Egypt. J. Chem. **Vol. 66,** No. **SI 13, 733-743** (2023)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Synthesis of Novel Thiazole-Based Heterocycles as New Anti-bacterial and Anti-fungal Agents.

Marwa M. Fouad,[a*] Ahmad M. Farag[b], Galal H. Elgemeie[c], N. O. Shaker[d], N. A. Alian[d]

[a] *Basic Science Department, Modern Academy for Engineering & Technology, Cairo, Egypt*

[b] *Chemistry department, Faculty of Science, Cairo University, Giza, Egypt*

[c] *Chemistry department, Faculty of Science, Helwan University, Cairo, Egypt*

[d] *Chemistry department, Faculty of Science (Girls), Al-Azhar University, Cairo, Egypt*

Abstract

Due to the potential biological and medicinal effects of heterocyclic moieties, they have attracted attention, so the objective of the current work is to create some newly generated heterocyclic compounds with anticipated biological activity. This can be accomplished by reacting 5-methylthiazol-2-amine (**1**) and ethyl cyanoacetate (**2**) to yield 2-cyano-*N*-(5-methylthiazol-2-yl)acetamide (**3**). Compouund **3** reacts with aromatic aldehydes, aromatic diazonium salts **5a-c**, hydrozonoyl halide derivatives **7a-c**, active methylene reagents **2,11,14** , hydrazines and ethyl 2-cyanoacrylate derivatives **19a,b** to form the corresponding acrylamide derivatives **4a,b**, hydrazones **6a-c**, aminopyrazoles **9a-c**, pyridine-3-carbonitrile derivatives **13a,b**,**16**, aminopyrazoles **18a,b** and oxopyridine-3-carboxylate derivatives **21a,b**, respectively. The sensitivity of acrylamide **4a** to several chemical substances was investigated through its reaction with ethyl cyanoacetate (**2**), hydrazines, 3-amino-(2*H*)-1,2,4-triazole (**28**) and 5-methylthiazol-2-amine (**1**) to form phenylpyridine-3-carboxylate derivative **24**, aminopyrazole derivatives **27a,b**, triazolo[1,5-*a*]pyrimidine derivative **30** and thiazolo[3,2-*a*]pyrimidine derivative **32**, respectively. All synthesized compounds' structures were verified using infrared radiation, ^{1}H-NMR, and ^{13}C-NMR. In addition, mass spectroscopy and elemental assessment were done. The antibacterial and antifungal properties of some of the created substances were also examined. From all the investigated substances, only **3**, **9a**, **9c**, **4a**, and **6c** demonstrated good antibacterial activity, while compounds **16**, **21a**, **21b**, and **24** demonstrated effective antifungal and antibacterial activities towards bacterial strains that were either Gram-positive or Gram-negative.

Keywords: Acrylamide , Aminopyrazole, Carbonitrile, Cyanoa acetamide, Hydrazines, Hydrozonoyl halide.

1. Introduction

The majority of biologically active substances contain the valuable structural pattern known as a thiazole ring structure. It has been a key ingredient in several organic substances, including carboxylase, vitamin B1 (thiamine), and penicillin. A significant component in medicine is 2-aminothiazole and it is used to treat hypersensitivity [1], high blood pressure [2], inflammatory responses [3], psychiatric disorders [4], infections caused by bacteria [5], as well as Aids virus [6]. Additionally, Aminothiazoles was described as oestrogen receptor ligands [7] and a newly developed family of antagonists for the adenosine receptor [8]. Some equivalents, in contrast, have been employed to kill the fungus to prevent the spread of Xanthomonas in vivo, for components killing herbs, schistosomes and worms [9]. Moreover, cyanoacetamides are substances that react quickly due to the carbonyl and cyano functionalities of these compounds, which make reactions with typical bidentate reagents easier. They can also be employed as reaction ingredients or intermediates in processes to produce a range of heterocyclic compounds. However, the active hydrogen on carbon number two of such substances can participate in numerous condensation in addition to substitution processes. Additionally, biochemists have recently devoted attention to the diverse biological functions of several cyanoacetamide derivatives. In accordance with these facts and continuing our prior studies [10-14], we have discovered that a crucial, essential constituent enabling the production of innovative heterocyclic ingredients that possess prospective pharmacological effects is 5-methylthiazol-2-amine (**1**). Consequently, the objective of the present research is to generate novel heterocyclic compounds with expected biological activity. This can be achieved by reacting 5-methylthiazol-2-amine (**1**) and

*Corresponding author e-mail: mar.mfouad@gmail.com (Marwa M. Fouad)

Receive Date: 13 December 2022, Revise Date: 04 May 2023, Accept Date: 06 May 2023

DOI: 10.21608/EJCHEM.2023.180589.7326

ethyl cyanoacetate (**2**) to form 2-cyano-*N*-(5-methylthiazol-2-yl)acetamide (**3**). By employing this subsequently synthesized product in subsequent reactions, new chemicals were then created.

2. Experimental

On a Gallenkamp melting point device, all melting points have been measured. The infrared radiation spectra in potassium bromide discs were collected using a Shimadzu FT IR 8101 PC infrared spectrophotometer and a Pye Unicam SP 3300. Using a Varian Mercury VXR-300 NMR spectrometer, the ^{1}H-NMR and ^{13}C-NMR spectra have been determined in deuterated chloroform ($CDCl_3$) or dimethyl sulfoxide (DMSO-d6) and acquired at 300 MHz. Both a Shimadzu GCMS-QP 5000 EI mass spectrometer and a Shimadzu GCMS-QP 2010 Plus EI mass spectrometer were used to record mass spectra at 70 eV. The Regional Centre for Mycology and Biotechnology at Al-Azhar University in Cairo, Egypt, and the Micro-analytical Centre of Cairo University in Giza, Egypt, performed spectral and elemental studies.

Materials and Reagents

Aldrich Chemical Co. provided hydrazine, phenylhydrazine, ethyl cyanoacetate, ethyl acetoacetate, aniline, 3-nitroaniline, o-toluidine, 4-chloroaniline, 4-methylaniline, 4-nitroaniline, benzaldehyde, 4-methoxybenzaldehyde and thiourea. We bought sodium metal, triethylamine, piperidine, sulfuryl chloride and propionaldehyde from British Drug Houses (BDH). Acetophenone, 3-amino-(2*H*)-1,2,4-triazole, potassium hydroxide and chlorine were obtained from the German company Merck Co.

We bought hydrochloric acid, sodium hydroxide, methyl benzoate, sodium acetate trihydrate, ammonium acetate, sodium carbonate, sodium methoxide and sodium nitrite from El-Nasr Pharmaceutical and Chemical Co. (ADWIC), in Egypt.

5-Methylthiazol-2-amine (**1**) [15], chloro-(arylhydrazono)ethylacetate **7a-c** [16], 1,3-diphenylpropane-1,3-dione (**14**) [17] and ethyl 2-cyanoacrylate derivatives **19a,b** [18] were achieved using the procedures explained in the published works.

*Synthesis of 2-Cyano-N-(5-methylthiazol-2-yl)-acetamide (**3**).*

Compound **3** was developed by two different methods, Method A: Ethyl cyanoacetate (**2**) (1.697 g, 15 mmol) was heated to 150°C, then 5-methylthiazol-2-amine (**1**) (1.142 g, 0.01 mol) has been added gradually over a duration of one hour. Additionally, it was heated for an extra hour, subsequently allowed to chill to ambient temperature to crystallize out. The final outcome was filtered, cleaned using petroleum ether (60/80), then dried and finally recrystallized using ethanol, affording 1.593 g (88% yield) of cyanoacetamide derivative **3**. Method B: Ethyl cyanoacetate (**2**) (1.131 g, 0.01 mol) was introduced in an equivalent amount to a solution of 5-methylthiazol-2-amine (**1**) (1.142 g, 0.01 mol) in 30 ml of 1,4-dioxane. For three hours, the reaction mixture had been refluxed. The resulting solid product after the elimination of the solvent under lower pressure was extracted, dried, and crystallized using ethanol, producing 1.358 g (75% Yield) of compound **3**. m.p.110-112°C (EtOH/H_2O); IR (KBr) νmax/cm^{-1}: 3419 (NH), 2259 (C≡N), 1693 (C=O); ^{1}H NMR ($CDCl_3$): δ 2.29 (s, 3H, CH_3), 3.76 (s, 2H, CH_2), 6.71 (s, 1H, CH), 12.2 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 11.53, 25.75, 115.05, 126.61, 134.32, 161.11, 167.15; MS m/z (%): 181 (M^+, 6.46), 141 (7.66), 115 (100), 82 (22.31), 72 (69.87), 59 (55.76); For $C_7H_7N_3SO$ (181.22): Calcd.: C, 46.39; H, 3.89; N, 23.19; S, 17.69%. Found: C, 46.41; H, 3.87; N, 23.19; S, 17.68%.

