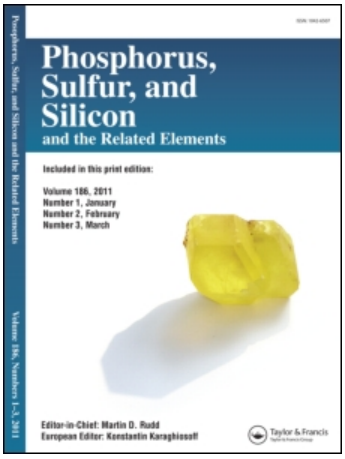

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Synthesis, Characterization, and Biological Activity of Substituted Thiazole-5-carboxaldehydes and Their Ylidenenitriles Derivatives

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Synthesis, Characterization, and Biological Activity of Substituted Thiazole-5-carboxaldehydes and Their Ylidenenitriles Derivatives

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*The Vilsmeier–Haack reaction of 2-amino -4-(4-substituted phenyl)-thiazoles **1**, in the presence of micellar media, gives formylated derivatives **2**, which upon hydrolysis afforded thiazole-5-carboxaldehydes **3**. Microwave-assisted Knoevenagel condensation of **3** with active methylene compounds, in the presence of piperidine as catalyst, gives excellent yields of ylidenenitrile compounds **4**. The structures of the newly synthesized compounds were established on the basis of elemental analysis, IR, ^{1}H NMR, and ^{13}C NMR spectral analysis. All newly synthesized compounds were screened for antibacterial activity using two Gram-positive and one Gram-negative bacterial species and their antifungal activity was screened using two fungal species.*

Keywords Arylaminothiazole; biological activity; Knoevenagel condensation; micelles; Vilsmeier–Haack reaction

INTRODUCTION

Thiazoles are a familiar group of heterocyclic compounds that possess a wide variety of biological activities, and their utility as medicines is well-established.[1–4] The thiazole nucleus is also an integral part of all the available penicillins, which have revolutionized the therapy of bacterial diseases.[5–10] A detailed literature survey[11,12] reveals that a large number of thiazole derivatives containing other heterocyclic systems have been designed, synthesized, and evaluated for their antimicrobial activity involving several strains of bacteria, fungi, and viruses.[13–17]

The Vilsmeier–Haack reaction in micellar media[18,19] plays an important role for synthesizing a variety of aromatic and biologically active

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heterocyclic compounds in good yield with improved reaction time. Micelles by their solubilization capacity increase the reactant concentration within the hydrophilic or hydrophobic micellar regions facilitating the reactions. They act as microreactors, by which rate and selectivity of the reaction increases. Sodium dodecyl sulfate (SDS) is one of the inexpensive, nontoxic, and readily available micelles used in the Vilsmeier–Haack reaction.

Ylidenenitriles have increasing applications[20] in industry, medicine, agriculture, and biological sciences; are useful substrates for cycloaddition reactions; and are precursors to heterocyclic compounds with potential pharmacologically active heterocycles.

In continuation of our work[21,22] in synthesizing sulfur-containing biologically active heterocyclic compounds, and in view of the biological significance of the aminothiazole derivatives, we report the Vilsmeier–Haack reaction of substituted amino thiazole in the presence of SDS to obtain formylated derivatives, which upon Knoevenagel condensation with active methylene compounds, give ylidenenitrile derivatives. The structures of the synthesized derivatives were well characterized by their elemental analysis, IR, ^{1}H NMR, and ^{13}C NMR spectral data, and were screened for their biological activity using Gram-positive and Gram-negative bacterial species and their antifungal activity was screened using fungal species.

RESULTS AND DISCUSSION

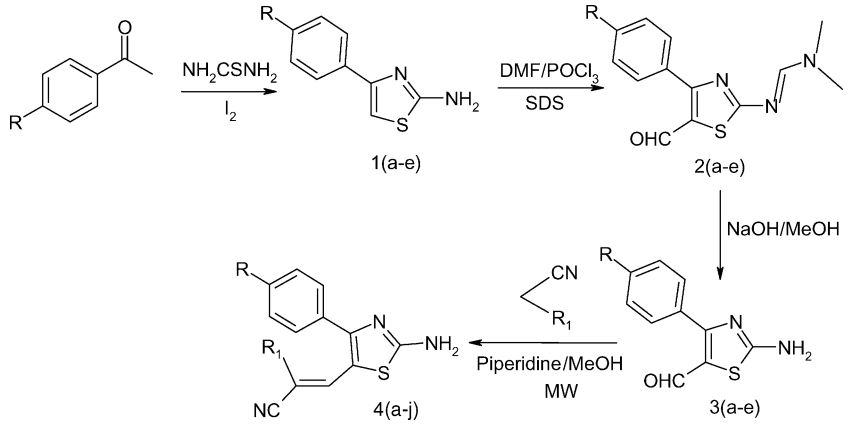
4-(4-substituted phenyl)-2-aminothiazoles **1** was prepared by the solid phase reaction of thiourea, substituted acetophenones, and iodine. The Vilsmeier–Haack reaction of 4-(4-substituted phenyl)-2-aminothiazoles **1**, in the presence of SDS, afforded intermediates **2**. It is observed that the reaction time decreased from 4–5 h to 1–1.5 h by using an equimolar amount of SDS in the reaction media. The IR spectrum of the intermediates **2** showed an absorption band in the region of 1730–1690 cm^{-1} (C=O) and 1385–1340 cm^{-1} (-N $(CH_3)_2$), whereas the band due to $-NH_2$ was absent. The ^{1}H NMR ($CDCl_3$) spectra of intermediates **2** exhibited the signal around 9.81–9.88 δ (1H, s, -C<u>H</u>O-), which confirms the formylation and the presence of signal around 3.21–3.87 δ (6H, s, -N (C<u>H</u>$_3)_2$), 8.38–8.50 δ (1H, s, -N=C<u>H</u>-N =), and the absence of a signal due to $-NH_2$ indicates the conversion of $-NH_2$ to –N=CH-N $(CH_3)_2$. There are reports in the literature[23] where such a conversion of the $-NH_2$ group has taken place upon Vilsmeier–Haack adduct. In addition, the ^{13}C NMR ($CDCl_3$) spectra of intermediates **2** shows a peak around 178.43–180.78 δ (<u>C</u>=O), 41.57–47.10 δ (-N (<u>C</u>H$_3)_2$), and 150.26–153.24

