - 248 °C. Anal. Calcd. for $C_{28}H_{25}N_3O_4S$: C, 67.32; H, 5.04; N, 8.41. Found: C, 67.10; H, 5.23; N, 8.18. ^{1}H- NMR (400 MHz, DMSO-d_6) δ 1.15 (t, 4H, J = 6.6 Hz, 2CH$_2$), 3.16 (t, 4H, J = 6.6 Hz, 2CH$_2$), 4.31 (s, 2H, CH$_2$), 6.40- 6.47 (d, 2H, ArH), 6.67-6.75 (d, 2H, ArH), 7.13-7.21 (m, 3H, ArH), 7.33-7.41 (m, 5H, ArH), 7.68-7.77 (m, 2H, ArH), 12.41 (s, 1H, COOH). Mass spectrum (ES) *m*/*z* 498 (M-1).

General procedure for synthesis of compound 8a-f and 9a-e. A mixture of compound **7** (0.30 mmol), corresponding amine derivative (0.30 mmol), diisopropyl ethyl amine (DIPEA) (0.60 mmol) and *N*,*N*-dimethyl amino pyridine (0.03 mmol) in THF (10 mL) was stirred at 10 °C. 1-Ethyl-3-(3'-dimethylamino-propyl)carbodiimide (EDCI) (0.36 mmol) was added to above stirred solution portion wise. Reaction mixture was stirred at room temperature for 4 - 7 h. Solvent was evaporated under vacuum, water was added to residue and acidified to pH-6 by addition of dil. HCl. Solid separated was filtered, washed with water (10 mL) and suck dried. Solid was recrystallized from 95% ethanol giving pure compound **8a-f** and **9a-e**.

***N*-Phenyl-2-((4-phenyl-thiazol-2-yl)-{4-[2-(pyrrolidine-1-carbonyl)-phenoxy]-phenyl}-amino)-acetamide (8a).** Obtained as white crystals, Yield 80%, mp 113 - 115 °C. Anal. Calcd. for $C_{34}H_{30}N_4O_3S$: C, 71.06; H, 5.26; N, 9.75. Found: C, 71.30; H, 5.09; N, 9.59. IR υ (cm^{-1}) 3436 (CON-H), 1701 (C=O). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.17-1.19 (m, 4H, 2CH$_2$), 3.21 (t, 4H, J = 6.6 Hz, 2CH$_2$), 4.68 (s, 2H, CH$_2$), 7.03-7.10 (m, 4H, ArH), 7.20-7.52 (m, 9H, ArH), 7.61-7.73 (dd, 4H, ArH), 7.81-7.89 (dd, 2H, ArH), 10.40 (s, 1H, CONH). Mass spectrum (ES) *m*/*z* 575 (M+1).

***N*-(4-Bromo-phenyl)-2-((4-phenyl-thiazol-2-yl)-{4-[2-(pyrrolidine-1-carbonyl)-phenoxy]-phenyl}-amino)-acetamide (8b).** Obtained as off-white crystals, Yield 76%, mp 85 - 87 °C. Anal. Calcd. for $C_{34}H_{29}BrN_4O_3S$: C, 62.48; H, 4.47; N, 8.57. Found: C, 62.61; H, 4.70; N, 8.31. IR υ (cm^{-1}) 3431 (CON-H), 1678 (C=O). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.18-1.20 (m, 4H, 2CH$_2$), 3.22 (t, 4H, J = 6.6 Hz, 2CH$_2$), 4.68 (s, 2H, CH$_2$), 7.00-7.11 (m, 4H, ArH), 7.19-7.49 (m, 8H, ArH), 7.63-7.77 (m, 4H, ArH), 7.81-7.89 (m, 2H, ArH), 10.64 (s, 1H, CONH). Mass spectrum (ES) *m*/*z* 653 (M+1).

***N*-(4-Cyano-phenyl)-2-((4-phenyl-thiazol-2-yl)-{4-[2-(pyrrolidine-1-carbonyl)-phenoxy]-phenyl}-amino)-acetamide (8c).** Obtained as white crystals, Yield 71%, mp 95 - 97 °C. Anal. Calc. for $C_{35}H_{29}N_5O_3S$: C, 70.10; H, 4.87; N, 11.68. Found: C, 69.91; H, 5.05; N, 11.43. IR υ (cm^{-1}) 3448 (CON-H), 1684 (C=O). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.16-1.19 (m, 4H, 2CH$_2$), 3.21 (t, 4H, J = 6.5 Hz, 2CH$_2$), 4.66 (s, 2H, CH$_2$), 7.03-7.10 (m, 4H, ArH), 7.20-7.48 (m, 8H, ArH), 7.60-7.75 (m, 4H, ArH), 7.80-7.88 (m, 2H, ArH), 10.61 (s, 1H, CONH). Mass spectrum (ES) *m*/*z* 600 (M+1).

