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DESIGN AND SYNTHESIS OF SOME NOVEL THIAZOLE MOLECULES

Jaysinh I. Jadeja and Mahesh M. Savant *

Department of Chemistry, Atmiya University, Rajkot - 360005, Gujarat, India.

Keywords:

Thiazole, Hydrazide, N, S-heterocyle, Heterocycles, Ketene Dithioacetal

Correspondence to Author:
Dr. Mahesh M. Savant

Associate Professor,
Department of Chemistry,
Atmiya University, Rajkot - 360005,
Gujarat, India.

E-mail: mahesh.savant@atmiyauni.ac.in

ABSTRACT: A series of novel (*Z*)-3-((5-(2-((*E*)-arylidene) hydrazine-1-carbonyl)-4-methylthiazol-2-yl)amino)-2-cyano-3-(methylthio) acrylate 4a-t molecules have been synthesized and characterized by ^{1}H NMR, ^{13}C NMRand mass spectral analysis. Starting from ethyl 2-amino-4-methylthiazole-5-carboxylate 1 was reacted with hydrazine hydrate to obtain carbohydrazide molecule 2. Furthermore, reaction of molecule 2 with various aldehyde and the adduct 3a-t formed was reacted with ethyl 2-cyano-3,3-bis(methylthio) acrylate to get novel thiazole derivatives 4a-t, furthermore it was reacted with lithium hydroxide to form acid containing novel thiazole molecule 5a. The significant features of this reaction procedure are novel, easy and less time consuming with analytically pure product formation.

INTRODUCTION: Thiazole moiety is present in several medicinal compounds and natural sources. The first widely used antibiotic penicillin, also have thiazole moiety in its core structure. Numerous medicinal drugs available for various types of illness also hold thiazole moiety, as shown in **Fig. 1**. Thiazoles and their derivatives also play a significant role in the field of medicinal chemistry where they found to exhibit a wide variety of activities such as, antiviral [1], antioxidant [2], antituberculosis [3], antimicrobial [4], anticancer [5], anticonvulsant [6], anti-inflammatory [7], anti-infective [8], antidiabetic [9], anticonvulsant [10], antifungal [11], antiepileptic [12], antidepressant [13]. Some of the thiazole molecules also showed inhibition against SARS-CoV-2 virus disease [14, 15]. Several procedures for synthesizing thiazole derivatives are described in the literature [16-23].

Our continuous research in synthesizing various bioactive heterocyclic compounds [24, 25] motivated us to develop some novel thiazoles for medicinal interest.

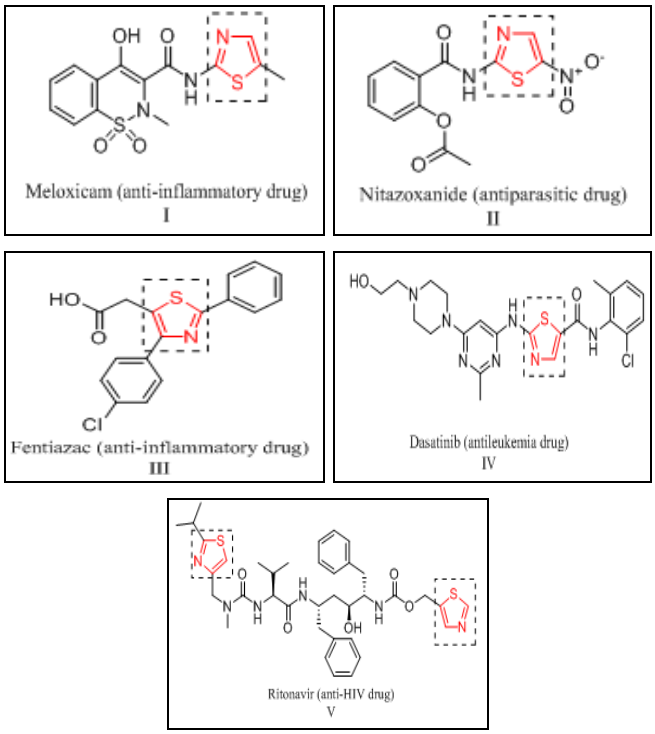

FIG. 1: SEVERAL BIOACTIVE THIAZOLES I-V

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EXPERIMENTAL SECTION:

MATERIAL AND METHODS: The melting points were determined on an electrothermal device using open capillaries and are uncorrected. Thin-layer chromatography was performed on precoated silica-gel 60 F254 (Merck) and compounds were visualized with UV light at 254 nm and 365 nm or with iodine vapor. The IR spectra were recorded on a Shimadzu FT-IR spectrometer using the ATR technique.