δ (-N=CH-N $(CH_3)_2$), and also confirms formylation and blocking of the amino group. The hydrolysis of intermediates **2** using NaOH afforded 2-amino-4-(4-substituted phenyl) 1, 3-thiazole-5-carboxaldehyde **3.** The IR spectrum of **3** showed a band in the region of the 3500–3200 cm^{-1}(-NH_2); the ^{1}H NMR (DMSO-d_6) spectra of product **3** exhibited the signal around 8.25–8.42 δ (-NH_2); the disappearance of peaks due to -N $(CH_3)_2$ and -N=CH-N = group indicates the deblocking of the -NH_2 group upon hydrolysis; and the ^{13}C-NMR (DMSO-d_6) spectra of **3** indicates the absence of peaks due to -N $(CH_3)_2$ and -N=CH-N = group, which confirms the hydrolysis. The microwave-assisted Knoevenagel condensation of thiazole-5-carboxaldehydes **3** with active methylene compounds in the presence of piperidine as catalyst afforded ylidenenitrile compounds **4**, which were confirmed by the disappearance of band for the aldehyde (C=O) and appearance of band at 2250–2180 cm^{-1} (CN) in the IR; the absence of peak due to the –CHO group and the presence of a signal around 7.20–7.35 δ (–CH=C $(CN)_2$) in the ^{1}H NMR spectrum; and also the ^{13}C-NMR (DMSO-d_6) spectra of the ylidenenitrile compounds **4** shows the 20.10–23.09($COOCH_2CH_3$), 64.18–65.82(-$COOCH_2CH_3$), and 111.63–114.15 δ (-CN), which supports the Knoevenagel condensation (Scheme 1).

Antimicrobial Activity

Twenty synthesized compounds were screened in vitro for their antimicrobial activities against two strains of Gram-positive bacterial species, namely *Bacillus subtilis* and *Staphylococcus aureus*; one strain of Gram-negative bacterial species, namely *Escherichia coli*, and two strains of fungi, namely *Aspergillus niger* and *Rhizopus nigricans*, by the disc diffusion method.[24] Nutrient agar and potato dextrose agars were used to culture the bacteria and fungi, respectively. The agar media were inoculated with different microorganisms and culture tested. The compounds were tested at 1000 ppm in DMF solution. DMF was used as control. The inhibition zones of microbial growth surrounding the disc were measured in millimeters at the end of 24 h incubation period at 30°C for bacteria and 48 h of incubation period at 35°C for fungi. All the compounds were screened with reference to the standard drugs Ampicillin and Ciprofloxacin for antibacterial and Grisofulvine for antifungal activities, respectively. The antimicrobial activity of synthesized compounds **2a–e**, **3a–e**, and **4a–j** were tested, and the protocols are summarized in Table I.

The antibacterial evaluation of the synthesized compounds revealed that only compounds **2a** and **2c** are moderately active against Gram-positive bacterial species *B. subtilis*, and compounds **2a**, **2d**, and **2e** are



Compd.	R	Compd.	R	Compd.	R	R_1
1a	H	**3a**	H	**4a**	H	CN
1b	Br	**3b**	Br	**4b**	Br	CN
1c	Cl	**3c**	Cl	**4c**	Cl	CN
1d	OCH_3	**3d**	OCH_3	**4d**	OCH_3	CN
1e	CH_3	**3e**	CH_3	**4e**	CH_3	CN
2a	H			**4f**	H	$COOC_2H_5$
2b	Br			**4g**	Br	$COOC_2H_5$
2c	Cl			**4h**	Cl	$COOC_2H_5$
2d	OCH_3			**4i**	OCH_3	$COOC_2H_5$
2e	CH_3			**4j**	CH_3	$COOC_2H_5$

SCHEME 1

moderately to fairly active against Gram-positive bacterial species *S. aureus*, whereas all other compounds are inactive. On the other hand, it was found that the compounds **2b** and **3e** showed good activity against Gram-negative bacterial species *E. coli*, whereas all other compounds showed moderate to fair activity.

The investigation of fungicidal screening data revealed that the compounds **2b**, **4h**, and **4i** exhibited good activity against the fungal strain *A. niger*, whereas all other compounds had a moderate inhibitory effect. Moreover, the compounds **3a** and **4e** exhibited a moderate inhibitory effect, whereas all other compounds showed lower inhibition against the fungal strain *R. nigricans*.