*Reaction between 2-cyano-N-(5-methylthiazol-2-yl)-acetamide (**3**) and aromatic aldehydes.*

General procedure:

A little droplets of piperidine were placed into a solution of the cyanoacetamide derivative **3** (0.362 g, 2 mmol) and a adequate aromatic aldehyde, either benzaldehyde (2 mmol) or 4-methoxybenzaldehyde (2 mmol) in 15 ml ethanol. After allowing the reaction to reflux for three hours, it was cooled, filtered off, and washed using ethanol before being dried. The acrylamide derivatives **4a** and **4b** were obtained respectively, through recrystallization from the appropriate solvent.

2-Cyano-*N*-(5-methylthiazol-2-yl)-3-phenylacryl-amide (**4a**): Yield 77%; m.p.138-140°C (EtOH/DMF); IR (KBr) νmax/cm^{-1}: 3419 (NH), 2200 (C≡N), 1660 (C=O); ^{1}H NMR ($CDCl_3$): δ 2.29 (s, 3H, CH_3), 6.71 (s, 1H, CH), 7.27-8.02 (m, 5H, Ar-H), 8.46 (s, 1H, CH), 8.95 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 12.08, 107.21, 116.63, 119.47, 126.47, 128.24, 128.90, 135.05, 151.68, 162.46, 167.12; MS m/z (%): 269 (M^+, 9.04), 240 (9.93), 201 (18.04), 128 (58.92), 71 (88.07), 51(100); For $C_{14}H_{11}N_3SO$ (269.32): Calcd.: C, 62.43; H, 4.12; N, 15.60; S, 11.91%. Found: C, 62.43; H, 4.13; N, 15.62; S, 11.90%.

2-Cyano-3-(4-methoxyphenyl)-*N*-(5-methylthiazol-2-yl)acrylamide (**4b**): Yield 75%; m.p.154°C (EtOH/DMF); IR (KBr) νmax/cm^{-1}: 3402 (NH), 2205 (C≡N), 1684 (C=O); ^{1}H NMR ($CDCl_3$): δ 2.44 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 6.97 (s, 1H, CH), 7.01-8.04 (m, 4H, Ar-H), 8.38 (s, 1H, CH), 8.86 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 12.08, 55.50, 104.64, 114.58, 117.09, 124.41, 126.10, 138.55, 150.35,

161.76, 162.37, 163.80; MS m/z (%): 299 (M^+, 18.06), 284 (3.49), 186 (100), 158 (28.04), 115 (21.96), 77(18.56); For $C_{15}H_{13}N_3SO_2$ (299.35): Calcd.: C, 60.18; H, 4.38; N, 14.04; S, 10.71%. Found: C, 60.19; H, 4.38; N, 14.02; S, 10.72%.

*Reaction between 2-cyano-N-(5-methylthiazol-2-yl)acetamide (**3**) and aromatic diazonium salts.*
common practise:
The proper diazonium salt of the equivalent aromatic amines **5a–c**, which were made by mixing the corresponding aromatic amine, hydrochloric acid, and sodium nitrite in the appropriate amounts, was subsequently incorporated into a cold solution of 2-cyano-*N*-(5-methylthiazol-2-yl)acetamide (**3**) (0.362 g, 2 mmol), in 30 ml ethanol, and sodium acetate trihydrate (0.5 g). The incorporation was performed gradually over a 30-minute period during being agitated at a temperature of 0 to 5°C. The mixture have been constantly agitated for an extra 4 hours at 0-5°C. After that, the resulting solution was maintained in a frozen container for 12 hours before being diluted by water. The precipitated material was recovered by filtration, cleaned with water, dried, and then recrystallized using a suitable solvent to produce the corresponding hydrazones **6a–c**.
(*E*)-2-(2-phenylhydrazono)-2-cyano-*N*-(5-methyl-thiazol-2-yl)acetamide (**6a**): Yield 75%; m.p.220ºC (EtOH/H_2O); IR (KBr) νmax/cm^{-1}: 3426, 3201 (2NH), 2262 (C≡N), 1692 (C=O); ^{1}H NMR ($CDCl_3$): δ 2.59 (s, 3H, CH_3), 7.10 (s, 1H, CH), 7.37-7.81 (m, 5H, Ar-H), 8.90 (s, 1H, NH), 10.30 (s, 1H, NH); MS m/z (%): 285 (M^+, 2.77), 218 (12.33), 141 (23.10), 92 (62.60), 72 (67.93), 59 (100); For $C_{13}H_{11}N_5SO$ (285.33): Calcd.: C, 54.72; H, 3.89; N, 24.54; S, 11.24%. Found: C, 54.74; H, 3.87; N, 24.54; S, 11.26%.

(*E*)-2-(2-*o*-tolylhydrazono)-2-cyano-*N*-(5-methyl-thiazol-2-yl)acetamide (**6b**): Yield 78%; m.p.228ºC (EtOH/H_2O); IR (KBr) νmax/cm^{-1}: 3445, 3205 (2NH), 2263 (C≡N), 1693 (C=O); ^{1}H NMR (DMSO-d6): δ 2.42 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 6.68 (s, 1H, CH), 6.89-7.60 (m, 4H, Ar-H), 8.00 (s, 1H, NH), 12.31 (s, 1H, NH); MS m/z (%): 299 (M^+, 80.25), 285 (93.83), 246 (90.12), 203 (100), 140 (97.53), 108 (100); For $C_{14}H_{13}N_5SO$ (299.35): Calcd.: C, 56.17; H, 4.38; N, 23.40; S, 10.71%. Found: C, 56.15; H, 4.37; N, 23.41; S, 10.71%.

(*E*)-2-(2-(3-nitrophenyl)hydrazono)-2-cyano-*N*-(5-methylthiazol-2-yl)acetamide (**6c**): Yield 80%; m.p.210ºC (EtOH/H_2O); IR (KBr) νmax/cm^{-1}: 3441, 3210 (2NH), 2262 (C≡N), 1692 (C=O); ^{1}H NMR (DMSO-d6): δ 2.48 (s, 3H, CH_3), 7.22 (s, 1H, CH), 7.30-8.90 (m,4H, Ar-H), 9.10 (s, 1H, NH), 12.30 (s, 1H, NH); MS m/z (%): 330 (M^+, 76.83), 318 (85.37), 240 (100), 166 (100), 132 (98.78), 95 (79.27); For $C_{13}H_{10}N_6SO_3$ (330.32): Calcd.: C, 47.27; H, 3.05; N, 25.44; S, 9.71%. Found: C, 47.27; H, 3.03; N, 25.45; S, 9.72%.

*Reaction between 2-cyano-N-(5-methylthiazol-2-yl)acetamide (**3**) and hydrazonoyl halide derivatives.*
General procedure:
20 ml absolute ethanol was used for dissolution of the sodium metal (0.046 g, 2 mmol) to create an ethanolic sodium ethoxide solution, to which the cyanoacetamide derivative **3** (0.362 g, 2 mmol) was then stirred in for 20 minutes. The relevant hydrazonoyl chloride derivatives **7a–c** (2 mmol) were gradually added over the course of 30 minutes to the resulting solution. An extra 12 hours were spent stirring the mixture at ambient temperature. The generated product was filtered out, rinsed by water, dried, and then recrystallized using a compatible solvent to obtain the respective aminopyrazole derivatives **9a-c**.