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE III (400 MHz) spectrometer in DMSO-d6. As an internal standard, chemical shifts are expressed in δppm downfield from Tetra-methylsilane (TMS). Mass spectra were recorded using a direct input probe on Shimadzu GCMS QP2010 Ultra mass spectrometer. All reactions were carried out under an ambient atmosphere. All reagents were purchased from Loba, Molychem, SRL and CDH and used without further purification.

General Procedure for the Synthesis of (*E*)-2-Amino-*N*'-benzylidene-4-methylthiazole-5-Carbohydrazide (3a-t): A mixture of compound 2 (10 mmol) and substituted benzaldehyde (10 mmol) in 10mL of MeOH and catalytical amount of glacial acetic acid was stirred and heated to reflux temperature for 1 hr.

After the completion of the reaction, the reaction mixture was cooled to room temperature, poured into ice-cold water and neutralized with dil. HCl. The separated solid was filtered, washed with water and purified by recrystallization from DMF to afford crystals **(**3a-t).

General Procedure for the Synthesis of Ethyl (*Z*) - 3-((5-(2-((*E*)-arylidene) hydrazine-1-carbonyl)-4 – methylthiazol – 2 - yl) amino) – 2 - cyano-3-(methylthio) acrylate (4a-t): A mixture of 3a-t (10 mmol) and ethyl 2-cyano-3,3-bis (methylthio) acrylate (10 mmol) in 10 mL of DMF and anhydrous potassium carbonate (10 mmol) was stirred at room temperature for 1 h.

After the completion of the reaction, the reaction mixture was cooled to room temperature and poured into ice-cold water. The separated solid was filtered, washed with water and purified by recrystallization from DMF to afford pure compound (4a-t).

General procedure for the synthesis of (Z) - 3 - ((5-(2 - ((E) - 4 - arylbenzylidene) hydrazine-1-carbonyl) -4-methylthiazol-2-yl)amino)-2-cyano-3-(methylthio) Acrylic Acid (5a): A mixture of **4a** (10 mmol) and lithium hydroxide (20 mmol) in 10 mL of THF:MeOH:H_2O in the ration of 3:2:1 was stirred at room temperature for 6 h.

After the completion of the reaction, the reaction mixture was cooled to room temperature, poured into ice-cold water, and acidified using dilute HCl. The separated solid was filtered, washed with water, and purified by recrystallization from DMF to afford a pure compound (5a).

Ethyl (*Z*) - 3-((5-(2-((*Z*) – 4 - chlorobenzylidene) hydrazine – 1 - carbonyl) – 4 - methylthiazol- 2-yl) amino) – 2 - cyano -3-(methylthio)acrylate (4a):

Yellow Solid, Yield: 83%, mp 205-207 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.81 (s, 1H), 11.88 (s, 1H), 8.00 (s, 1H), 7.72 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.2 Hz, 2H), 4.13 (d, J = 7.5 Hz, 2H), 2.54 (s, 3H), 2.33 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.13 (s, 1H), 7.49 (d, J = 8.9 Hz, 2H), 6.93 (d, J = 9.0 Hz, 2H), 4.48 (q, J = 7.1 Hz, 2H), 4.36 (q, J = 7.1 Hz, 2H), 3.84 (s, 3H), 2.69 (s, 3H), 2.59 (s, 3H), 1.43 (t, J = 7.1 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6);184.56, 168.49, 165.73, 161.96, 155.58, 147.32, 136.58, 132.76, 131.93, 129.22, 127.78, 117.22, 95.47, 60.55, 17.34, 16.98, 15.04; MS (m/z): 463 (M^+).Anal. Calcd. For $C_{19}H_{18}ClN_5O_3S_2$: C, 49.19; H, 3.91; N, 15.10; Found: C, 49.32; H, 3.89; N, 15.18.