TABLE I Antimicrobial Screening Results of the Compounds 2a–e, 3a–e, and 4a–j

	Antibacterial activity Zone of inhibition (in mm)			Antifungal activity Zone of inhibition (in mm)	
Compd.	*B. subtilis*	*S. aureus*	*E. coli*	*A. Niger*	*Rhizopus n.*
2a	14	20	25	17	17
2b	–	–	28	23	16
2c	22	–	26	14	15
2d	–	18	25	19	15
2e	–	13	26	18	20
3a	–	–	26	16	22
3b	–	–	24	15	20
3c	–	–	18	12	15
3d	–	–	23	12	16
3e	–	–	27	13	15
4a	–	–	22	19	19
4b	–	–	21	17	21
4c	–	–	17	16	16
4d	–	–	20	18	19
4e	–	–	25	15	23
4f	–	–	20	17	21
4g	–	–	20	12	16
4h	–	–	21	21	17
4i	–	–	20	20	18
4j	–	–	20	16	19
Ampicillin	33	33	31	–	–
Ciprofloxacin	37	34	35	–	–
Griseofulvin	–	–	–	25	28

CONCLUSION

Some new 2-[(1E)-1-aza-2-(dimethylamino)vinyl]-4-(4-substituted phenyl)-1,3-thiazole-5-carboxaldehydes (**2a–e**), 2-amino-4-(4-substituted phenyl)-1,3-thiazole-5-carboxaldehydes (**3a–e**), [(2-amino-4-(4-substituted phenyl)-1,3-thiazol-5-yl)methylene]methane-1,1-dicarbonitriles (**4a–e**), and ethyl(2E)-3-[2-amino-4-(4-substituted phenyl)(1,3-thiazol-5-yl)]-2-cyanoprop-2-enoates (**4f–j**) were synthesized and screened for their antibacterial and antifungal activities. The antimicrobial study revealed that compounds have moderate to fair activity against the tested organisms *Escherichia coli*, *Aspergillus niger*, and *Rhizopus nigricans*. Most of the synthesized compounds are inactive against the species *Bacillus subtilis* and *Staphylococcus aureus*.

EXPERIMENTAL

All melting points were taken in open capillaries and are uncorrected. The IR spectra were recorded in KBr on a Nicolet 400D spectrophotometer, and only the characteristic peaks are reported. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$/DMSO-d_6 on a Bruker Avance 400F (400 MHz) using TMS as an internal standard. Chemical shifts are reported in parts per million (ppm). Purity of the compounds was checked by thin layer chromatography (TLC) on silica gel plates using a toluene:ethyl acetate (7:3) solvent system. UV radiation and iodine were used as the visualizing agents.

General Synthesis Procedure: 2-[(1E)-1-Aza-2-(dimethylamino) vinyl]-4-(4-substituted phenyl)-1,3-thiazole-5-carboxaldehyde (2a–e)

To a solution of DMF (7.7 mL, 10 mmol) cooled to 0°C, $POCl_3$ (9.3 mL, 10 mmol) was added, and the mixture was stirred for 30 min at 0°C. Sodium dodecyl sulfate (2.88 g, 10 mmol) and **1a–e** (10 mmol) was added to the above pre-cooled Vilsmeier complex in one portion. The temperature of the reaction mixture was gradually raised to 90°C and maintained for 1 h. The reaction mixture was gradually run into well-stirred chilled water (25 mL). The pH was adjusted to 8 by the addition of Na_2CO_3 (~10 g). The separated solid product thus obtained was filtered, washed thoroughly with water, dried, and crystallized from methanol to give compounds **2a**–**e**.

Analytical and spectroscopic characterization data of the synthesized compounds **2a**–**e** are given below:

2-[(1E)-1-Aza-2-(dimethylamino)vinyl]-4-phenyl-1,3-thiazole-5-carboxaldehyde (2a)

Mp 130–131°C[25], R_f 0.425 (toluene:ethyl acetate, 7:3), Yield 93%, anal. calcd. for $C_{13}H_{13}N_3OS$: C 60.21, H 5.05, N 16.20; found C 60.05, H 5.00, N 16.29. ^{1}H-NMR δ_H ($CDCl_3$, 400 MHz): 3.21(6H, s, -N($C\underline{H}_3$)$_2$), 7.35–7.50(5H, m, Ar-$\underline{H}$), 8.48(1H, s, -N=C$\underline{H}$-N(CH_3)$_2$), 9.81(1H, s, -C$\underline{H}$O). IR: ν_{max} (KBr, cm^{-1}): 3075(CH-arom.str.), 1690(C=O str.), 1579(C=C arom. str.), 1381 & 1374(-N (CH_3)$_2$ str.), 1154(C = S str.). ^{13}C-NMR δ_c ($CDCl_3$): 46.09(-N($\underline{C}H_3$)$_2$), 118.54, 124.18, 123.13, 128.76, 129.15, 131.15(aromatic), 151.50(-N=$\underline{C}$H-N (CH_3)$_2$), 160.87(-C=$\underline{C}$-N =), 175.23(-S-$\underline{C}$=N-), 180.54(Ar-$\underline{C}$HO).

2-[(1E)-1-Aza-2-(dimethylamino) vinyl]-4-(4-bromophenyl)-1,3-thiazole-5-carboxaldehyde (2b)

Mp 149–150°C, R_f 0.350 (toluene:ethyl acetate, 7:3), Yield 88%, anal. calcd. for $C_{13}H_{12}BrN_3O_3S$: C 46.17, H 3.58, N 12.42; found C

46.23, H 3.49, N 12.32. ^{1}H-NMR δ_H ($CDCl_3$, 400 MHz): 3.27(6H, s, -N($C\underline{H}_3$)$_2$), 7.31(2H, d, J = 8.4 Hz, Ar-$\underline{H}$), 7.46(2H, d, J = 8.4 Hz, Ar-$\underline{H}$), 8.41(1H, s, -N=C$\underline{H}$-N(CH_3)$_2$), 9.87(1H, s, -C$\underline{H}$O). IR: ν_{max} (KBr, cm^{-1}): 3086(CH-arom. str.), 1710(C ; O str.), 1582(C=C arom. str.), 1364 & 1343(-N (CH_3)$_2$ str.), 1218(C = S str.), 554(C-Br str.). ^{13}C-NMR δ_c ($CDCl_3$): 44.23(-N($\underline{C}H_3$)$_2$), 122.23, 125.86, 128.20, 130.16, 131.24(aromatic), 153.24(-N=$\underline{C}$H-N (CH_3)$_2$), 161.65(-C=$\underline{C}$-N =), 175.69(-S-$\underline{C}$=N-), 180.78(Ar-$\underline{C}$HO).

