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A new route for the synthesis of 4-arylacetamido-2-aminothiazoles and their biological evaluation

Abstract: A series of 4-arylacetamido-2-amino- and 2-arylamino-1,3-thiazoles (**4a**–**o**) were synthesized in a single step in high yields from ω-bromoacetoacetanilides and thiourea/phenyl thioureas and were characterized by spectral and analytical methods. The compounds were evaluated for their in vitro antibacterial antifungal and antioxidant activities. In vitro antimicrobial evaluation of these compounds indicated their specificity towards Gram-positive species. *p*-Tolyl and *m*-chlorophenyl substituents on the arylamino moiety (compounds **4b** and **4g**) exhibited the lowest minimum inhibitory concentration values. The other compounds exhibited promising antimicrobial and moderate antioxidant activity.

Keywords: antimicrobial activity; antioxidant; 4-arylacetamido-2-amino-1,3-thiazole; ω-bromoacetoacetanilide; phenyl thiourea.

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1 Introduction

The 1,3-thiazole nucleus has been a seat of diverse biological activities through its innumerable derivatives [1–4]. 2,4- and 2,5-disubstituted thiazoles have exhibited promising anti-inflammatory, analgesic and antipyretic activities [5–9]. Cystothiazoles isolated from the *Cystobacter fuscus* have been reported for their selective, broad-spectrum antifungal activity without affecting the bacterial growth [10]. Arylamides from 2-amino-1,3-thiazoles have been reported as antiviral agents [11]. The introduction of a phenoxypropanolamine side chain in 2-amino-1,3-thiazole-4-acetic acid has resulted in selective β3-adrenergic receptor agonists [12]. 2-Amino-1,3-thiazole with a methoxyimino function at C-4 forms part of cefotaxime [13]. 2-Aminothiazole-4-carboxylates and carboxamides have been reported to exhibit potent antimicrobial activity (Fig. 1) [14].

It is also pertinent to mention that the amides reported in the literature were prepared by the two-step route [12] involving the synthesis of thiazole esters or acids **5** followed by amidation. In the present paper, we describe a single-step synthesis of 4-arylacetamido-2-amino-1,3-thiazoles by the reaction of ω-bromoacetoacetanilide and thioureas through route B (Fig. 2). Retrosynthetic analysis (Fig. 2) shows that the target molecules can be obtained by a two-step route (A) through intermediate 2-amino-1,3-thiazole-4-acetic acid esters **5**, which have been reported earlier in the literature [5, 6, 12]. A similar method has been reported, where morpholine derivatives of 1,3-thiazole were synthesized and found to function as ion channel modulators [15]. This route requires amidation of the intermediate esters **5**. The steps involved in the synthesis are outlined in Scheme 1.

2 Results and discussion

ω-Bromoacetoacetanilides **2** were prepared by the bromination of acetoacetanilides **1** [16] and were refluxed with equimolar quantities of phenyl thioureas **3** [17] in ethanol to obtain the target compounds in a single step. Sufficiently pure compounds were obtained in good yields and the structures were confirmed by spectral methods.

As a typical case, compound **4b** (R = 4-CH_3, R′ = H) gave an IR spectrum which exhibited NH–Ar stretching frequency at 3299 cm^{-1}, amide NH at 3392 cm^{-1} and amide carbonyl at 1665 cm^{-1}. In the ^{1}H NMR spectrum, singlets at δ = 2.20, 3.59 and 6.68 ppm were assigned to 4-CH_3, CH_2 protons and thiazole 5-H, respectively. Aminothiazole NH appeared at 10.01 ppm and amide NH at 10.12 ppm. In the ^{13}C NMR spectrum of **4b**, the two upfield signals at δ = 20.29 and 30.63 ppm were assigned to CH_3 and CH_2 carbons, respectively. Two low-intensity downfield signals at 163.36 and 167.83 ppm were due to carbonyl and azomethine carbon, respectively. Aromatic carbons resonated in the expected range between 103.86 ppm and 146.02 ppm.

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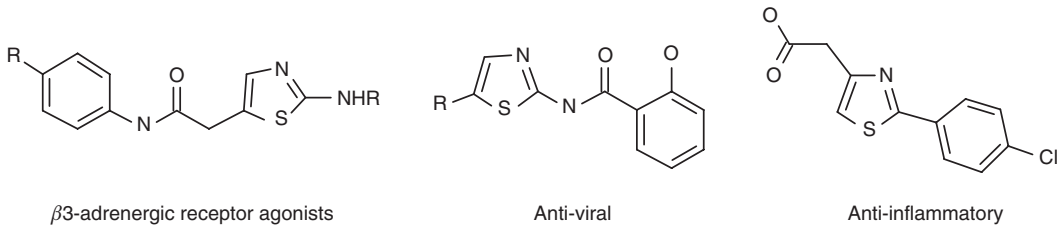


Fig. 1: Structurally related biologically active thiazoles.