Ethyl (*Z*) - 3-((5-(2-((*Z*) – 4 - bromobenzylidene) hydrazine – 1 - carbonyl) – 4 – methylthiazol - 2-yl) amino) - 2-cyano – 3 -(methylthio)acrylate (4b):

Yellow Solid, Yield: 91%, mp 231-233 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.83 (s, 1H), 11.91 (s, 1H), 7.98 (s, 1H), 7.69 – 7.57 (m, 4H), 4.14 (d, J = 8.1 Hz, 2H), 2.54 (s, 3H), 2.33 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6);184.55, 168.41, 165.39, 161.83, 154.89, 146.95, 136.57, 132.98, 131.82, 128.91, 128.03, 117.18, 95.50, 59.39, 17.60, 17.00, 15.18; MS (m/z): 508 (M^+).

Anal. Calcd. For $C_{19}H_{18}BrN_5O_3S_2$: C, 44.89; H, 3.57; N, 13.78; Found: C, 44.92; H, 3.76; N, 13.55.

Ethyl (*Z*) – 2 – cyano – 3 - ((5-(2-((*Z*)-4-methoxybenzylidene) hydrazine -1-carbonyl)-4 methylthiazol-2-yl) amino) – 3 - (methylthio) acrylate (4c):

Yellow Solid, Yield: 72%, mp 213-215°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.79 (s, 1H), 11.71 (s, 1H), 7.94 (s, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.3 Hz, 2H), 4.12 (s, 2H), 3.81 (s, 3H), 2.55 (s, 3H), 2.33 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6);184.63, 168.39, 165.42, 162.78, 154.89, 146.97, 136.44, 132.98, 130.23, 126.66, 117.32, 115.11, 95.51, 59.55, 17.72, 17.02, 14.92; MS (*m*/*z*): 459 (M^+). Anal. Calcd. For $C_20H_{21}N_5O_4S_2$: C, 52.27; H, 4.61; N, 15.24; Found: C, 52.30; H, 4.59; N, 15.29.

Ethyl (*Z*) – 2 – cyano – 3 - ((4-methyl – 5 - (2-((*Z*)-4-nitrobenzylidene) hydrazine-1-carbonyl) thiazol-2-yl) amino)-3-(methylthio)acrylate (4d):

Yellow Solid, Yield: 67%, mp 228-230 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.79 (s, 1H), 11.71 (s, 1H), 8.82 (d, *J* = 8.4 Hz, 2H), 8.24 (s, 1H), 8.92 (d, *J* = 8.3 Hz, 2H), 4.12 (d, *J* = 8.1 Hz, 2H), 2.55 (s, 3H), 2.33 (s, 3H), 1.16 (s, 3H); MS (*m*/*z*): 474 (M^+).Anal. Calcd. For $C_{19}H_{18}N_6O_5S_2$: C, 48.09; H, 3.82; N, 17.71; Found: C, 48.01; H, 3.62; N, 17.60.

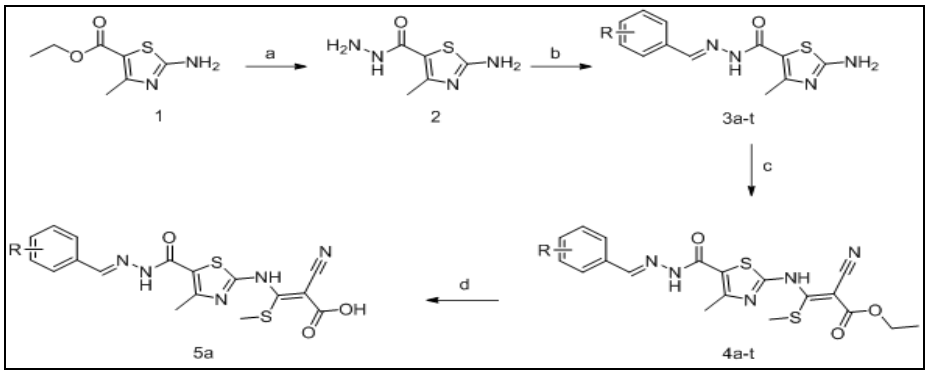
(*Z*) – 3 - ((5 - (2-((*E*) – 4 - chlorobenzylidene) hydrazine-1-carbonyl) – 4 – methylthiazol - 2-yl) amino) - 2 -cyano-3-(methylthio) acrylic acid (5a):