2-[(1E)-1-Aza-2-(dimethylamino) vinyl]-4-(4-chlorophenyl)-1,3-thiazole-5-carboxaldehyde (2c)

Mp 144–145°C, R_f 0.325 (toluene:ethyl acetate, 7:3), Yield 89%, anal. calcd. for $C_{13}H_{12}ClN_3OS$: C 53.15, H 4.12, N 14.30; found C 53.05, H 4.17, N 14.17. ^{1}H-NMR δ_H ($CDCl_3$, 400 MHz): 3.36 (6H, s, -N($C\underline{H}_3$)$_2$), 7.30(2H, d, J = 8.8 Hz, Ar-$\underline{H}$), 7.39(2H, d, J = 8.8 Hz, Ar-$\underline{H}$), 8.38(1H, s, -N=C$\underline{H}$-N(CH_3)$_2$), 9.84(1H, s, -C$\underline{H}$O). IR: ν_{max} (KBr, cm^{-1}): 3094(CH-arom. str.), 1720(C=O str.), 1592(C=C arom. str.), 1379 & 1360(-N (CH_3)$_2$ str.), 1312(C = S str.), 895(C-Cl str.). ^{13}C-NMR δ_c ($CDCl_3$): 45.05(-N($\underline{C}H_3$)$_2$), 122.29, 125.94, 128.56, 130.58, 131.54(aromatic), 151.54(-N=$\underline{C}$H-N (CH_3)$_2$), 159.98(-C=$\underline{C}$-N =), 176.45(-S-$\underline{C}$=N-), 181.68(Ar-$\underline{C}$HO).

2-[(1E)-1-Aza-2-(dimethylamino)vinyl]-4-(4-methoxyphenyl)-1,3-thiazole-5-carboxaldehyde (2d)

Mp 154–155°C, R_f 0.350 (toluene:ethyl acetate, 7:3), Yield 85%, anal. calcd. for $C_{14}H_{15}N_3O_2S$: C 58.11, H 5.23, N 14.52; found C 58.05, H 5.13, N 14.43. ^{1}H-NMR δ_H ($CDCl_3$, 400 MHz): 3.49(3H, s, -O$C\underline{H}_3$), 3.87(6H, s, -N($C\underline{H}_3$)$_2$), 7.41(2H, d, J = 8.0 Hz, Ar-$\underline{H}$), 7.53(2H, d, J = 8.0 Hz, Ar-$\underline{H}$), 8.45(1H, s, -N=C$\underline{H}$-N(CH_3)$_2$), 9.85(1H, s, -C$\underline{H}$O). IR: ν_{max} (KBr, cm^{-1}): 3025(CH-arom. str.), 1680(C=O str.), 1609(C=C arom. str.), 1380 & 1369(-N (CH_3)$_2$ str.), 1230(C = S str.). ^{13}CNMR δ_c ($CDCl_3$): 41.57(-N($\underline{C}H_3$)$_2$), 56.65(Ar-O$\underline{C}H_3$), 121.40, 123.09, 128.02, 129.14, 131.26(aromatic), 152.59(-N=$\underline{C}$H-N (CH_3)$_2$), 159.89(-C=$\underline{C}$-N =), 174.35(-S-$\underline{C}$=N-), 178.43(Ar-$\underline{C}$HO).

2-[(1E)-1-Aza-2-(dimethylamino)vinyl]-4-(4-methylphenyl)-1,3-thiazole-5-carboxaldehyde (2e)

Mp 136–137°C, R_f 0.400 (toluene:ethyl acetate, 7:3), Yield 87%, anal. calcd. for $C_{14}H_{15}N_3OS$: C 61.51, H 5.53, N 15.37; found C 61.60, H 5.44, N 15.49. ^{1}H-NMR δ_H ($CDCl_3$, 400 MHz): 1.90(3H, s, -C$\underline{H}_3$), 3.23(6H, s, -N($C\underline{H}_3$)$_2$), 7.33(2H, d, J = 8.0 Hz, Ar-$\underline{H}$), 7.47(2H, d, J = 8.0 Hz, Ar-$\underline{H}$), 8.50(1H, s, -N=C$\underline{H}$-N(CH_3)$_2$), 9.88(1H, s, -C$\underline{H}$O). IR: ν_{max} (KBr,

cm^{-1}): 3050(CH-arom. str.), 1721(C=O str.), 1533(C=C arom. str.), 1372 & 1358(-N $(CH_3)_2$ str.), 1172(C = S str.). ^{13}C-NMR δ_c ($CDCl_3$): 20.08(Ar-$\underline{C}H_3$), 47.10(-N ($\underline{C}H_3)_2$), 120.83, 123.25, 128.47, 129.88, 131.26(aromatic), 150.26(-N=$\underline{C}$H-N $(CH_3)_2$), 160.08(-C=$\underline{C}$-N =), 175.79(-S-$\underline{C}$=N-), 180.68(Ar-$\underline{C}$HO).