2.1 Biological evaluation

All synthesized compounds were screened for in vitro antibacterial, antifungal and antioxidant activities.

2.1.1 Antibacterial activity

All the synthesized compounds were evaluated for their antibacterial activity against (i) Gram-positive bacteria, *Enterococcus faecalis* (ATCC 35550) and *Staphylococcus aureus* (ATCC 12598), and (ii) Gram-negative bacteria, *Klebsiella pneumoniae* (ATCC 29665) and *Escherichia coli* (ATCC 25922). The compounds showed very good antibacterial activity especially against Gram-positive species (Table 1). Some of the compounds (**4b**, **4d**, **4f**, **4g**, **4m**, **4n**, **4o**) were found to be more potent than standard ciprofloxacin against *S. aureus*, and almost all compounds were found to be more potent (0.2–0.8 μg mL^{-1}) than the standard ciprofloxacin against *E. faecalis*. Compounds were inactive against Gram-negative bacteria. Compound **4f** showed a minimum inhibitory concentration (MIC) of 12.5 μg mL^{-1}, while the rest of the compounds showed MIC values of 100 μg mL^{-1}.

The absence of any substitutions on both the aryl rings makes compound **4e** totally inactive, but the introduction of –Cl at the *meta*-position of the aryl-acetamide moiety activates compound **4k** to some extent against *S. aureus* (MIC 3.25 μg mL^{-1}). The presence of a free –NH_2 group without any substitution on the aryl(acetamide) ring (compound **4a**) was found to give the least active compound (MIC = 12.5 μg mL^{-1}) against *S. aureus*, but the presence of Cl at position C-3 or C-4 of the aryl(acetamide) ring may be the reason for better activity (**4h** and **4j**) with MIC = 1.6 μg mL^{-1}. The presence of the chloro group at the *ortho*-position of the aryl amino moiety makes it the least active one amongst the synthesized compounds with MIC = 12.5 μg mL^{-1}.

2.1.2 Antifungal activity

All the synthesized title compounds were screened for their antifungal activity against *Candida albicans* (ATCC 2091) and *Aspergillus niger* (ATCC 9029). The antifungal data (Table 1) revealed that all the synthesized compounds irrespective of the substituent present showed very good antifungal activity against *C. albicans* and *A. niger* with MIC values between 0.2 and 1.6 μg mL^{-1} compared to standard fluconazole (MIC values 16 and 8 μg mL^{-1}). Compounds **4d**, **4g**, **4l**, **4n** (against *C. albicans*) and compounds **4a**–**4e**, **4g**, **4i**, **4j**, **4n** (against *A. niger)* showed highest activity with an MIC of 0.2 μg mL^{-1}.

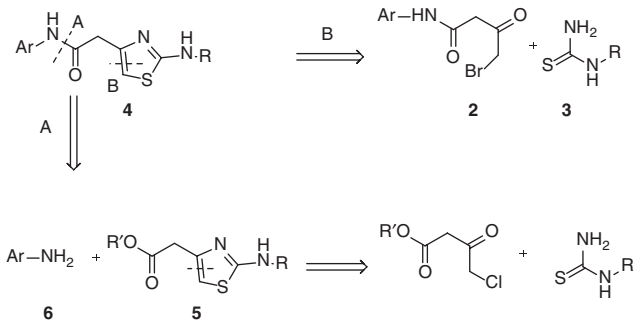
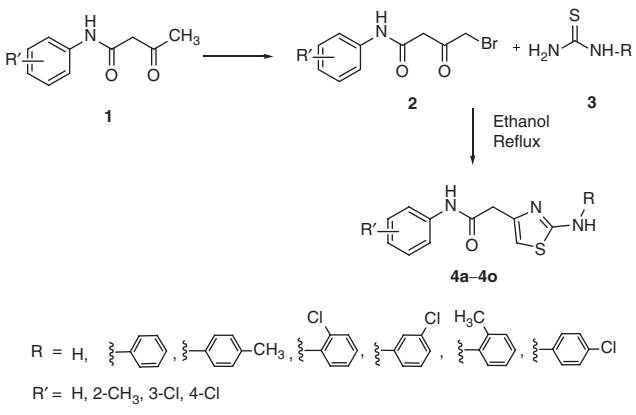


Fig. 2: Retrosynthetic analysis of *N*-phenyl-2-(2-(arylamino)-1,3-thiazol-4-yl)acetamide.