***N*-(4-Acetyl-phenyl)-2-((4-phenyl-thiazol-2-yl)-{4-[2-(pyrrolidine-1-carbonyl)-Phenoxy]-phenyl}-amino)-acetamide (8d).** Obtained as off-white crystals, Yield 69%, mp 105 - 107 °C. Anal. Calcd. for $C_{36}H_{32}N_4O_4S$: C, 70.11; H, 5.23; N, 9.08. Found: C, 69.96; H, 5.48; N, 9.26. IR υ (cm^{-1}): 3449 (CON-H), 1700 (C=O). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.17-1.20 (m, 4H, 2CH$_2$), 2.53 (s, 3H, CH$_3$), 3.23 (t, 4H, J = 6.6 Hz, 2CH$_2$), 4.67 (s, 2H, CH$_2$), 7.03-7.10 (m, 4H, ArH), 7.20-7.52 (m, 8H, ArH), 7.61-7.73 (m, 4H, ArH), 7.80-7.89 (m, 2H, ArH), 10.50 (s, 1H, CONH). Mass spectrum (ES) *m*/*z* 617 (M+1).

***N*-(4-Isopropyl-phenyl)-2-((4-phenyl-thiazol-2-yl)-{4-[2-(pyrrolidine-1-carbonyl)-phenoxy]-phenyl}-amino)-acetamide (8e).** Obtained as white crystals, Yield 73%, mp 113 - 115 °C. Anal. Calcd. for $C_{37}H_{36}N_4O_3S$: C, 72.05; H, 5.88; N, 9.08. Found: C, 72.21; H, 6.02; N, 9.19. IR υ (cm^{-1}) 3431 (CON-H), 1687 (C=O). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.18-1.20 (m, 4H, 2CH$_2$), 1.29 (d, 6H, J = 6.6 Hz, 2CH$_3$), 3.11- 3.14 (m, 1H, CH), 3.21 (t, 4H, J = 6.6 Hz, 2CH$_2$), 4.68 (s, 2H, CH$_2$), 7.00-7.11 (m, 4H, ArH), 7.19-7.49 (m, 8H, ArH), 7.63-7.77 (m, 4H, ArH), 7.81-7.89 (m, 2H, ArH), 10.38 (s, 1H, CONH). Mass spectrum (ES) *m*/*z* 617 (M+1).

2-((4-Phenyl-thiazol-2-yl)-{4-[2-(pyrrolidine-1-carbonyl)-phenoxy]-phenyl}-amino)-*N*-thiazol-2-yl-acetamide (8f). Obtained as pale yellow crystals, Yield 73%, mp 90 - 92 °C. Anal. Calcd. for $C_{31}H_{27}N_5O_3S_2$: C, 64.01; H, 4.68; N, 12.04. Found: C, 63.90; H, 5.89; N, 11.89. IR υ (cm^{-1}) 3434 (N-H), 1669 (C=O). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.16-1.19 (m, 4H, 2CH$_2$), 3.22 (t, 4H, J = 6.6 Hz, 2CH$_2$), 4.66 (s, 2H, CH$_2$), 6.90-7.08 (m, 3H, ArH), 7.20-7.52 (m, 7H, ArH), 7.60-7.75 (m, 4H, ArH), 7.80-7.88 (m, 2H, ArH), 10.68 (s, 1H, CONH). Mass spectrum (ES) *m/z* 582 (M+1).

2-((4-Phenyl-thiazol-2-yl)-{4-[2-(pyrrolidine-1-carbonyl)-phenoxy]-phenyl}-amino)-1-piperidin-1-yl-ethanone (9a). Obtained as white crystals, Yield 81%, mp 65 - 67 °C. Anal. Calcd. for $C_{33}H_{34}N_4O_3S$: C, 69.94; H, 6.05; N, 9.89. Found: C, 70.17; H, 5.89; N, 10.11. IR υ (cm^{-1}) 1637 (C=O). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.60-1.69 (m, 4H, $2CH_2$), 1.76-1.81 (m, 6H, $3CH_2$), 3.34 (t, 4H, J = 6.6 Hz, $2CH_2$), 3.45 (t, 4H, J = 6.5 Hz, $2CH_2$), 4.81 (s, 2H, CH_2), 7.01-7.16 (m, 4H, ArH), 7.23-7.29 (m, 2H, ArH), 7.36-7.47 (m, 4H, ArH), 7.53-7.58 (dd, 2H, ArH), 7.80-7.84 (dd, 2H, ArH). Mass spectrum (ES) *m/z* 567 (M+1).