2-Amino-4-(4-substituted phenyl)-1,3-thiazole-5-carboxaldehyde (3a–e)

The compound **2a–e** (10 mmol), 10 mL ethanol, and NaOH (0.04 g, 10 mmol) were charged in a 100 mL round bottom flask, and the mixture was refluxed for 4–5 h. The reaction mixture was cooled and poured onto crushed ice. The solid thus separated was filtered, washed thoroughly with water, dried, and crystallized from ethyl acetate to give compounds **3a–e**. Analytical and spectroscopic characterization data of the synthesized compounds **3a**–**e** are given below:

2-Amino-4-phenyl-1,3-thiazole-5-carboxaldehyde (3a)

Mp 212–214°C[25], R_f 0.500 (toluene:ethyl acetate, 7:3), Yield 87%, anal. calcd. for $C_{10}H_8N_2OS$: C 58.50, H 3.95, N 13.72; found C 58.43, H 3.89, N 13.66. ^{1}H-NMR δ_H (DMSO-d_6, 400 MHz): 7.30–7.61(5H, m, Ar-$\underline{H}$), 8.30(2H, s, -N$\underline{H}_2$) 9.61(1H, s, -C$\underline{H}$O). IR: ν_{max} (KBr, cm^{-1}): 3430–3250(NH_2), 3090(CH-arom. str.), 1723(C=O str.), 1612(C=C arom. str.), 1235(C = S str.). ^{13}CNMR δ_c (DMSO-d_6): 122.67, 129.66, 129.85, 131.09, 140.06(aromatic), 163.95(-C=$\underline{C}$-N =), 173.11(-S-$\underline{C}$=N-), 181.86(Ar-$\underline{C}$HO).

2-Amino-4-(4-bromophenyl)-1,3-thiazole-5-carboxaldehyde (3b)

Mp 224–226°C, R_f 0.425 (toluene:ethyl acetate, 7:3), Yield 85%, anal. calcd. for $C_{10}H_7BrN_2OS$: C 42.42, H 2.49, N 9.89; found C 42.33, H 2.33, N 9.76. ^{1}H-NMR δ_H (DMSO-d_6, 400 MHz): 7.32(2H, d, J = 8.4 Hz, Ar-$\underline{H}$), 7.57(2H, d, J = 8.4 Hz, Ar-$\underline{H}$), 8.41(2H, s, -N$\underline{H}_2$) 9.54(1H, s, -C$\underline{H}$O). IR: ν_{max} (KBr, cm^{-1}): 3490–3350(NH_2 str.), 3034(CH-arom. str.), 1685(C=O str.), 1545(C=C arom. str.), 1185(C = S str.), 555(C-Br str.). ^{13}CNMR δ_c (DMSO-d_6): 122.42, 129.62, 130.22, 131.37, 140.63(aromatic), 164.58(-C=$\underline{C}$-N =), 172.74(-S-$\underline{C}$=N-), 182.66(Ar-$\underline{C}$HO).

2-Amino-4-(4-chlorophenyl)-1,3-thiazole-5-carboxaldehyde (3c)

Mp 209–210°C, R_f 0.450 (toluene:ethyl acetate, 7:3), Yield 86%, anal. calcd. for $C_{10}H_7ClN_2OS$: C 50.20, H 2.81, N 11.90; found C 50.42, H 2.61, N 11.60. ^{1}H-NMR δ_H (DMSO-d_6, 400 MHz): 7.54(2H, d, J = 8.4

Hz, Ar-H), 7.73(2H, d, J = 8.8 Hz, Ar-H), 8.37(2H, s, -NH_2), 9.66(1H, s, -CHO). IR: ν_{max} (KBr, cm^{-1}): 3420–3220(NH_2 str.), 3076(CH-arom. str.), 1672(C=O str.), 1529(C=C arom. str.), 1293(C = S str.), 770(C-Cl str.). ^{13}C-NMR δ_c (DMSO-d_6): 123.29, 123.15, 131.64, 132.62, 135.05(aromatic), 162.12(-C=C-N =), 173.18(-S-C=N-), 181.79(Ar-CHO).

2-Amino-4-(4-methoxyphenyl)-1,3-thiazole-5-carboxaldehyde (3d)

Mp 231–233°C, R_f 0.475 (toluene:ethyl acetate, 7:3), Yield 84%, anal. calcd. for $C_{11}H_{10}N_2O_2S$: C 56.40, H 4.30, N 11.96; found C 56.28, H 4.27, N 11.99. ^{1}H-NMR δ_H (DMSO-d_6, 400 MHz): 3.62(3H, s, -OCH_3), 7.25(2H, d, J = 8.4 Hz, Ar-H), 7.62(2H, d, J = 8.0 Hz, Ar-H), 8.42(2H, s, -NH_2) 9.42(1H, s, -CHO). IR: ν_{max} (KBr, cm^{-1}): 3460–3200(NH_2 str.), 3049(CH-arom. str.), 1720(C=O str.), 1525(C=C arom. str.), 1315(C = S str.). ^{13}C-NMR δ_c (DMSO-d_6): 54.9(Ar-OCH_3), 123.15, 129.72, 130.37, 131.93, 141.34(aromatic), 162.41(-C=C-N =), 171.43(-S-C=N-), 182.16(Ar-CHO).