Scheme 1: Synthesis of substituted 4-arylacetamido 2-amino-1,3-thiazoles **4a–4o**.

Table 1: Results of biological evaluation of compounds **4a–4o** (MICs in μg mL^{-1}).

Compound	R	R′	Antibacterial				Antifungal	
			Gram-positive		Gram-negative			
			S. aureus	*E. faecalis*	*E. coli*	*K. pneumoniae*	*C. albicans*	*A. niger*
4a	H	H	12.5	0.2	100	100	0.4	0.2
4b	4-$CH_3C_6H_4$	H	0.2	0.2	100	100	0.4	0.2
4c	2-ClC_6H_4	H	12.5	0.2	100	100	0.8	0.2
4d	2-$CH_3C_6H_4$	H	0.2	0.8	100	100	0.2	0.2
4e	C_6H_5	H	–	1.6	–	–	0.8	0.2
4f	4-ClC_6H_4	H	0.2	0.2	12.5	100	0.8	0.4
4g	3-ClC_6H_4	H	0.2	0.2	50	100	0.2	0.2
4h	H	4-Cl	1.6	0.2	50	100	1.6	0.4
4i	4-$CH_3C_6H_4$	4-Cl	3.125	0.4	100	100	0.4	0.2
4j	H	3-Cl	1.6	0.4	100	100	0.8	0.2
4k	C_6H_5	3-Cl	3.125	0.2	100	25	0.4	0.4
4l	4-ClC_6H_4	3-Cl	1.6	0.2	–	100	0.2	0.4
4m	4-$CH_3C_6H_4$	3-Cl	0.4	0.8	–	100	0.2	0.4
4n	C_6H_5	2-CH_3	0.2	0.8	100	100	0.2	0.2
4o	4-$CH_3C_6H_4$	2-CH_3	0.2	0.8	100	–	0.4	0.8
Ciprofloxacin			2	2	2	2	–	–
Fluconazole			–	–	–	–	16	8

2.1.3 Antioxidant activity

Compounds **4a**–**4o** were tested for antioxidant property with 1,1-diphenylpicrylhydrazyl (DPPH). Hydrogen or electron donation ability of the compounds was measured from the bleaching of the purple colored methanolic solution of 2,2-diphenyl-1-picrylhydrazyl (DPPH) [18, 19]. The spectrophotometric assay uses the stable radical DPPH as a reagent. One milliliter of various concentrations of the test compounds (150, 200, 250 and 300 mg mL^{-1}) in methanol was added to 4 mL of 0.004 % (*w*/*v*) methanol solution of DPPH. After a 30-min incubation period at room temperature, the absorbance was read against blank at 517 nm. The percent of inhibition (*I* %) of free radical production from DPPH was calculated by the following equation,

$$I_0 = (A_{\text{control}} - A_{\text{sample}}) / A_{\text{control}} \times 100,$$

where A_{control} is the absorbance of the control reaction (containing all reagents except the test compound) and A_{sample} is the absorbance of the test compound. Tests were carried out in triplicate.

2.2 IC_{50} values

The 50 % inhibitory concentration value (IC_{50}) is indicated as the effective concentration of the sample that is required to scavenge 50 % of the DPPH free radicals which can be obtained by linear regression of plots, where the abscissa represents the concentration of the tested compounds and the ordinate the average percent of scavenging capacity.

Compounds show moderate antioxidant properties (Table 2). Compound **4i** shows maximum activity amongst the synthesized compounds. Substituents on the aromatic ring attached to amide NH do not make much contribution to the activity, whereas a phenyl ring attached to amino nitrogen of the aminothiazole moiety has a greater contribution. The absence of the phenyl ring renders the compounds least active. Compounds **4a**, **4h**, **4j** did not show any scavenging activity even at 300 μg mL^{-1}. Further, substituents on the phenyl ring contribute to the activity. A methyl group at *para*-position (**4c**, **4b**, **4o**, **4m**) and Cl at *ortho*-position (4**c**) favors scavenging activity, whereas the presence of a methyl group (**4d**) at *ortho*-position and Cl at *meta*-position (**4g**) inhibits the scavenging activity to some extent.

3 Experimental section

Melting points were determined in open capillaries and are uncorrected. IR spectra (KBr disk) were recorded on a Nicolet-5700 FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on Bruker 300 MHz and 400 MHz spectrometers using $CDCl_3$ and [D_6]DMSO as solvents and tetramethylsilane

Table 2: Results of antioxidant activity for compounds **4a–4o**.