Ethyl 4-(5-methylthiazol-2-ylcarbamoyl)-5-amino-1-(4-chlorophenyl)-1*H*-pyrazole-3-carboxylate (**9a**): Yield 84%; m.p.120ºC (EtOH/DMF); IR (KBr) νmax/cm^{-1}: 3448, 3328 (NH_2), 3298 (NH), 1724, 1650 (2C=O); ^{1}H NMR ($CDCl_3$): δ 1.53 (t, 3H, CH_3, J=7.5 Hz), 2.43 (s, 3H, CH_3), 4.40 (s, 2H, NH_2), 4.55 (q, 2H, CH_2, J=7.2 Hz), 7.24 (s, 1H, CH), 7.27-8.30 (m, 4H, Ar-H), 11.30 (s, 1H, NH); MS m/z (%): 407 (M^++2, 9.54), 406 (M^++1, 12.53), 405 (M^+, 51.96), 369 (53.76), 304 (3.70), 155 (18.84), 52 (100); For $C_{17}H_{16}N_5SO_3Cl$ (405.86): Calcd.: C, 50.31; H, 3.97; N, 17.26; S, 7.90; Cl, 8.74%. Found: C, 50.33; H, 3.95; N, 17.26; S, 7.91; Cl, 8.73%.

Ethyl 4-(5-methylthiazol-2-ylcarbamoyl)-5-amino-1-*p*-tolyl-1*H*-pyrazole-3-carboxylate (**9b**): Yield 80%; m.p.104ºC (EtOH/DMF); IR (KBr) νmax/cm^{-1}: 3417, 3367 (NH_2), 3190 (NH), 1710, 1658 (2C=O); ^{1}H NMR ($CDCl_3$): δ 1.51 (t, 3H, CH_3, J=6.9 Hz), 2.33 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 4.40 (s, 2H, NH_2), 4.58 (q, 2H, CH_2, J=7.2 Hz), 7.15 (s, 1H, CH), 7.29-8.09 (m, 4H, Ar-H), 11.22 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 11.59, 13.31, 20.45, 62.16, 101.72, 113.10, 116.68, 118.06, 124.88, 129.70, 138.28, 139.88, 146.07, 147.78, 155.90; MS m/z (%): 385 (M^+, 0.6), 311 (4.33), 270 (21.42), 140 (30.31), 106 (100), 92 (96.74); For $C_{18}H_{19}N_5SO_3$ (385.44): Calcd.: C, 56.09; H, 4.97; N, 18.17; S, 8.32%. Found: C, 56.08; H, 4.96; N, 18.19; S, 8.33%.

Ethyl4-(5-methylthiazol-2-ylcarbamoyl)-5-amino-1-(4-nitrophenyl)-1*H*-pyrazole-3-carboxylate (**9c**): Yield 82%; m.p.152-154ºC (EtOH/DMF); IR (KBr) νmax/cm^{-1}: 3737, 3436 (NH_2), 3250 (NH), 1710, 1639 (2C=O); ^{1}H NMR ($CDCl_3$): δ 1.52 (t, 3H, CH_3, J=7.2 Hz), 2.45 (s, 3H, CH_3), 4.40 (s, 2H, NH_2), 4.59 (q, 2H, CH_2, J=7.2 Hz), 7.27 (s, 1H, CH), 7.32-8.45

(m, 4H, Ar-H), 10.90 (s, 1H, NH); MS m/z (%): 416 (M^+, 2.74), 307 (9.13), 234 (46.12), 210 (64.38), 155 (62.10), 115 (100); For $C_{17}H_{16}N_6SO_5$ (416.41): Calcd.: C, 49.03; H, 3.87; N, 20.18; S, 7.70%. Found: C, 49.04; H, 3.87; N, 20.16; S, 7.71%.

*Reaction of 2-cyano-N-(5-methylthiazol-2-yl)acetamide (**3**) with active methylene reagents*.

Typical practise:

A catalytic quantity of triethylamine was introduced to a cyanoacetamide derivative **3** (0.362 g, 2 mmol) solution in ethanol (20 ml), then an equivalent amount of either ethyl cyanoacetate (**2**) (2 mmol), ethyl 3-oxobutanoate (**11**) (2 mmol) or 1,3-diphenylpropane-1,3-dione (**14**) (2 mmol) was added. After five hours of reflux heating, the resulting mixture proceeded to chill to ambient temperature. After that, it was dropped into a solution of ice and water, and then neutralized using dilute hydrochloric acid. The relevant pyridine-3-carbonitrile derivatives **13a,b**, and **16** respectively, were obtained by filtering the resulting solid product, drying it, and recrystallizing it using an appropriate solvent.

4-Amino-1,2-dihydro-6-hydroxy-1-(5-methylthiazol-2-yl)-2-oxopyridine-3-carbonitrile (**13a**): Yield 73%; m.p.218ºC (EtOH/H_2O); IR (KBr) νmax/cm^{-1}: 3419, 3207 (NH_2), 2262 (C≡N), 1693 (C=O); ^{1}H NMR ($CDCl_3$): δ 2.51 (s, 3H, CH_3), 3.75 (s, 2H, NH_2), 3.99 (s, 1H, OH), 4.44 (s, 1H, CH), 7.07 (s, 1H, CH); MS m/z (%): 248 (M^+, 15.25), 230 (16.72), 203 (19.06), 176 (18.48), 149 (32.26), 69 (100); For $C_{10}H_8N_4SO_2$ (248.26): Calcd.: C, 48.38; H, 3.25; N, 22.57; S, 12.92%. Found: C, 48.40; H, 3.26; N, 22.55; S, 12.92%.

1,2-Dihydro-6-hydroxy-4-methyl-1-(5-methylthiazol-2-yl)-2-oxo-pyridine-3-carbonitrile (**13b**): Yield 82%; m.p.202ºC (EtOH/H_2O); IR (KBr) νmax/cm^{-1}: 2263 (C≡N), 1693 (C=O); ^{1}H NMR ($CDCl_3$): δ 1.26 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 3.7 (s, 1H, OH), 4.80 (s, 1H, CH), 7.10 (s, 1H, CH); MS m/z (%): 247 (M^+, 0.52), 205 (0.73), 181 (16.39), 141 (7.37), 114 (100), 69 (48.06); For $C_{11}H_9N_3SO_2$ (247.27): Calcd.: C, 53.43; H, 3.67; N, 16.99; S, 12.97%. Found: C, 53.44; H, 3.66; N, 16.98; S, 12.98%.

1,2-Dihydro-1-(5-methylthiazol-2-yl)-2-oxo-4,6-diphenylpyridine-3-carbonitrile (**16**): Yield 93%; m.p.86ºC (EtOH/H_2O); IR (KBr) νmax/cm^{-1}: 2357 (C≡N), 1698 (C=O); ^{1}H NMR (DMSO-d6): δ 2.50 (s, 3H, CH_3), 4.88 (s, 1H, CH), 7.10 (s, 1H, CH), 7.35-8.19 (m, 10H, Ar-H); ^{13}C NMR (DMSO-d6): δ 25.77, 93.09, 115.90, 120.80, 126.40, 127.16, 128.24, 128.58, 132.74, 133.37, 134.36, 158.40, 166.18, 184.97; MS m/z (%): 369 (M^+, 34.11), 302 (36.92), 223 (66.82), 147 (65.42), 105 (81.31), 77 (100); For $C_{22}H_{15}N_3SO$ (369.44): Calcd.: C, 71.52; H, 4.09; N, 11.37; S, 8.68%. Found: C, 71.51; H, 4.09; N, 11.38; S, 8.66%.

*Reactions between 2-cyano-N-(5-methylthiazol-2-yl)acetamide (**3**) and hydrazine derivatives.*

General approach:

Hydrazine (2 mmol) or phenylhydrazine (2 mmol) was incorporated into cyanoacetamide derivative **3** (0.362 g, 2 mmol) with 20 ml ethanol. After being refluxed for five hours, the mixture had chilled to atmospheric temperature. Then, the produced substance was removed using a filter, rinsed with ethanol, and then dried. The appropriate aminopyrazole derivatives **18a** and **18b** were produced respectively through recrystallization from the proper solvent.

N^5-(5-methylthiazol-2-yl)-1*H*-pyrazole-3,5-diamine (**18a**): Yield 74%; m.p.84ºC (EtOH/H_2O); IR (KBr) νmax/cm^{-1}: 3421, 3263 (NH_2), 3116, 3063 (2NH); ^{1}H NMR (DMSO-d6): δ 2.15 (s, 3H, CH_3), 3.76 (s, 2H, NH_2), 6.57 (s, 1H, CH), 6.62 (s, 1H, CH), 10.40 (s, 1H, NH), 12.2 (s, 1H, NH); ^{13}C NMR (DMSO-d6): δ 11.54, 76.40, 119.47, 135.05, 151.70, 152.70, 166.97; MS m/z (%): 195 (M^+, 25.64), 178 (26.50), 145 (23.50), 126 (25.64), 114 (100), 71 (77.78). For $C_7H_9N_5S$ (195.25): Calcd.: C, 43.06; H, 4.65; N, 35.87; S, 16.42%. Found: C, 43.04; H, 4.66; N, 35.88; S, 16.42%.