White Solid, Yield: 62%, mp 285-287°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.22 (s, 1H), 12.80 (s, 1H), 11.88 (s, 1H),), 7.80 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 2H), 4.13 (d, *J* = 7.5 Hz, 2H), 2.54 (s, 3H), 2.33 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 3H); MS (*m*/*z*): 435 (M^+); Anal. Calcd. For $C_{17}H_{14}ClN_5O_3S_2$: C, 48.09; H, 3.82; N, 17.71; Found: C, 48.12; H, 3.32; N, 17.54.

RESULTS AND DISCUSSION: We report newly synthesized molecules with thiazole in their main structure to find novel heterocyclic molecules. The compounds 4a-t were elucidated by inspecting their spectroscopic data, such as ^{1}H-NMR and Mass spectroscopy.

In the first step, Ethyl 2-amino-4-methylthiazole-5-carboxylate 1 and hydrazine hydrate reacted in MeOH at reflux temperature to get 2-amino-4-methylthiazole – 5 - carbohydrazide 2. Then compound 2 was reacted with various substituted aldehydes to obtain compound (*E*) – 2 – amino - *N*' – arylidene – 4 -methylthiazole – 5 – carbohydrazide 3a-t. The compound 3a-twas reacted with ethyl 2-cyano-3,3-bis(methylthio)acrylate with potassium carbonate in DMF to obtain novel and highly functionalized derivatives of thiazole 4a-t as shown in Scheme 1. Furthermore, molecule 4a reacted with lithium hydroxide in tetrahydrofuran, methanol and water, forming another novel thiazole molecule 5a.

The ^{1}H-NMR graph of molecules revealed that methyl proton of ester seen at t 1.16-1.19 ppm (CH_3) which were triplet peaks, at s 2.33 ppm (SCH_3) for thiomethyl protons as a singlet peak. Thiazole methyl protons were detected at s 2.54-2.55 ppm (CH_3) as a singlet, ester methylene protons were seen at t 4.12-4.14 ppm (CH_3) which were triplet peaks. Aromatic region was seen between 7.58-8.82 ppm.

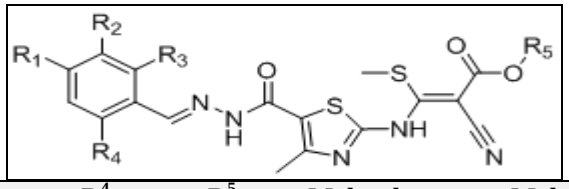


SCHEME 1: REAGENTS AND CONDITIONS: (A) $NH_2NH_2.H_2O$, MEOH, REFLUX, 1 H (B) R-C_6H_4CHO, CH_3COOH, MEOH, REFLUX, 1 H (C) ETHYL 2-CYANO-3,3-BIS(METHYLTHIO)ACRYLATE, K_2CO_3, DMF, RT, 1 H. (D) LIOH, THF, MEOH, H_2O, RT, 6 H

A singlet peak seen at s 7.94-8.24 ppm (CH) indicated the single proton. Thiazole NH proton were observed between s 11.71-11.91 ppm (NH) and acetamide protons were observed at s 12.79-12.83 ppm (NH) as a singlet. Acid hydrogen of 5a was detected at 13.33 ppm (COOH) in downfield. To improve the experimental conditions for the preparation of molecules 4a-t, several bases, such as anhydrous potassium carbonate and triethylamine were used in different solvents such as methanol, ethanol, tetrahydrofuran and acetonitrile. As a result, we found that the reaction of 3a-t with ethyl 2-cyano-3,3-bis(methylthio) acrylate was faster and gave thiazole derivatives 4a-t a good yield when potassium carbonate was used with DMF. Molecule **1** was synthesized according to the reported procedure by Meng[26]. Furthermore, the reaction of molecule **1** with hydrazine hydrate was carried out using the reported procedure [27].