Compound	R	R′	300 (μg mL^{-1})	250 (μg mL^{-1})	200 (μg mL^{-1})	150 (μg mL^{-1})	IC_{50} (μg mL^{-1})
4a	H	H	–	–	–	–	–
4b	4-$CH_3C_6H_4$	H	70.00	64.65	46.09	36.31	207.41
4c	2-ClC_6H_4	H	58.63	49.00	46.90	40.71	237.20
4d	2-$CH_3C_6H_4$	H	46.18	35.95	35.72	35.25	402.00
4e	C_6H_5	H	54.98	48.53	45.25	36.45	258.03
4f	4-ClC_6H_4	H	51.46	45.36	43.96	37.74	288.58
4g	3-ClC_6H_4	H	28.30	22.00	20.64	17.79	655.00
4h	H	4-Cl	–	–	–	–	–
4i	4-$CH_3C_6H_4$	4-Cl	66.50	60.32	52.03	44.99	184.89
4j	H	3-Cl	–	–	–	–	–
4k	C_6H_5	3-Cl	49.69	48.45	35.28	33.12	293.36
4l	4-ClC_6H_4	3-Cl	51.78	45.56	34.96	33.24	291.06
4m	4-$CH_3C_6H_4$	3-Cl	62.04	34.07	30.08	25.49	278.45
4n	C_6H_5	2-CH_3	45.12	38.19	32.90	25.14	338.00
4o	4-$CH_3C_6H_4$	2-CH_3	58.87	36.66	33.25	31.49	283.21
Ascorbic acid	–	–	–	–	–	–	20.23

(TMS) as an internal standard. The chemical shifts are expressed in δ (ppm). Mass spectra were recorded on a Shimadzu GCMS-QP2010S instrument. Elemental analysis was carried out using a Hereaus CHN rapid analyzer. The purity of the compounds was checked by thin layer chromatography (TLC). All the chemicals used were purchased from Sigma-Aldrich, Bangalore, Karnatak, India.

3.1 Synthesis of (substituted phenyl) thioureas [17]

To a cold methanolic solution of the appropriate aniline (0.25 mol) were added conc. HCl (20 mL) and potassium thiocyanate (0.30 mol). The mixture was shaken well and heated over a steam bath for 3 h. The potassium chloride that separated was filtered out; the filtrate concentrated to a small volume to separate the phenyl thiourea. It was collected by filtration after cooling and purified by crystallization from methanol or rectified ethanol.

3.2 Synthesis of ω-bromoacetoacetanilides [16]

A solution of 0.022 mol of substituted acetoacetanilide in 12 mL of glacial acetic acid was treated dropwise with a solution of bromine (0.022 mol) in 17 mL of glacial acetic acid containing a small crystal of iodine, over a period of 1 h at room temperature. The mixture was stirred further for 3 h and poured into water to give ω-bromoacetoacetanilide which was crystallized from ethanol.

3.3 Synthesis of N-phenyl-2-(2-(phenylamino)-1,3-thiazol-4-yl)acetamide/2-(2-aminothiazol-4-yl)-N-phenylacetamide (3)

A mixture of 0.01 mol of substituted ω-bromoacetoacetanilide and 0.01 mol of urea/substituted phenyl thiourea was refluxed in ethanol on a water bath for 4 h; the reaction mixture was concentrated and poured into crushed ice and neutralized with few drops of liquor ammonia. The separated solid was washed thoroughly with water and dried to get analytically pure **3**.

3.4 2-(2-Amino-1,3-thiazol-4-yl)-N-phenylacetamide (4a)

Off-white solid. Yield: 70 %; m.p.: 160–61 °C. – FT-IR (KBr, cm^{-1}): υ = 1672 (C=O), 3407 (amide N–H), 3276 (asymmetric), 3188 (symmetric) (NH_2). – ^{1}H NMR (300 MHz, [D_6] DMSO, 25 °C, TMS): δ = 3.47 (s, 2H, –CH_2), 6.31 (s, 1H, thiazole H), 6.90 (s, 2H, NH_2, D_2O-exchangeable), 7.03 (m, 1H, Ar-H), 7.29 (m, 2H, Ar-H), 7.60 (d, J = 7.5 Hz, 2H, Ar-H), 10.07 (s, 1H, amide NH, D_2O-exchangeable). – MS: m/z (%) = 233 (1) [M]$^+$. – $C_{11}H_{11}N_3OS$ (233.06): calcd. C 56.63 H 4.75, N 18.01, S 13.74; found C 56.67, H 4.73, N 18.05, S 13.70.