N^5-(5-methylthiazol-2-yl)-1-phenyl-1*H*-pyrazole-3,5-diamine (**18b**): Yield 78%; m.p.200ºC (EtOH/H_2O); IR (KBr) νmax/cm^{-1}: 3698, 3417 (NH_2), 3264 (NH); ^{1}H NMR (DMSO-d6): δ 2.35 (s, 3H, CH_3), 3.30 (s, 2H, NH_2), 6.58 (s, 1H, CH), 6.62 (s, 1H, CH), 6.63-7.15 (m, 5H, Ar-H), 12.10 (s, 1H, NH); MS m/z (%): 271 (M^+, 68.42), 248 (100), 226 (100), 182 (92.11), 158 (85.53), 98 (96.05); For $C_{13}H_{13}N_5S$ (271.34): Calcd.: C, 57.54; H, 4.83; N, 25.81; S, 11.82%. Found: C, 57.55; H, 4.83; N, 25.83; S, 11.81%.

*Reaction of 2-cyano-N-(5-methylthiazol-2-yl)acetamide (**3**) with ethyl 2-cyanoacrylate derivatives.*

General procedure:

Ammonium acetate (0.5 g) was supplied to a combination of cyanoacetamide derivative **3** (0.362 g, 2 mmol) and the proper ethyl 2-cyanoacrylate derivatives **19a,b** (2 mmol) in acetic acid. After that, the mixture which resulted was refluxed for six hours before being poured over crushed ice. To obtain the precipitated outcome, it was filtered, purified with water, dried, and then recrystallized using ethanol to produce the equivalent oxopyridine-3-carboxylate derivatives, **21a** and **21b**, respectively.

Ethyl 2-amino-4-(4-chlorophenyl)-5-cyano-1,6-dihydro-1-(5-methylthiazol-2-yl)-6-oxopyridine-3-carboxylate (**21a**): Yield 85%; m.p.88ºC (EtOH/H_2O); IR (KBr) νmax/cm^{-1}: 3419, 3037 (NH_2), 2219 (C≡N), 1722, 1607 (2C=O); ^{1}H NMR (DMSO-d6): δ 1.36 (t, 3H, CH_3, J=7.2 Hz), 2.58 (s, 3H, CH_3), 4.37 (q, 2H, CH_2, J=7.5 Hz), 7.7 (s, 1H, CH), 7.71-8.43 (m, 4H, Ar-H), 8.42 (s, 2H, NH_2); ^{13}C NMR (DMSO-d6): δ 13.93, 14.20, 62.33, 99.31, 115.30, 120.80, 129.23, 130.01, 132.18, 135.50, 137.74, 153.39, 158.40, 165.22, 169.4, 170.90; MS m/z (%): 416 (M^++2, 70.73), 415 (M^++1, 79.27), 414 (M^+, 85.37), 337 (82.93), 257 (86.59), 197 (75.61), 97 (100). For $C_{19}H_{15}N_4SO_3Cl$ (414.87): Calcd.: C, 55.01; H, 3.64; N, 13.50; S, 7.73; Cl, 8.55%. Found: C, 55.03; H, 3.65; N, 13.51; S, 7.73; Cl, 8.53%

Ethyl 2-amino-5-cyano-1,6-dihydro-4-(4-methoxyphenyl)-1-(5-methylthiazol-2-yl)-6-oxopyridine-3-carboxylate (**21b**). Yield 87%; m.p.90ºC (EtOH/H_2O); IR (KBr) νmax/cm^{-1}: 3417, 3141 (NH_2), 2211 (C≡N), 1715, 1606 (2C=O); ^{1}H NMR (DMSO-d6): δ 1.30 (t, 3H, CH_3, J=7.2 Hz), 2.50 (s, 3H, CH_3), 3.34 (s, 2H, NH_2), 3.87 (s, 3H, OCH_3), 4.30 (q, 2H, CH_2, J=6.9 Hz), 7.14 (s, 1H, CH), 7.17-8.31(m, 4H, Ar-H); ^{13}C NMR (DMSO-d6): δ 13.97, 14.20, 55.63, 61.92, 98.40, 114.72, 115.96, 123.72, 124.90, 127.40, 133.23, 154.09, 162.04, 163.23, 166.01, 169.40. 171.03; MS m/z (%): 410 (M^+, 38.51), 391 (60.14), 318 (49.32), 231 (100), 186 (78.38), 114 (75.00). For $C_{20}H_{18}N_4SO_4$ (410.45): Calcd.: C, 58.52; H, 4.42; N, 13.65; S, 7.81%. Found: C, 58.52; H, 4.44; N, 13.64; S, 7.83%.

*Preparation of Ethyl 2-amino-5-cyano-1,6-dihydro-1-(5-methylthiazol-2-yl)-6-oxo-4-phenylpyridine-3-carboxylate (**24**).*

A catalytic amount of triethylamine and an equivalent amount of ethyl cyanoacetate (**2**) (0.113 g, 1 mmol) were dissolved in a solution containing acrylamide **4a** (0.269 g, 1 mmol) in 20 ml absolute ethanol. After being heated up to three hours in a reflux system, the solution mixture was dumped over an ice and water solution and neutralized using HCl. Then, the solid resulting was extracted using a filter, cleaned using water, dried, and crystallized with a compatible solvent to yield the chemical (**24**). Yield 89%; m.p.80ºC (EtOH/H_2O); IR (KBr) νmax/cm^{-1}: 3430, 3067 (NH_2), 2221 (C≡N), 1725, 1605 (2C=O); ^{1}H NMR (DMSO-d6): δ 1.32 (t, 3H, CH_3, J=7.2 Hz), 2.50 (s, 3H, CH_3), 3.30 (s, 2H, NH_2), 4.33 (q, 2H, CH_2, J=7.2 Hz), 7.2 (s, 1H, CH), 7.57-8.41 (m, 5H, Ar-H); MS m/z (%): 380 (M^+, 43.45), 336 (43.45), 223 (52.41), 156 (84.14), 128 (100), 77 (87.59). For $C_{19}H_{16}N_4SO_3$ (380.42): Calcd.: C, 59.99; H, 4.24; N, 14.73; S, 8.43%. Found: C, 59.97; H, 4.25; N, 14.75; S, 8.43%.

*Reaction of 2-cyano-N-(5-methylthiazol-2-yl)-3-phenylacrylamide (**4a**) with hydrazine derivatives.*

Main technique:

Hydrazine (1 mmol) or phenylhydrazine (1 mmol) was incorporated into a solution of acrylamide **4a** (0.269 g, 1 mmol) in ethanol (15 ml). The solution mixture was refluxed for four hours before being left to cool to atmospheric temperature. The produced solid was extracted using a filter, rinsed with ethanol, and then dried. The equivalent 3-aminopyrazole derivatives, **27a** and **27b**, were produced respectively by recrystallization from the appropriate solvent.

3-Amino-*N*-(5-methylthiazol-2-yl)-5-phenyl-1*H*-pyrazole-4-carboxamide (**27a**): Yield 75%; m.p.78ºC (EtOH/H_2O); IR (KBr) νmax/cm^{-1}: 3427, 3203 (NH_2), 3055, 3020 (2NH), 1692 (C=O); ^{1}H NMR (DMSO-d6): δ 2.51 (s, 3H, CH_3), 4.00 (s, 2H, NH_2), 7.15 (s, 1H, CH), 7.22-7.38 (m, 5H, Ar-H), 8.72 (s, 1H, NH), 12.22 (s, 1H, NH); MS m/z (%): 299 (M^+, 61.34), 283 (81.51), 198 (68.91), 149 (82.35), 112 (100), 58 (95.80); For $C_{14}H_{13}N_5SO$ (299.35): Calcd.: C, 56.17; H, 4.38; N, 23.40; S, 10.71%. Found: C, 56.17; H, 4.36; N, 23.42; S, 10.71%.