1-Morpholin-4-yl-2-((4-phenyl-thiazol-2-yl)-{4-[2-(pyrrolidine-1-carbonyl)-phenoxy]-phenyl}-amino)-ethanone (9b). Obtained as white crystals, Yield 78%, mp 73 - 75 °C. Anal. Calcd. for $C_{32}H_{32}N_4O_4S$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.41; H, 5.53; N, 9.67. IR υ (cm^{-1}) 1640 (C=O). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.59-1.67 (m, 4H, $2CH_2$), 3.35 (t, 4H, J = 6.6 Hz, $2CH_2$), 3.44 (t, 4H, J = 6.6 Hz, $2CH_2$), 3.59- 3.66 (m, 4H, $2CH_2$), 4.79 (s, 2H, CH_2), 7.08-7.19 (m, 4H, ArH), 7.28-7.31 (m, 2H, ArH), 7.37-7.49 (m, 4H, ArH), 7.50-7.58 (m, 2H, ArH), 7.82-7.86 (m, 2H, ArH). Mass spectrum (ES) *m/z* 569 (M+1).

1-(4-Phenyl-piperidin-1-yl)-2-((4-phenyl-thiazol-2-yl)-{4-[2-(pyrrolidine-1-carbonyl)-phenoxy]-phenyl}-amino)-ethanone (9c). Obtained as off-white crystals, Yield 71%, mp 101 - 103 °C, Anal. Calcd. for $C_{39}H_{38}N_4O_3S$: C, 72.87; H, 5.96; N, 8.72. Found: C, 72.60; H, 6.18; N, 8.51. IR υ (cm^{-1}) 1639 (C=O). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.58-1.64 (m, 4H, $2CH_2$), 1.72-1.79 (m, 4H, $2CH_2$), 2.71-2.78 (m, 1H, CH), 3.32- 3.35 (t, 4H, J = 6.6 Hz, $2CH_2$), 3.42-3.48 (t, 4H, J = 6.6 Hz, $2CH_2$), 4.69 (s, 2H, CH_2), 7.05-7.12 (m, 5H, ArH), 7.15-7.19 (m, 4H, ArH), 7.29-7.33 (m, 2H, ArH), 7.39-7.48 (m, 4H, ArH), 7.51-7.59 (m, 2H, ArH), 7.81-7.85 (m, 2H, ArH). Mass spectrum (ES) *m/z* 643 (M+1).

1-(4-Methyl-piperazin-1-yl)-2-((4-phenyl-thiazol-2-yl)-{4-[2-(pyrrolidine-1-carbonyl)-phenoxy]-phenyl}-amino)-ethanone (9d). Obtained as white crystals, Yield 77%, mp 101 - 103 °C. Anal. Calcd. for $C_{33}H_{35}N_5O_3S$: C, 68.13; H, 6.06; N, 12.00. Found: C, 68.39; H, 5.87; N, 12.22. IR υ (cm^{-1}) 1643 (C=O). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.60-1.69 (m, 4H, $2CH_2$), 2.27 (s, 3 H, CH_3), 2.58 (t, 4 H, J = 6.6 Hz, $2CH_2$), 3.34 (t, 4H, J = 6.6 Hz, $2CH_2$), 3.46 (t, 4 H, J = 6.6 Hz, $2CH_2$), 4.72 (s, 2H, CH_2), 7.01-7.16 (m, 4 H, ArH), 7.23-7.29 (m, 2 H, ArH), 7.36-7.47 (m, 4 H, ArH), 7.53-7.58 (dd, 2 H, ArH), 7.80-7.84 (dd, 2 H, ArH). Mass spectrum (ES) *m/z* 582 (M+1).

1-(4-Phenyl-piperazin-1-yl)-2-((4-phenyl-thiazol-2-yl)-{4-[2-(pyrrolidine-1-carbony)-phenoxy]-phenyl}-amino)-ethanone (9e). Obtained as off white crystals, Yield 81%, mp 113 - 115 °C. Anal. Calcd. for $C_{38}H_{37}N_5O_3S$: C, 70.89; H, 5.79; N, 10.80. Found: C, 70.51; H, 5.97; N, 10.51. IR υ (cm^{-1}) 1639 (C=O). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.59-1.64 (m, 4H, $2CH_2$), 3.33 (t, 4H, J = 6.6 Hz, $2CH_2$), 3.46 (t, 4H, J = 6.6 Hz, $2CH_2$), 3.58 (t, 4H, J = 6.6 Hz, $2CH_2$), 4.69 (s, 2H, CH_2), 7.05-7.12 (m, 5H, ArH), 7.15-7.19 (m, 4H, ArH), 7.29-7.33 (m, 2H, ArH), 7.39-7.48 (m, 4H, ArH), 7.51-7.59 (m, 2H, ArH), 7.81-7.85 (m, 2H, ArH). Mass spectrum (ES) *m/z* 644 (M+1).

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