2-Amino-4-(4-methylphenyl)-1,3-thiazole-5-carboxaldehyde (3e)

Mp 217–218°C, R_f 0.500 (toluene:ethyl acetate, 7:3), Yield 82%, anal. calcd. for $C_{11}H_{10}N_2OS$: C 60.53, H 4.62, N 12.83; found C 60.42, H 4.50, N 12.97. ^{1}H-NMR δ_H (DMSO-d_6, 400 MHz): 2.15(3H, s, -CH_3), 7.29(2H, d, J = 8.0 Hz, Ar-H), 7.59(2H, d, J = 8.0 Hz, Ar-H), 8.25(2H, s, -NH_2) 9.71(1H, s, -CHO). IR: ν_{max} (KBr, cm^{-1}): 3450–3250(NH_2 str.), 3071(CH-arom. str.), 1725(C=O str.), 1540(C=C arom. str.), 1290(C = S str.). ^{13}C-NMR δ_c (DMSO-d_6): 21.38(Ar-CH_3), 122.67, 129.66, 129.85, 131.09, 140.06(aromatic), 163.95(-C=C-N =), 173.11(-S-C=N-), 181.86(Ar-CHO).

[(2-Amino-4-(4-substituted phenyl)-1,3-thiazol-5-yl) methylene]methane-1,1-dicarbonitrile (4a–e) and Ethyl (2E)-3-[2-Amino-4-(4-substituted phenyl) (1,3-Thiazol-5-yl)]-2-cyanoprop-2-enoate (4f–j)

To a solution of **3a–e** (10mmol) in 5 mL ethanol, malononitrile or cyano ethyl acetate (10 mmol) and piperidine was added as catalyst. The reaction mixture was then irradiated in the microwave oven for 5–7 min. The cooled mixture was filtered, repeatedly washed with ethanol, dried, and crystallized from ethyl acetate to give compounds **4a–j**. Analytical and spectroscopic characterization data of the synthesized compounds **4a–j** are given below:

[(2-Amino-4-phenyl-1,3-thiazol-5-yl)methylene]methane-1,1-dicarbonitrile (4a)

Mp 228–230°C, R_f 0.550 (toluene:ethyl acetate, 7:3), Yield 89%, anal. calcd. for $C_{13}H_8N_4S$: C 61.89, H 3.20, N 22.20; found C 61.76, H 3.05, N 22.07. ^{1}H-NMR δ_H (DMSO-d_6, 400 MHz): 7.23(1H, s, –CH=C(CN)$_2$), 7.62–7.89(5H, m, Ar-H), 8.12(2H, s, -NH$_2$). IR: ν_{max} (KBr, cm^{-1}): 3350–3200 (NH_2 str.), 3090(CH-arom. str.), 2210 & 2200(CN str.), 1520(C=C arom. str.), 1350(C = S str.). ^{13}C-NMR δ_c (DMSO-d_6): 84.37(Ar-CH = C(CN)$_2$), 111.63(-CN), 122.02, 123.09, 124.69, 128.82, 131.59(aromatic), 141.56(Ar-CH = C(CN)$_2$), 153.72(-C=C-N =), 173.56(-S-C=N-).

[(2-Amino-4-(4-bromophenyl)-1,3-thiazol-5-yl)methylene] methane-1,1-dicarbonitrile (4b)

Mp 236–238°C, R_f 0.500 (toluene:ethyl acetate, 7:3), Yield 86%, anal. calcd. for $C_{13}H_7BrN_4OS$: C 47.15, H 2.13, N 16.92; found C 47.22, H 2.19, N 16.81. ^{1}H-NMR δ_H (DMSO-d_6, 400 MHz): 7.31(1H, s, –CH=C(CN)$_2$), 7.57(2H, d, J = 8.4 Hz, Ar-H), 7.88(2H, d, J = 8.4 Hz, Ar-H), 8.21(2H, s, -NH$_2$). IR: ν_{max} (KBr, cm^{-1}): 3410–3270(NH_2 str.), 3054(CH-arom. str.), 2252 & 2225(CN str.), 1555(C=C arom. str.), 1275(C = S str.), 559(C-Br str.). ^{13}C-NMR δ_c (DMSO-d_6): 84.20(Ar-CH = C(CN)$_2$), 111.12(-CN), 122.28, 123.59, 124.23, 128.12, 131.13(aromatic), 142.72(Ar-CH = C(CN)$_2$), 153.83(-C=C-N =), 173.57(-S-C=N-).

[(2-Amino-4-(4-chlorophenyl)-1,3-thiazol-5-yl)methylene] methane-1,1-dicarbonitrile (4c)

Mp 240–241°C, R_f 0.550 (toluene:ethyl acetate, 7:3), Yield 87%, anal. calcd. for $C_{13}H_4ClOS$: C 54.45, H 2.46, N 19.54; found C 54.33, H 2.57, N 19.62. ^{1}H-NMR δ_H (DMSO-d_6, 400 MHz): 7.25(1H, s, –CH=C(CN)$_2$), 7.50(2H, d, J = 8.4 Hz, Ar-H), 7.82(2H, d, J = 8.0 Hz, Ar-H), 8.31(2H, s, -NH$_2$). IR: ν_{max} (KBr, cm^{-1}): 3495–3210(NH_2 str.), 3065(CH-arom. str.), 2215 & 2208(CN str.), 1575(C=C arom. str.), 1180(C = S str.), 795(C-Cl str.). ^{13}C-NMR δ_c (DMSO-d_6): 85.02(Ar-CH = C(CN)$_2$), 112.67(-CN), 123.05, 123.68, 124.34, 127.63, 131.25(aromatic), 141.67(Ar-CH = C(CN)$_2$), 155.78(-C=C-N =), 174.87(-S-C=N-).