3-Amino-*N*-(5-methylthiazol-2-yl)-1,5-diphenyl-1*H*-pyrazole-4-carboxamide (**27b**): Yield 77%; m.p.122ºC (EtOH/H_2O); IR (KBr) νmax/cm^{-1}: 3308, 3191 (NH_2), 3054 (NH), 1612 (C=O); ^{1}H NMR (DMSO-d6): δ 2.50 (s, 3H, CH_3), 3.35 (s, 2H, NH_2), 6.72 (s, 1H, CH), 7.06-7.86 (m, 10H, Ar-H), 10.34 (s, 1H, NH); MS m/z (%): 375 (M^+, 11.35), 308 (15.46), 264 (13.31), 196 (82.58), 92 (85.52), 65 (100); For $C_{20}H_{17}N_5SO$ (375.45): Calcd.: C, 63.98; H, 4.56; N, 18.65; S, 8.54%. Found: C, 63.96; H, 4.56; N, 18.67; S, 8.53%.

*Reaction of 2-cyano-N-(5-methylthiazol-2-yl)-3-phenylacrylamide (**4a**) with heterocyclic amines.*

Basic approach:

The proper heterocyclic amine, 3-amino-(2*H*)-1,2,4-triazole (**28**) (1 mmol) or 5-methylthiazol-2-amine (**1**) (1 mmol), in 15 ml absolute ethanol, a small quantity of piperidine, and acrylamide **4a** (0.269 g, 1 mmol) were combined and refluxed for 7 hours before being proceeded to chill to ambient temperature. The developed substance have been extracted, cleaned using ethanol, and dried. Recrystallization using an appropriate solvent afforded compounds **30** and **32**, respectively.

5-Amino-*N*-(5-methylthiazol-2-yl)-7-phenyl-[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxamide (**30**): Yield 88%; m.p.98ºC (EtOH/DMF); IR (KBr) νmax/cm^{-1}: 3412, 3067 (NH_2), 3020 (NH), 1602 (C=O); ^{1}H NMR (DMSO-d6): δ 2.50 (s, 3H, CH_3), 3.30 (s, 2H, NH_2), 6.57 (s, 1H, CH), 7.22 (s, 1H, CH), 7.43-8.38 (m, 5H, Ar-H), 9.00 (s, 1H, NH); ^{13}C

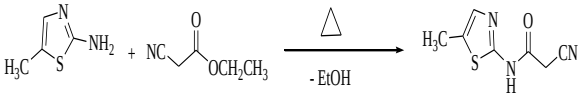
NMR (DMSO-d6): δ 11.73, 111.50, 120.80, 127.58, 128.27, 128.42, 132.53, 134.88, 147.30, 148.20, 149.30, 150.80, 157.57, 166.99; MS m/z (%): 351 (M^+, 58.52), 300 (56.30), 225 (64.44), 201 (77.78), 128 (100), 114 (91.85); For $C_{16}H_{13}N_7SO$ (351.39): Calcd.: C, 54.69; H, 3.73; N, 27.90; S, 9.13%. Found: C, 54.66; H, 3.75; N, 27.91; S, 9.11%.

7-Imino-2-methyl-*N*-(5-methylthiazol-2-yl)-5-phenyl -*7H*-thiazolo[3,2-*a*]pyrimidine-6-carboxamide (**32**): Yield 86%; m.p.110ºC (EtOH/DMF); IR (KBr) νmax/cm^{-1}: 3421, 3181 (2NH), 1669 (C=O); ^{1}H NMR (DMSO-d6): δ 2.33 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 6.57 (s, 1H, CH), 7.22 (s, 1H, CH), 7.33-8.01 (m, 5H, Ar-H), 8.37 (s, 1H, NH), 9.00 (s, 1H, NH); MS m/z (%): 381 (M^+, 8.17), 333 (7.17), 269 (9.07), 201 (75.05), 114 (53.36), 71 (100); For $C_{18}H_{15}N_5S_2O$ (381.48): Calcd.: C, 56.67; H, 3.96; N, 18.36; S, 16.81%. Found: C, 56.66; H, 3.98; N, 18.34; S, 16.82%.

3. Results and Discussion

The intereaction between 5-methylthiazol-2-amine (**1**) and ethyl cyanoacetates (**2**) yielded 2-cyano-*N*-(5-methylthiazol-2-yl)acetamide (**3**) by using different reaction conditions, as explained in Scheme 1.

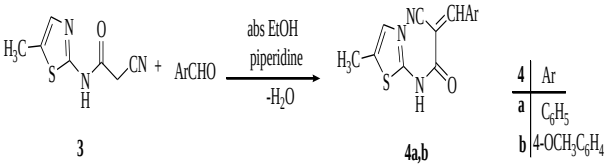
By using the compound's accurate elemental studies and spectrum data, the compound **3** structure was confirmed. In its IR spectra, the NH group exhibited a band of absorption at 3419 cm^{-1}, and the nitrile and carbonyl groups exhibited respective prominent absorption bands at 2259 and 1693 cm^{-1}. The ^{1}H NMR spectrum of ingredient **3** showed two distinctive signals at δ 2.29 and 3.76 related to CH_3 and methylene hydrogens, respectively, a characteristic signal at δ 6.71 relevant to C-H_4 in the thiazole ring as well as a singlet (D_2O-exchangable) signal at δ 12.2, related to NH proton. The molecular ion of chemical **3** had a peak in its mass spectrum at m/z 181, which was visible.



1 2 3

Scheme 1

Compound **3** was treated with benzaldehyde and 4-methoxybenzaldehyde in ethanol under reflux, catalyzed by piperidine, affording, in each instance, the corresponding condensation product, which have been revealed to be 2-cyano-*N*-(5-methylthiazol-2-yl)-3-phenylacrylamide (**4a**) and 2-cyano-3-(4-methoxyphenyl)-*N*-(5-methylthiazol-2-yl)acrylamide (**4b**), respectively (Scheme 2). As an outlier, compound **4a**'s IR spectra showed prominent bands associated with carbonyl at 1660 cm^{-1}, NH at 3419 cm^{-1}, and nitrile absorption at 2200 cm^{-1}. An aromatic multiplet at δ 7.27-8.02 caused by phenyl hydrogens, a singlet signal at δ 8.46 caused by a methine proton, and a D_2O-exchangeable signal at δ 8.95 caused by an amide hydrogen, were all seen in the ^{1}H NMR spectrum of compound **4a**. Additionally, a molecular ion peak at m/z 269 was visible in its mass report.

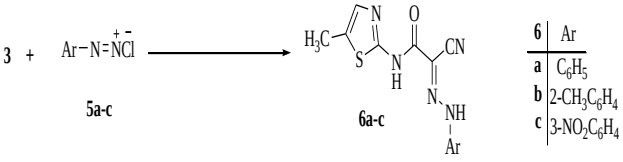


3 4a,b

4	Ar
a	C_6H_5
b	4-$OCH_3C_6H_4$

Scheme 2

When 2-cyano-N-(5-methylthiazol-2-yl)acetamide (**3**) and arene diazonium salts **5a-c** were coupled in a cold ethanolic sodium acetate solution, the equivalent hydrazone derivatives **6a-c** were produced, as shown in Scheme 3. Using their spectrum data and elemental studies, later products' building structures were clarified, as shown in the experimental portion. For instance, in each case, the products' IR spectra revealed the existence of two NH absorption regions between 3201-3445 cm^{-1}, one band around 2262 cm^{-1} that is indicative of a nitrile function, as well as a carbonyl absorption band close to 1692 cm^{-1}. Each of their mass spectra had a peak that corresponded to the molecular ion. As a representative example of the series, compound **6a**'s ^{1}H NMR spectra revealed: beside the expected chemical shifts, two D_2O-exchangable signals δ at 8.90 and 10.30 due to two NH protons.