3.5 2-(2-(p-Toluidino)-4,5-dihydro-1,3-thiazol-4-yl)-N-phenylacetamide (4b)

Off-white solid. Yield: 80 %; m.p.: 175–76 °C. – FT-IR (KBr, cm^{-1}): υ = 1665 (C=O), 3392 (amide N–H), 3299 (NH). – ^{1}H

NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 2.20 (s, 3H, CH_3), 3.59 (s, 2H, $-CH_2$), 6.68 (s, 1H, thiazole H), 7.02 (t, J = 8.3 Hz, 3H, Ar-H), 7.28 (t, J = 8.0 Hz, 2H, Ar-H), 7.45 (d, J = 8.2, 2H, Ar-H), 7.58 (d, J = 8.2 Hz, 2H, Ar-H), 10.01 (s, 1H, NH, D_2O-exchangeable), 10.12 (s, 1H, amide NH, D_2O-exchangeable). – ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 20.29 (CH_3), 30.63 (CH_2), 103.86 (thiazole C-5), 116.93, 119.03, 123.12, 128.65, 129.22, 129.92, 138.78, 139.18, 146.02 (Ar-C), 163.36 (C=O), 167.83 (thiazole C-2). – MS: m/z (%) = 323 (6) $[M]^+$. – $C_{18}H_{17}N_3OS$ (323.11): calcd. C 66.85, H 5.30, N 12.99, S 9.91; found C 66.88, H 5.36, N 12.94, S 9.88.

3.6 2-(2-(2-Chlorophenylamino)-1,3-thiazol-4-yl)-N-phenylacetamide (4c)

Off-white solid. Yield: 65 %; m.p.: 114–15 °C. – FT-IR (KBr, cm^{-1}): υ = 1664 (C=O), 3381 (amide N–H), 3261 (NH). – ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 3.59 (s, 2H, $-CH_2$), 6.68 (s, 1H, thiazole H), 7.00 (q, J = 8.1 Hz, 2H, Ar-H), 7.20 (t, J = 8.1 Hz, 1H, Ar-H), 7.28 (t, J = 7.5 Hz, 2H, Ar-H), 7.42 (d, J = 8.0 Hz, 1H, Ar-H), 7.57 (d, J = 8.1 Hz, 2H, Ar-H), 8.25 (d, J = 7.5 Hz, 1H, Ar-H), 9.55 (s, 1H, NH, D_2O-exchangeable), 10.11 (s, 1H, amide NH, D_2O-exchangeable). – MS: m/z (%) = 343 (10) $[M]^+$, 345 (3) $[M+2]^+$. – $C_{17}H_{14}ClN_3OS$ (343.05): calcd. C 59.38, H 4.10, N 12.22, S 9.33; found C 59.43, H 4.13, N 12.15, S 9.29.

3.7 2-(2-(o-Toluidino)-1,3-thiazol-4-yl)-N-phenylacetamide (4d)

Light yellow solid. Yield: 75 %; m.p.: 155–56 °C. – FT-IR (KBr, cm^{-1}): υ = 1663 (C=O), 3410 (amide N–H), 3297 (NH). – ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 2.21 (s, 3H, CH_3), 3.56 (s, 2H, $-CH_2$), 6.68 (s, 1H, thiazole H), 6.98 (m, 2H, Ar-H), 7.13 (m, 2H, Ar-H), 7.25 (t, J = 7.5 Hz, 2H, Ar-H), 7.56 (d, J = 7.8 Hz, 2H, Ar-H), 7.77 (d, J = 7.8 Hz, 1H, Ar-H), 9.22 (s, 1H, NH, D_2O-exchangeable), 10.10 (s, 1H, amide NH, D_2O-exchangeable). – MS: m/z (%) = 323 (18) $[M]^+$. – $C_{18}H_{17}N_3OS$ (323.11): calcd. C 66.85, H 5.30, N 12.99, S 9.91; found C 66.87, H 5.33, N 12.96, S 9.93.

3.8 N-Phenyl-2-(2-(phenylamino)-1,3-thiazol-4-yl)acetamide (4e)

Light brown solid. Yield: 70 %; m.p.: 142–43 °C. – FT-IR (KBr, cm^{-1}): υ = 1665 (C=O), 3425 (amide N–H), 3298 (NH). – ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C, TMS): δ = 3.63 (s, 2H, $-CH_2$), 6.62 (s, 1H, thiazole H), 6.90 (t, J = 7.2 Hz, 1H, Ar-H), 7.03 (t, J = 7.2 Hz, 1H, Ar-H), 7.22–7.31 (m, 4H, Ar-H), 7.57–7.61 (m, 4H, Ar-H), 10.01 (s, 1H, NH, D_2O-exchangeable), 10.12 (s, 1H, amide NH, D_2O-exchangeable). – MS: m/z (%) = 309 (16) $[M]^+$. – $C_{17}H_{15}N_3OS$ (309.09): calcd. C 66.00, H 4.89, N 13.58, S 10.36; found C 66.02, H 4.85, N 13.63, S 10.40.