Physicochemical Properties:

TABLE 2: PHYSICOCHEMICAL CHARACTERISTICS OF THE THIAZOLE MOLECULES 4A-T



Entry	R^1	R^2	R^3	R^4	R^5	Molecular weight	Molecular formula	Yield (%)	Melting point (°C)
1	Cl	H	H	H	CH_2CH_3	463.96	$C_{19}H_{18}ClN_5O_3S_2$	83	205-207
2	Br	H	H	H	CH_2CH_3	508.41	$C_{19}H_{18}BrN_5O_3S_2$	91	231-233
3	OCH_3	H	H	H	CH_2CH_3	459.54	$C_20H_{21}N_5O_4S_2$	72	213-215
4	NO_2	H	H	H	CH_2CH_3	474.51	$C_{19}H_{18}N_6O_5S_2$	67	228-230
5	CN	H	H	H	CH_2CH_3	454.52	$C_20H_{18}N_6O_3S_2$	87	221-223
6	CH_3	H	H	H	CH_2CH_3	443.54	$C_20H_{21}N_5O_3S_2$	89	230-232
7	F	H	H	H	CH_2CH_3	447.50	$C_{19}H_{18}FN_5O_3S_2$	65	198-200
8	H	H	H	H	CH_2CH_3	429.51	$C_{19}H_{19}N_5O_3S_2$	61	204-206
9	CH_3	CH_3	H	H	CH_2CH_3	457.57	$C_{21}H_{23}N_5O_3S_2$	86	237-239
10	$N(CH_3)_2$	H	H	H	CH_2CH_3	472.58	$C_{21}H_{24}N_6O_3S_2$	90	223-225
11	H	NO_2	H	H	CH_2CH_3	474.51	$C_{19}H_{18}N_6O_5S_2$	72	219-221
12	H	H	NO_2	H	CH_2CH_3	474.51	$C_{19}H_{18}N_6O_5S_2$	65	210-212
13	H	H	Cl	H	CH_2CH_3	463.96	$C_{19}H_{18}ClN_5O_3S_2$	83	200-202
14	F	F	H	H	CH_2CH_3	465.49	$C_{19}H_{17}F_2N_5O_3S_2$	68	187-189
15	Cl	Cl	H	H	CH_2CH_3	498.40	$C_{19}H_{17}Cl_2N_5O_3S_2$	75	193-195
16	OCH_3	H	OCH_3	H	CH_2CH_3	489.57	$C_{21}H_{23}N_5O_5S_2$	83	231-232
17	H	H	CH_3	H	CH_2CH_3	443.54	$C_20H_{21}N_5O_3S_2$	80	225-227
18	CH_3	H	CH_3	H	CH_2CH_3	457.57	$C_{21}H_{23}N_5O_3S_2$	85	217-219
19	H	H	Cl	Cl	CH_2CH_3	498.40	$C_{19}H_{17}Cl_2N_5O_3S_2$	80	209-211
20	H	Cl	Cl	H	CH_2CH_3	498.40	$C_{19}H_{17}Cl_2N_5O_3S_2$	64	201-203
21	Cl	H	H	H	OH	435.90	$C_{17}H_{14}ClN_5O_3S_2$	62	185-187

[a]Yield is given for isolated product without purification. [a]All products are in amorphous form.

CONCLUSIONS: In conclusion, a very efficient and easy technique for the synthesis of ethyl (*Z*)-3-((5-(2-((*E*)-arylidene) hydrazine-1-carbonyl)-4-methylthiazol-2-yl) amino)-2-cyano-3-(methylthio) acrylate 4a-t and (*Z*) – 3 - ((5 - (2 - ((*E*) – 4 - arylbenzylidene) hydrazine – 1 - carbonyl) – 4 - methylthiazol-2-yl) amino)-2-cyano-3-(methylthio) acrylic acid 5a have been synthesized which contains thiazole moiety in its core structure. The adopted method is simple, easy and novel. The synthesized molecules were characterized by various analytical techniques such as MS, ^{1}H and ^{13}C.

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CONFLICTS OF INTEREST: The authors declare that there is no conflict of interest regarding the publication of this article.

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