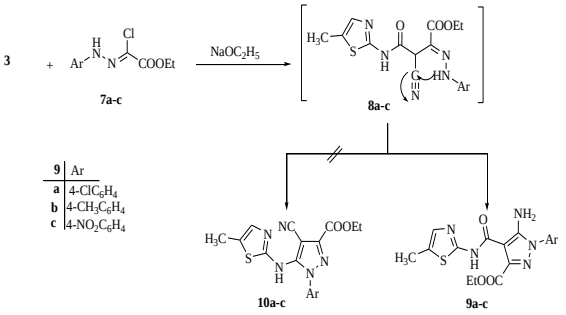
5a-c 6a-c

6	Ar
a	C_6H_5
b	2-$CH_3C_6H_4$
c	3-$NO_2C_6H_4$

Scheme 3

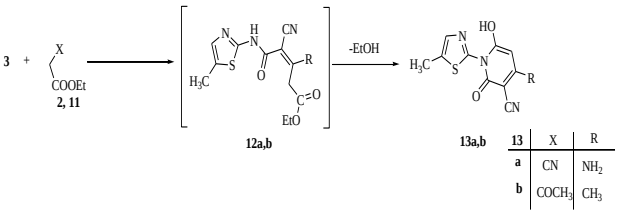
When chemical **3** was reacted with the hydrazonoyl chloride derivatives **7a–c** in an ethanolic sodium ethoxide solution at atmospheric temperature, only a single product (as determined by TLC) was produced in each case, for which the two potential structures **9a–c** and **10** appeared to be feasible, as depicated in Scheme 4. The reaction products' elemental analyses and spectrum data, however, only matched the aminopyrazole structures **9a–c**. For instance, The IR spectra for ingredient **9b** revealed two bands at 3417 and 3367 cm^{-1} that can be diagnostic for the amino group, one band at 3190 cm^{-1} that is typically associated with the amide-NH group, as well as two carbonyl bands of absorption at 1710 and 1658 cm^{-1}.

The mass chart of **9b** exhibited a peak at m/z 385 that matched its molecular ion. Moreover, Its ^{1}H NMR spectrum provided two D_2O-exchangeable signals at δ 4.40 and 11.22 representing the amino and NH protons, respectively, as well as a multiplet at δ 7.29-8.09 caused by aromatic hydrogens (see Experimental part).



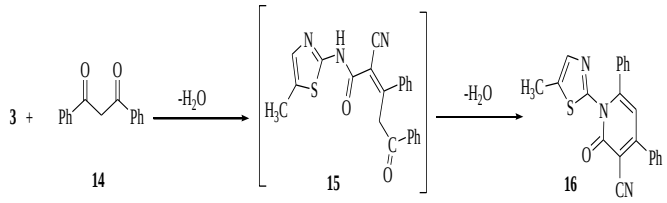
Scheme 4

In this work, the reactivity of compound **3** towards the active methylene reagents was studied. Thus, treatment of compound **3** with equimolar amount of either ethyl cyanoacetate (**2**) or ethyl 3-oxobutanoate (**11**) yielded the corresponding pyridine-3-carbonitrile derivatives **13a** and **13b**, respectively. It is assumed that the latter products form via intermediates **12a,b** which underwent ready intra-molecular cyclization to give compounds **13a** and **13b**, respectively (Scheme 5). Depending on their elemental investigations and spectral studies, the structures of the separated substances were determined. In this respect, the insulated products' infrared wavelengths **13a** and **13b** illustrated that there was only one absorbance band present in each case near 2262 cm^{-1} characteristic for nitrile function and a carbonyl absorption band at 1693 cm^{-1}. Compound **13a** showed in its ^{1}H NMR spectrum, two D_2O-exchangable signals at δ 3.75 and 3.99 for NH_2 and OH protons, respectively. While that of compound **13b** showed a singlet distinctive signal at δ 1.26 diagnostic for CH_3 protons and D_2O-exchangable signal at δ 3.7 for the OH proton. Compounds **13a** and **13b** both displayed a singlet characterisic signals at δ 4.44 and 4.80, respectively, for the proton of the pyridine ring at C-3. Additionally, the mass spectra of the products illustrated a peak for each molecular ion in every instance.



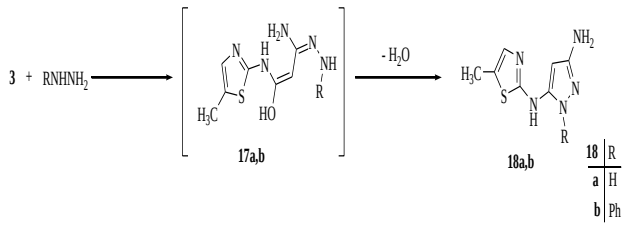
Scheme 5

Similarly, compound **3** reacts with 1,3-diphenylpropane-1,3-dione (**14**) under the same reaction conditions to afford, 1,2-dihydro-1-(5-methylthiazol-2-yl)-2-oxo-4,6-diphenylpyridine-3-carbonitrile (**16**), as shown in Scheme 6. Due to the presence of nitrile and carbonyl groups, compound **16**'s IR spectra displayed the corresponding extensive absorption bands at 2357 cm^{-1} and 1698 cm^{-1}. **16**'s ^{1}H NMR spectrum displayed a single, distinct signal at δ 4.88 for the proton in the pyridine ring at C-3. Moreover, a multiplet signal at δ 7.35-8.19 was caused by aromatic hydrogen ions. A peak at m/z 369, which corresponded to its molecular ion, was visible in the mass report.



Scheme 6

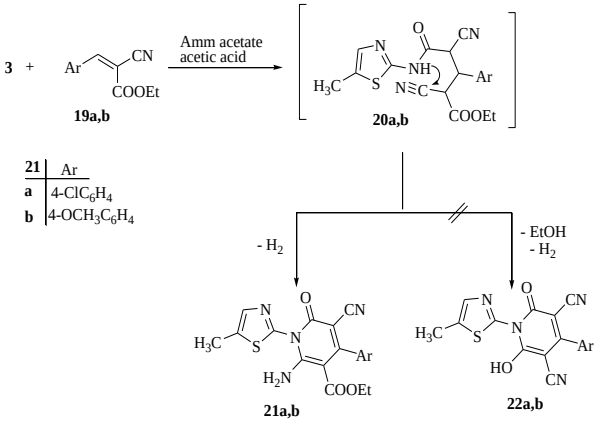
This study also extended to investigate the reactivity of compound **3** towards nitrogen nucleophilic reagents. Thus, compound **3** reacted with an equimolar amount of either hydrazine or phenylhydrazine in ethanol under reflux to give, in each instance, a single isolable product that became known as *N5*-(5-methylthiazol-2-yl)-1*H*-pyrazole-3,5-diamine (**18a**) and *N5*-(5-methylthiazol-2-yl)-1-phenyl-1*H*-pyrazole-3,5-diamine (**18b**), respectively (Scheme 7). The reaction happened through a facile addition of hydrazine or phenylhydrazine to the nitrile group in chemical **3** to form a pair of intermediates **17a,b** that readily afforded compounds **18a,b** via water elimination. A case in point is the chemical **18b**'s IR spectra., demonstrated two bands of absorption at 3698 and 3417 cm^{-1} indicative of NH_2 function and one band of absorption at 3264 cm^1 characteristic for NH function. In addition, in its mass spectrum, a peak of molecular ion at m/z 271 was discernible.



Scheme 7

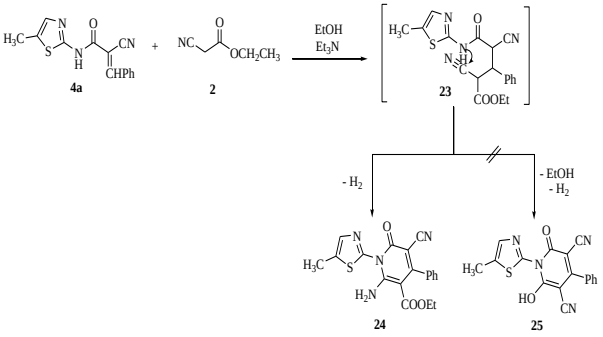
On the other hand, oxopyridine-3-carboxylate derivatives **21a** and **21b** were formed from the reaction between 2-cyano-*N*-(5-methylthiazol-2-yl)-acetamide (**3**) and ethyl 2-cyanoacrylate derivatives **19a,b** respectively, while acetic acid is refluxing and

ammonium acetate is present (Scheme 8). The compound **21a**'s IR spectra, used as a representative example, displayed three absorption spectrum bands around 2219, 1722, and 1607 cm^{-1}, which are diagnostic of a nitrile and two carbonyl functions, respectively, as well as two absorption bands at 3419 and 3037 cm^{-1}, which are characteristic for NH_2 group. Additionally, among other fragments, the fragment at m/z 414 in its mass chart was generated by its molar mass. Also a triplet signal at δ1.36, J=7.2 Hz, a quartet at δ 4.37, J=7.5 Hz which are characteristic of the ethyl ester group and a multiplet caused by aromatic protons between δ 7.71-8.43, were visible in the **21a** ^1H NMR spectrum. Also provide a D_2O-exchangable signal at δ 8.42 due to NH_2 protons. The forgoing spectral data support the assigned structures **21a,b** and excluded the other possible structures **22a,b**. This indicates that the reaction between compound **3** and ethyl 2-cyanoacrylate derivatives **19a,b** proceeds, in each case, via the formation of acyclic Micheal type addition intermediate **20** that undergoes intra-molecular cycloaddition and subsequent aromatization by the release of H_2 to afford the resultant product **21**. A suggested approach to the synthesis of oxopyridine-3-carboxylate derivatives **21a,b** is decipated in Scheme 8.