3.9 2-(2-(4-Chlorophenylamino)-1,3-thiazol-4-yl)-N-phenylacetamide (4f)

Light brown solid. Yield: 80 %; m.p.: 183–84 °C. – FT-IR (KBr, cm^{-1}): υ = 1662 (C=O), 3373 (amide N–H), 3251 (NH). – ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 3.58 (s, 2H, $-CH_2$), 6.72 (s, 1H, thiazole H), 7.02 (t, J = 6.0 Hz, 1H, Ar-H), 7.28 (t, J = 9.0 Hz, 4H, Ar-H), 7.61 (t, J = 9.0 Hz, 4H, Ar-H), 10.13 (s, 1H, NH, D_2O-exchangeable), 10.29 (s, 1H, amide NH, D_2O-exchangeable). – MS: m/z (%) = 343 (9) $[M]^+$, 345 (3) $[M+2]^+$. – $C_{17}H_{14}ClN_3OS$ (343.05): calcd. C 59.38, H 4.10, N 12.22, S 9.33; found C 59.35, H 4.14, Cl 10.31, N 12.18, S 9.30.

3.10 2-(2-(3-Chlorophenylamino)-1,3-thiazol-4-yl)-N-phenylacetamide (4g)

Off-white solid. Yield: 65 %; m.p.: 110–11 °C. – FT-IR (KBr, cm^{-1}): υ = 1665 (C=O), 3265 (amide N–H), 3189 (NH). – ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 3.63 (s, 2H, $-CH_2$), 6.70 (s, 1H, thiazole H), 6.92 (d, J = 7.3 Hz, 1H, Ar-H), 7.04 (d, J = 7.3 Hz, 1H, Ar-H), 7.27 (t, J = 9.0 Hz, 3H, Ar-H), 7.40 (d, J = 7.3 Hz, 1H, Ar-H), 7.60 (d, J = 9.0 Hz, 2H, Ar-H),7.85 (s, 1H, Ar-H), 10.15 (s, 1H, NH, D_2O-exchangeable), 10.37 (s, 1H, amide NH, D_2O-exchangeable). – MS: m/z (%) = 343 (9) $[M]^+$, 345 (3) $[M+2]^+$. – $C_{17}H_{14}ClN_3OS$ (343.05): calcd. C 59.38, H 4.10, N 12.22, S 9.33; found C 59.41, H 4.09, N 12.15, S 9.28.

3.11 2-(2-Amino-1,3-thiazol-4-yl)-N-(4-chlorophenyl)acetamide (4h)

Light brown solid. Yield: 65 %; m.p.: 152–53 °C. – FT-IR (KBr, cm^{-1}): υ = 1663 (C=O), 3293 (amide N–H), 3178 (asymmetric), 3139 (symmetric) (NH_2). – ^{1}H NMR (300 MHz, [D_6] DMSO, 25 °C, TMS): δ = 3.43 (s, 2H, $-CH_2$), 6.28 (s, 1H, thiazole H), 6.89 (s, 2H, NH_2, D_2O-exchangeable), 7.32 (d, J = 7.0 Hz, 2H, Ar-H), 7.61 (d, J = 7.0 Hz, 2H, Ar-H), 10.21 (s, 1H, amide NH, D_2O-exchangeable). – MS: m/z (%) = 267 (8) $[M]^+$, 269 (2.5) $[M+2]^+$. – $C_{11}H_{10}ClN_3OS$ (267.02): calcd.

C 49.35, H 3.76, N 15.69, S 11.98; found C 49.38, H 3.72, N 15.72, S 12.02.

3.12 2-(2-(p-Toluidino)-1,3-thiazol-4-yl)-N-(4-chlorophenyl)acetamide (4i)

Off-white solid. Yield: 60 %; m.p.: 174–75 °C. – FT-IR (KBr, cm^{-1}): υ = 1668 (C=O), 3405 (amide N–H), 3295 (NH). – ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 2.18 (s, 3H, $-CH_3$), 4.22 (s, 2H, $-CH_2$), 6.56 (s, 1H, thiazole H), 7.02 (d, J = 7.1 Hz, 2H, Ar-H), 7.33 (d, J = 7.3 Hz, 2H, Ar-H), 7.40 (d, J = 7.1 Hz, 2H, Ar-H), 7.59 (d, J = 7.3 Hz, 2H, Ar-H), 9.99 (s, 1H, NH, D_2O-exchangeable), 10.28 (s, 1H, amide NH, D_2O-exchangeable). – ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 14.06 (CH_3), 36.99 (CH_2), 103.94 (thiazole C-5), 116.93, 120.55, 126.67, 128.57, 129.22, 129.94, 138.13, 138.76, 145.80 (Ar-C), 163.38 (C=O), 168.02 (thiazole C-2). – MS: m/z (%) = 357 (18) $[M]^+$, 359 (6) $[M+2]^+$. – $C_{18}H_{16}ClN_3OS$ (357.07): calcd. C 60.41, H 4.51, N 11.74, S 8.96; found C 60.47, H 4.54, N 11.70, S 8.99.