[(2-Amino-4-(4-methoxyphenyl)-1,3-thiazol-5-yl)methylene] methane-1,1-dicarbonitrile (4d)

Mp 224–226°C, R_f 0.575 (toluene:ethyl acetate, 7:3), Yield 83%, anal. calcd. for $C_{14}H_{10}N_4OS$: C 59.56, H 3.57, N 19.85; found C 59.41., H 3.42, N 19.91. ^{1}H-NMR δ_H (DMSO-d_6, 400 MHz): 3.55(3H, s, -OCH$_3$), 7.29(1H, s, –CH=C(CN)$_2$), 7.42(2H, d, J = 8.0 Hz, Ar-H), 7.69(2H, d, J =

8.0 Hz, Ar-H), 8.10(2H, s, -NH_2). IR: ν_{max} (KBr, cm^{-1}): 3540–3280(NH_2 str.), 3045(CH-arom. str.), 2192 & 2180(CN str.), 1595(C=C arom. str.), 1345(C = S str.). ^{13}C-NMR δ_c (DMSO-d_6): 54.13(Ar-OCH_3), 87.48(Ar-CH = $C(CN)_2$), 113.15(-CN), 121.56, 123.10, 124.46, 127.74, 130.90(aromatic), 141.30(Ar-CH = $C(CN)_2$), 155.82(-C=C-N =), 175.91(-S-C=N-).

[(2-Amino-4-(4-methylphenyl)-1,3-thiazol-5-yl)methylene] methane-1,1-dicarbonitrile (4e)

Mp 234–236°C, R_f 0.575 (toluene:ethyl acetate, 7:3), Yield 84%, anal. calcd. for $C_{14}H_{10}N_4S$: C 63.14, H 3.79, N 21.04; found C 63.43, H 3.63, N 21.15. ^{1}H-NMR δ_H (DMSO-d_6, 400 MHz): 1.95(3H, s, -CH_3), 7.35(1H, s, –CH=$C(CN)_2$), 7.37(2H, d, J = 8.4 Hz, Ar-H), 7.65(2H, d, J = 8.4 Hz, Ar-H), 8.33(2H, s, -NH_2). IR: ν_{max} (KBr, cm^{-1}): 3560–3190(NH_2 str.), 3010(CH-arom. str.), 2240 & 2225 (CN str.), 1585(C=C arom. str.), 1320(C = S str.). ^{13}C-NMR δ_c (DMSO-d_6): 23.45(Ar-CH_3), 85.11(Ar-CH = $C(CN)_2$), 114.15(-CN), 120.53, 124.11, 124.45, 128.37, 131.91(aromatic),142.14(Ar-CH = $C(CN)_2$), 155.28(-C=C-N =), 174.89(-S-C=N-).

Ethyl (2E)-3-(2-Amino-4-phenyl(1,3-thiazol-5-yl))-2-cyanoprop-2-enoate (4f)

Mp 230–231°C, R_f 0.550 (toluene:ethyl acetate, 7:3), Yield 88%, anal. calcd. for $C_{15}H_{13}N_3O_2S$: C 60.19, H 4.38, N 14.04; found C 60.11, H 4.50, N 14.15. ^{1}H-NMR δ_H (DMSO-d_6, 400 MHz): 1.92–2.18(3H, t, -CH_2-CH_3), 3.61–3.74(2H, q, -CH_2-CH_3), 7.20(1H, s, –CH=$C(CN)_2$), 7.63–7.89(5H, m, Ar-H), 8.12(2H, s, -NH_2). IR: ν_{max} (KBr, cm^{-1}): 3490–3250(NH_2 str.), 3080(CH-arom. str.), 2198 (CN str.), (C=O str.), 1578(C=C arom. str.), 1255(C = S str.). ^{13}C-NMR δ_c (DMSO-d_6): 20.37(COO$CH_2$$CH_3$), 64.18(-COO$CH_2$$CH_3$), 95.63(EtOOC-C-CN), 113.18(-CN), 123.13, 125.60, 128.76, 129.15, 131.50(aromatic), 139.87(Ar-CH = $C(CN)_2$), 147.24(-C=C-N =), 163.11(-COO$CH_2$$CH_3$), 173.95(-S-C=N-).

Ethyl (2E)-3-[2-Amino-4-(4-bromophenyl) (1,3-Thiazol-5-yl)]-2-cyanoprop-2-enoate (4g)

Mp 220–222°C, R_f 0.525 (toluene:ethyl acetate, 7:3), Yield 86%, anal. calcd. for $C_{15}H_{12}BrN_3O_2S$: C 47.63, H 3.20, N 11.11; found C 47.51, H 3.05, N 11.27. ^{1}H-NMR δ_H (DMSO-d_6, 400 MHz): 1.77–1.94(3H, t, -CH_2-CH_3), 3.63–3.91(2H, q, -CH_2-CH_3), 7.29(1H, s, –CH=$C(CN)_2$), 7.31(2H, d, J = 7.6 Hz, Ar-H), 7.51(2H, d, J = 8.0 Hz, Ar-H), 8.19(2H, s, -NH_2). IR: ν_{max} (KBr, cm^{-1}): 3420–3140(NH_2 str.), 3030(CH-arom. str.), 2220 (CN str.), 1600(C=C arom. str.), 1372(C = S str.), 566(C-Br str.). ^{13}C-NMR δ_c

(DMSO-d_6): 21.24($COOCH_2\underline{C}H_3$), 65.82(-$COO\underline{C}H_2CH_3$), 95.60(EtOOC-$\underline{C}$-CN), 113.48(-$\underline{C}N$), 123.41, 125.18, 128.344, 129.62, 131.36(aromatic), 138.60 (Ar-$\underline{C}H = C(CN)_2$), 147.70 (-C=$\underline{C}$-N =), 164.74 (-$\underline{C}OOCH_2CH_3$), 174.65(-S-$\underline{C}$=N-).