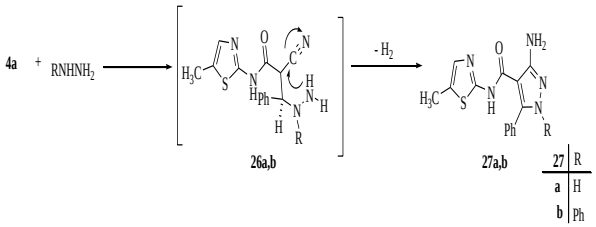
Scheme 8

It was examined the reactivity of the α,β-unsaturated nitrile moiety of 2-cyano-*N*-(5-methylthiazol-2-yl)-3-phenylacrylamide (**4a**) [prepared by condensation of cyanoacetamide derivative **3** with benzaldehyde] when interacting with several chemical reagents. Thus, compound **4a** and ethyl cyanoacetate (**2**) was reacted in refluxing ethanolic triethylamine solution to yield ethyl 2-amino-5-cyano-1,6-dihydro-1-(5-methylthiazol-2-yl)-6-oxo-4-phenylpyridine-3-carboxylate (**24**) via the intermediate **23** (Scheme 9). The compound **24**'s IR spectra showed two bands of absorption at 3430 and 3067 cm^{-1} attributable to NH_2 group, one band of absorption at 2221 cm^{-1} indicative of the nitrile function, and two bands of absorption for carbonyls at 1725 and 1605 cm^{-1}. Compound **24**'s ^1H NMR spectra showed a triplet and a quartet signals at δ 1.32 and δ 4.33, respectively. which are characteristic to ethyl ester group and a D_2O-exchangeable signal for the NH_2 group is present at δ 3.30. At m/z 380, the mass report of chemical **24** displayed a peak caused by its molecular ion. The assigned structure **24** is supported by the spectral data, which rules out the other potential structure **25**.



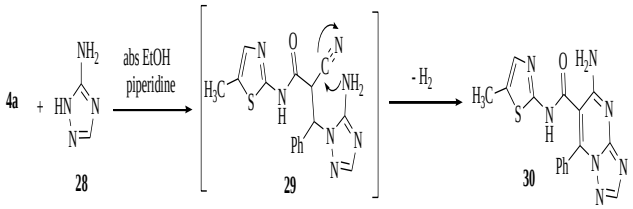
Scheme 9

Moreover, compound **4a** was treated with nucleophilic reagents such as hydrazine and phenylhydrazine to yield the respective aminopyrazole derivatives **27a** and **27b**, as dictated by Scheme 10. The intermolecular cyclization and subsequent dehydrogenation of the non-isolable intermediate **26** results in the development of the corresponding aminopyrazole derivatives **27a** and **27b,** respectively. Compound **27a**'s IR wavelength revealed two bands of absorptions at 3427 and 3203 cm^{-1} attributed to the amino group, two characteristic bands at 3055 and 3020 cm^{-1} for two NH functions. Moreover, a potent carbonyl band at 1692 cm^{-1}. The identical compound's ^1H NMR spectrum displayed three D_2O-exchangeable signals at δ 4.00, 8.72, and 12.22, caused by NH_2 and two NH protons, respectively. The IR wavelength of compound **27b** showed two bands of absorption at 3308 and 3191 cm^{-1}, which were ascribed to the amino group, a band at 3054 cm^{-1}, which is diagnostic for the NH group, in addition, one band of absorption at 1612 cm^{-1}, caused by the carbonyl function. Its ^1H NMR spectrum showed two D_2O-exchangeable signals, one at δ 3.35 and the other at δ 10.34, due to the NH_2 and NH hydrogens, respectively, and a multiplet signal at 7.06–7.86 caused by the phenyl ring (Scheme 10). The molecular ion's peak could be seen in each of their mass spectra.



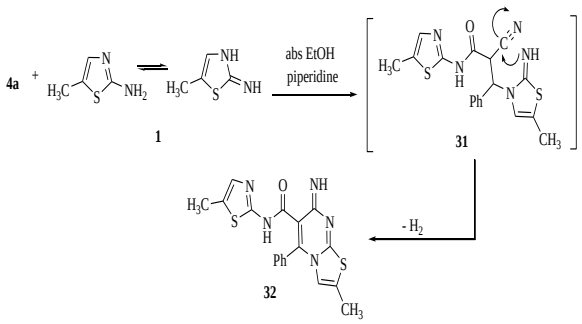
Scheme 10

Reaction of compound **4a** with 3-amino-(2*H*)-1,2,4-triazole (**28**) by ethanol reflux, with existence of piperidine, afforded only a single product that was identified as 5-amino-*N*-(5-methylthiazol-2-yl)-7-phenyl[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carbox-amide (**30**). Scheme 11 explains the suggested methodology for producing Product **30**. The reaction product's IR spectra indicated two bands of absorption caused by the amino group at 3412 and 3067 cm^{-1}, additionally, one NH band at 3020 cm^{-1}. Furthermore, a carbonyl group also displayed a significant absorbance band at 1602 cm^{-1}. In its ^1H NMR chart, it had a singlet unique signal at δ 7.22, which corresponded to a triazole proton, and two D_2O-exchangeable signals, which were observed at δ 3:30 and 9:00 and were brought on by NH_2 as well as NH hydrogens, respectively. Additionally, The molecular ion of compound **30** was matched to a peak in its mass spectrum at m/z 351.



Scheme 11

In the same way, under similar experimental conditions, compound **4a** reacted with 5-methylthiazol-2-amine (**1**) to produce 7-imino-2-methyl-*N*-(5-methylthiazol-2-yl)-5-phenyl-7*H*-thia-zolo[3,2-*a*]pyrimidine-6-carboxamide (**32**) (Scheme 12). The reaction product's IR spectra illustrated two bands of absorption at 3421 cm^{-1} and 3181 cm^{-1} caused by two NH groups and a potent band of absorption at 1669 cm^{-1} caused by a carbonyl function. The identical product's ^1H NMR spectra showed two thiazole proton-related signals at δ 6.57 and 7.22, and two D_2O-exchangeable signals from two NH hydrogen ions at δ 8.37 and 9.00. In its mass report, the peak for molecular ion at m/z 381 was seen.



Scheme 12

4. Microbiological Analysis

The Microanalytical Centre of Cairo University in Giza, Egypt, conducted microbiological investigations. In the present work we used: Gram-negative bacteria such as Escherichia coli, Gram-positive bacteria such as Staphylococcus aureus, and fungi such as Aspergillus flavus and Candida albicans. The technique of disc diffusion [19] was used to test antimicrobial activity using Potato-dextrose agar with fungi and Mueller-Hinton II agar medium (Becton Dickinson) with bacteria. (in accordance with CLSI standards) under standard circumstances, Using a chemical solution (DMSO), 500 mg of a predetermined material was applied to hygienic filter paper discs (5 mm in diameter; Whatman No. 3 chromatography paper). Dry discs have been positioned upon the outermost layer of the compatible agar medium. After 18 hours of culturing at 36°C, the outcome measurements for bacteria were recorded as the growth inhibition zone diameter, while the findings for fungi were read after 30 hours of culturing at 36°C. All of the microorganisms under study had final inoculums of 104 CFU/mL (colony forming units per millilitre). Utilizing a colorimeter, Spores' optical densities in 0.2% Tween 80 mixtures were modified for fungal cultures to 50 at 540 nm.

The effects of the chemicals investigated in the present study on bacteria and fungi were assessed by in vitro testing. (measured by growth inhibition zone diameter). The micro-organisms used in the current study were Staphylococcus aureus as Gram positive bacteria, Escherichia coli as Gram negative bacteria, Aspergillus flavus and Candida albicans as Fungi.