3.13 2-(2-Amino-1,3-thiazol-4-yl)-N-(3-chlorophenyl)acetamide (4j)

Off-white solid. Yield: 70 %; m.p.: 191–92 °C. – FT-IR (KBr, cm^{-1}): υ = 1661 (C=O), 3285 (amide N–H), 3186 (asymmetric), 3118 (symmetric) (NH_2). – ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 4.41 (s, 2H, $-CH_2$), 6.29 (s, 1H, thiazole H), 6.85 (s, 2H, NH_2, D_2O-exchangeable), 7.06 (d, J = 7.5 Hz, 1H, Ar-H), 7.29 (t, J = 7.9 Hz, 1H, Ar-H), 7.39 (d, J = 7.9 Hz, 1H, Ar-H), 7,75 (s, 1H, Ar-H), 10.29 (s, 1H, amide NH, D_2O-exchangeable). – ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 39.74 (CH_2), 102.73 (thiazole C-5), 117.32, 117.85, 118.40, 122.78, 123.09, 130.43, 133.01, 140.62, 145.39 (Ar-C), 168.24 (C=O), 168.40 (thiazole C-2). – MS: m/z (%) = 267 (6) $[M]^+$, 269 (2) $[M+2]^+$. – $C_{11}H_{10}ClN_3OS$ (267.02): calcd. C 49.35, H 3.76, N 15.69, S 11.98; found C 49.31, H 3.78, N 15.65, S 11.95.

3.14 N-(3-Chlorophenyl)-2-(2-(phenylamino)-1,3-thiazol-4-yl)acetamide (4k)

Off-white solid. Yield: 65 %; m.p.: 138–40 °C. – FT-IR (KBr, cm^{-1}): υ = 1659 (C=O), 3275 (amide N–H), 3191 (NH). – ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.69 (s, 2H, $-CH_2$), 6.43 (s, 1H, thiazole H), 7.04 (d, J = 7.8 Hz, 2H, Ar-H), 7.15–7.42 (m, 6H, Ar-H), 7.56 (s, 1H, Ar-H), 9.41 (s, 1H, NH, D_2O-exchangeable), 10.11 (s, 1H, amide NH, D_2O-exchangeable). – MS: m/z (%) = 343 (9) $[M]^+$, 345 (3) $[M+2]^+$. – $C_{17}H_{14}ClN_3OS$ (343.05): calcd. C 59.38, H 4.10, N 12.22, S 9.33; found C 59.42, H 4.05, N 12.20, S 9.29.

3.15 N-(3-Chlorophenyl)-2-(2-(4-chlorophenylamino)-1,3-thiazol-4-yl) acetamide (4l)

Off-white solid. Yield: 75 %; m.p.: 144–45 °C. – FT-IR (KBr, cm^{-1}): υ = 1664 (C=O), 3261 (amide N–H), 3192 (NH). – ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.69 (s, 2H, $-CH_2$), 6.41 (s, 1H, thiazole H), 7.04 (d, J = 7.4 Hz, 1H, Ar-H), 7.16–7.37 (m, 6H, Ar-H), 7.55 (s, 1H, Ar-H), 9.33 (s, 1H, NH, D_2O-exchangeable), 10.09 (s, 1H, amide NH, D_2O-exchangeable). – MS: m/z (%) = 377 (10) $[M]^+$, 379 (7) $[M+2]^+$, 381 (1.5) $[M+4]^+$. – $C_{17}H_{13}Cl_2N_3OS$ (377.02): calcd. C 53.98, H 3.46, N 11.11, S, 8.48; found C 54.01, H 3.50, N 11.06, S 8.44.