Ethyl (2E)-3-[2-Amino-4-(4-chlorophenyl) (1,3-Thiazol-5-yl)]-2-cyanoprop-2-enoate (4h)

Mp 242–243°C, R_f 0.500 (toluene:ethyl acetate, 7:3), Yield 84%, anal. calcd. for $C_{15}H_{12}ClN_3O_2S$: C 53.97, H 3.62, N 12.59; found C 53.75, H 3.51, N 12.73. ^{1}H-NMR δ_H (DMSO-d_6, 400 MHz): 1.72–2.08(3H, t,-CH_2-$C\underline{H}_3$), 3.48–3.62(2H, q, -$C\underline{H}_2$-CH_3), 7.23(1H, s, –$C\underline{H}$=$C(CN)_2$), 7.26(2H, d, $J = 7.6$ Hz, Ar-$\underline{H}$), 7.41(2H, d, $J = 7.6$ Hz, Ar-$\underline{H}$), 8.25(2H, s, -$N\underline{H}_2$). IR: ν_{max} (KBr, cm^{-1}): 3350–3190(NH_2 str.), 3085(CH-arom. str.), 2195 (CN str.), 1546(C=C arom. str.), 1285(C = S str.), 790(C-Cl str.). ^{13}C-NMR δ_c (DMSO-d_6): 20.10($COOCH_2\underline{C}H_3$), 65.38(-$COO\underline{C}H_2CH_3$), 95.77(EtOOC-$\underline{C}$-CN), 113.93(-$\underline{C}N$), 123.9, 125.01, 128.44, 128.55, 131.64(aromatic), 139.83(Ar-$\underline{C}H = C(CN)_2$), 147.56(-C=$\underline{C}$-N =), 165.23(-$\underline{C}OOCH_2CH_3$), 174.94(-S-$\underline{C}$=N-).

Ethyl (2E)-3-[2-Amino-4-(4-methoxyphenyl) (1,3-Thiazol-5-yl)]-2-cyanoprop-2-enoate (4i)

Mp 237–239°C, R_f 0.600(toluene:ethyl acetate, 7:3), Yield 82%, anal. calcd. for $C_{16}H_{15}N_3O_3S$: C 58.35, H 4.59, N 12.76; found C 58.22, H 4.51, N 12.88. ^{1}H-NMR δ_H (DMSO-d_6, 400 MHz): 1.67–2.02(3H, t, -CH_2-$C\underline{H}_3$), 3.51–3.62(2H, q, -$C\underline{H}_2$-CH_3), 3.81(3H, s, -$OC\underline{H}_3$), 7.28(1H, s, –$C\underline{H}$=$C(CN)_2$), 7.51(2H, d, J = 8.0 Hz, Ar-$\underline{H}$), 7.76(2H, d, J = 8.0 Hz, Ar-$\underline{H}$), 8.34(2H, s, -$N\underline{H}_2$). IR: ν_{max} (KBr, cm^{-1}): 3560–3200(NH_2 str.), 3025(CH-arom. str.), 2188 (CN str.), 1620(C=C arom. str.), 1156(C = S str.). ^{13}C-NMR δ_c (DMSO-d_6): 22.70($COOCH_2\underline{C}H_3$), 55.78(Ar-$O\underline{C}H_3$), 64.58(-$COO\underline{C}H_2CH_3$), 94.19(EtOOC-$\underline{C}$-CN), 112.36(-$\underline{C}N$), 122.37, 124.96 127.26, 130.15, 132.51(aromatic), 138.64(Ar-$\underline{C}H$ = $C(CN)_2$), 148.16(-C=$\underline{C}$-N =), 164.37(-$\underline{C}OOCH_2CH_3$), 174.16(-S-$\underline{C}$=N-).

Ethyl (2E)-3-[2-Amino-4-(4-methylphenyl) (1,3-Thiazol-5-yl)]-2-cyanoprop-2-enoate (4j)

Mp 230–232°C, R_f 0.625 (toluene:ethyl acetate, 7:3), Yield 88%, anal. calcd. for $C_{16}H_{15}N_3O_2S$: C 61.32, H 4.83, N 13.41; found C 61.42, H 4.77, N 13.33. ^{1}H-NMR δ_H (DMSO-d_6, 400 MHz): 1.60(3H, s, -$C\underline{H}_3$)1.88–2.12(3H, t, -CH_2-$C\underline{H}_3$), 3.52–3.68(2H, q, -$C\underline{H}_2$-CH_3), 7.22(1H, s, –$C\underline{H}$=$C(CN)_2$), 7.45(2H, d, J = 8.4 Hz, Ar-$\underline{H}$), 7.70(2H, d, J = 8.4 Hz, Ar-$\underline{H}$), 8.23(2H, s, -$N\underline{H}_2$). IR: ν_{max} (KBr, cm^{-1}): 3495–3210(NH_2 str.), 3075(CH-arom. str.), 2208 (CN str.),

1535(C=C arom. str.), 1295(C = S str.). ^{13}C-NMR δ_c (DMSO-d_6): 21.86 (Ar-$\underline{C}H_3$), 23.09(COO$CH_2\underline{C}H_3$), 65.46(-COO$\underline{C}H_2CH_3$), 95.65(EtOOC-$\underline{C}$-CN), 112.13(-$\underline{C}$N), 122.13, 123.18, 127.32, 130.24, 132.72(aromatic), 134.23(Ar-$\underline{C}$H = C$(CN)_2$), 140.41(-C=$\underline{C}$-N =), 162.42(-$\underline{C}$OOCH_2CH_3), 175.76(-S-$\underline{C}$=N-).

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