3.16 2-(2-(p-Toluidino)-1,3-thiazol-4-yl)-N-(3-chlorophenyl)acetamide (4m)

Off-white solid. Yield: 75 %; m.p.: 150–51 °C. – FT-IR (KBr, cm^{-1}): υ = 1665 (C=O), 3253 (amide N–H), 3188 (NH). – ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 2.35 (s, 3H, $-CH_3$), 3.67 (s, 2H, $-CH_2$), 6.38 (s, 1H, thiazole H), 7.03 (d, J = 8.4 Hz, 1H, Ar-H), 7.18–7.31 (m, 5H, Ar-H), 7.38 (d, J = 8.1 Hz, 1H, Ar-H), 7.52 (s, 1H, Ar-H), 9.49 (s, 1H, NH D_2O-exchangeable), 10.15 (s, 1H, amide NH, D_2O-exchangeable). – MS: m/z (%) = 357 (15) $[M]^+$, 359 (5) $[M+2]^+$. – $C_{18}H_{16}ClN_3OS$ (357.07): calcd. C 60.41, H 4.51, N 11.74, S 8.96; found C 60.45, H 4.49, N 11.77, S 9.00.

3.17 2-(2-(Phenylamino)-1,3-thiazol-4-yl)-N-o-tolylacetamide (4n)

Off-white solid. Yield: 74 %; m.p.: 135–36 °C. – FT-IR (KBr, cm^{-1}): υ = 1655 (C=O), 3263 (amide N–H), 3198 (NH). – ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.12 (s, 3H, $-CH_3$), 3.74 (s, 2H, $-CH_2$), 6.44 (s, 1H, thiazole H), 7.02 (d, J = 7.4 Hz, 1H, Ar-H), 7.09–7.31 (m, 7H, Ar-H), 7.97 (d, J = 7.6 Hz, 1H, Ar-H), 8.90 (s, 1H, NH, D_2O-exchangeable), 9.53 (s, 1H, amide NH, D_2O-exchangeable). – ^{13}C NMR (100 MHz, [D_6] DMSO): δ = 17.85 (CH_3), 40.33 (CH_2), 104.97 (thiazole C-5), 118.66, 122.09, 123.60, 124.52, 126.66, 128.15, 129.52, 130.28, 136.18, 139.80, 145.56 (Ar-C), 165.83 (C=O), 167.38 (thiazole C-2). – MS: m/z (%) = 323 (10) $[M]^+$. – $C_{18}H_{17}N_3OS$ (323.11): calcd. C 66.85, H 5.30, N 12.99, S 9.91; found C 66.81, H 5.33, N 13.02, S 9.86.

3.18 2-(2-(p-Toluidino)-1,3-thiazol-4-yl)-N-o-tolylacetamide (4o)

Off-white solid. Yield: 72 %; m.p.: 134–35 °C. – FT-IR (KBr, cm^{-1}): υ = 1664 (C=O), 3263 (amide N–H), 3188 (NH). – ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C, TMS): δ = 2.17 (s, 3H, $-CH_3$), 2.23 (s, 3H, $-CH_3$), 3.64 (s, 2H, $-CH_2$), 6.62 (s, 1H, thiazole H), 7.03–7.19 (m, 5H, Ar-H), 7.46–7.52 (m, 3H, Ar-H), 9.38 (s, 1H, NH, D_2O-exchangeable), 10.02 (s, 1H, amide NH, D_2O-exchangeable). – MS: m/z (%) = 337 (10) $[M]^+$. – $C_{19}H_{19}N_3OS$ (337.12): calcd. C 67.63, H 5.68, N 12.45, S 9.50; found C 67.68, H 5.66, N 12.41, S 9.53.

3.19 Procedure for the determination of minimum inhibitory concentration

Nine dilutions of each drug were prepared with brain heart infusion (BHI) for MIC. In the initial tube 20 µL of drug was added into the 380 µL of brain heart infusion (BHI) broth. For dilutions 200 µL of BHI broth was added into the next nine tubes separately. Then from the initial tube 200 µL was transferred to the first tube containing 200 µL of BHI broth. This was considered as 10^{-1} dilution. From the 10^{-1} diluted tube 200 µL was transferred to the second tube to make 10^{-2} dilution. The serial dilution was repeated up to 10^{-9} dilution for each drug. From the maintained stock cultures of required organisms, 5 µL was taken and added into 2 mL of BHI broth. In each serially diluted tube 200 µL of above culture suspension was added. The tubes were incubated for 24 h and observed for turbidity [20].

4 Conclusion

We have established a direct route for the synthesis of substituted 4-arylacetamido-2-aminothiazoles from ω-bromoacetoacetanilides and thiourea/phenyl thioureas, which can further be employed in the synthesis of different substituted aminothiazoles directly in a step by modifying the substituents. In preliminary screenings, the synthesized compounds were found to exhibit potent antibacterial activity against Gram-positive bacteria *S. aureus* and *E. faecalis* and antifungal activity against *A. niger* and *C. albicans*.

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