Among all tested compounds, compounds **16**, **21a**, **24** and **21b** demonstrated effective antifungal and antibacterial activities against bacterial species that were Gram-positive and / or Gram-negative, while compounds **3**, **9a**, **9c**, **4a** and **6c** showed good antibacterial activity only as shown in table 1. It could be concluded that the biologically active synthesized compounds are nearly as active as the standard antibacterial (Ampicillin) towards both gram-positive (Staphylococcus aureus) as well as

gram-negative (Escherichia coli) bacteria. Moreover, some of the biologically active generated substances have nearly the same activity as the standard antifungal (Amphotericin B) against both Aspergillus flavus and Candida albicans Fungi.

Table 1. Evaluation of Anti-bacterial and Anti-fungal Activities

Sample	Inhibition zone diameter (mm ÷ mg sample)			
	Staphylococcus aureus **(G^+)**	***Escherichia coli*** **(G^-)**	***Aspergillus flavus*** **(Fungus)**	***Candida albicans*** **(Fungus)**
***Control**	0.0	0.0	0.0	0.0
3	10	10	0.0	0.0
9a	19	12	0.0	0.0
9c	12	11	0.0	0.0
4a	11	12	0.0	0.0
4b	0.0	0.0	0.0	0.0
6c	12	12	0.0	0.0
16	14	12	0.0	11
21a	9	0.0	11	0.0
24	11	10	12	12
21b	10	0.0	10	12
Ampicillin	18	22	0.0	0.0
Amphotericin B	0.0	0.0	17	19

G: Gram reaction, *Control: DMSO

5. Conclusions

The present study's findings lead to the following conclusion:

Numerous novel heterocyclic compounds were produced from 5-methylthiazol-2-amine (**1**) such as cyanoacetamide, acrylamide, hydrazone, amino-pyrazole, pyridine-3-carbonitrile, oxopyridine-3-carboxylate, pyridine, pyrazole, triazolo[1,5-*a*]pyrimidine and thiazolo[3,2-*a*]pyrimidine derivatives. The created chemicals' structures were clarified using modern spectroscopic techniques. The majority of the synthesized compounds in the current investigation displayed significant antifungal and antibacterial activities towards both Gram-positive and Gram-negative strains, according to the growth inhibition zone diameter.

6. Conflicts of interest

There are no apparent conflicts.

7. Formatting of funding sources

No fund was received.

8. Acknowledgments

The Regional Center for Mycology and Biotechnology at Al-Azhar University and the Micro-analytical Center of Cairo University are acknowledged by the authors.

9. References

[1] Hargrave K.D., Hess F. K. and Oliver J.T., N-(4-Substituted-thiazolyl)oxamic Acid Derivatives, a New Series of potent, Orally Active Antiallergy Agents ,*J. Med. Chem*., **26** (8), 1158-1163 (1983). https://doi.org/10.1021/jm00362a014

[2] Patt W. C., Hamilton H.W, Taylor M.D., Ryan M.J., Jr. Taylor D.G., Connolly C. J. C., Doherty A.M., Klutchko S. R., Sircar I., Steinbaugh B.A.,. Batley B. L,. Painchaud C.A, Rapundalo S.T., Michniewicz B. M. and Olson S.C.J., Structure–Activity Relationships of a Series of 2-Amino- 4-thiazole-containing Renin Inhibitors, *J. Med. Chem*., **35**(14), 2562-2572 (1992). https://doi.org/10.1021/jm00092a006

[3] Haviv F., Ratajczyk J. D., DeNet R.W., Kerdesky F.A., Walters R.L., Schmidt S.P., Holms J. H., Young P.R. and Carter G.W., "3-[1-(2-Benzoxazolyl)hydrazino]Pro- panenitrile Derivatives: Inhibitors of Immune Complex Induced Inflammation, *J. Med.Chem*., **31**(9), 1719-1728 (1988); Clemence F., Martret O.L., Delevallee F, Benzoni J., Jouanen A., Jouquey S., Mouren M. and Deraedt R., 4-Hydroxy-3-quinoline-carboxamides with antiarthritic and analgesic activities,*J. Med. Chem*., **31**(7), 1453-1462 (1988). https://doi.org/10.1021/jm00402a034

[4] Jaen J. C., Wise L. D., Caprathe B.W., Tecle H., Bergmeier S. , Humblet C.C., Heffner T. G., Meltzner L.T. and Pugsley T.A., 4-(1,2,5,6-Tetrahydro-1-alkyl-3-pyridinyl)-2-thiazolamines: a Novel Class of Compounds with Central Dopamine Agonist Properties, *J. Med.Chem*., **33**(1), 311-317 (1990). https://doi.org/10.1021/jm00163a051

[5] Tsuji K. and Ishikawa H., Synthesis and Anti-pseudomonal Activity of New 2-isocephems with a dihydroxypyridone Moiety at C-7, *Bioorg. Med. Chem. Lett*., **4**(13), 1601-1606 (1994). https://doi.org/10.1016/S0960-894X(01)80574-6

[6] Bell F.W., Cantrell A.S., Hoegberg M., Jaskunas S. R., Johansson N. G., Jordon C. L., Kinnick M.D., Lind P., Morin J. M. Jr., Noreen R., O'berg B., Palkowitz J. A. Parrish C.A., Pranc P., Sahlberg C., Ternansky R. J., Vasileff R.T., Vrang L., West S.J., Zhang H. and Zhou X. X., Phenethylthiazolethiourea (PETT) Compounds, amNew Class of HIV-1 Reverse Transcriptase Inhibitors. 1. Synthesis and Basic Structure-Activity Relationship Studies of PETT Analogs, *J. Med. Chem*., **38**(25), 4929-4936 (1995). https://doi.org/10.1021/jm00025a010

[7] Fink B. E., Mortensen D. S., Stauffer S. R., Aron , Z. D. and Katzenellenbogen J. A. , Novel Structural Templates for Estrogen-receptor ligands and prospects for Combinatorial Synthesis of Estrogens, *Chem. Biol*., **6**(4), 205-219 (1999). https://doi.org/10.1016/s1074-5521(99)80037-4

[8] Van Muijlwijk-Koezen J. E., Timmerman H., Vollinga R.C., Von Drabbe Kunzel J. F., Groote M. De, Visser , S. and Ijzerman A. P., Thiazole and Thiadiazole Analogues as a Novel Class of Adenosine Receptor Antagonists, *J. Med. Chem*., , **44**(5), 749-762 (2001). https://doi.org/10.1021/jm0003945

[9] Metzger J. V., *Comp. Heterocycl. Chem. I*, **6**, 328 (1984).
[10] Darweesh A.F., Mekky A.E.M., Salman A.A. and Farag A.M., Synthesis of Novel Thiazole and 1,3,4-Thiadiazole Derivatives Incorporating Phenylsulfonyl Moiety, *Heterocycles*, **89**, 1827-1843 (2014).
[11] Dawood K.M., Moghazy S.M. and Farag A.M, Convenient Synthesis of Azolopyrimidine, Azolotriazine, Azinobenzimidazole and 1,3,4-Thiadiazole Derivatives, *Arab. J. Chem*., **10**, S2782-S2789 (2017). https://doi.org/10.1016/j.arabjc.2013.10.029
[12] Eldebss T.M.A, Yi X.J., Farag A.M., Khedr A.A., Abdulla M.M. and Mabkhot Y.N., Synthesis of New Pyrazolone-Based Heterocycles as Inhibitors of Monoamine Oxidase Enzymes, *J. Iran. Chem. Soc.*,**15**(8), 1785-1800 (2018). https://doi.org/10.1007/s13738-018-1376-1
[13] Eldebss T.M.A., Farag A.M., Abdalla M.M. and Khedr A.A., Synthesis of Some New Pyrazolone-Based Heterocycles Containing Sulphone Moiety Acting as α-Glucosidase and α-Amylase Inhibitors, *J. Heterocycl. Chem*., **56**(3), 765-780. (2019). https://doi.org/10.1002/jhet.3433
[14] Fahim A.M. and Farag A.M., Synthesis, Antimicrobial Evaluation, Molecular Docking and Theoretical Calculations of Novel Pyrazolo[1,5-*a*]-Pyrimidine Derivatives, *J. Mol. Struct*., **1199**, 127025 (2020). https://doi.org/10.1016/j.molstruc.2019.127025
[15] Takashi W., Toshiaki N., Tadashi M. , Kazuhiro I. and Hidenori M., SureChem, Patent No. 2001023340,(2001).
[16] Hegarty A.F., Cashoman M. P. and Scoti F. L., *Chem. Commun*., **13**, 884 (1971).
[17] Chisolm D. R.,. Weiss R. A. and Rozov L., Patent, U. S. 5,015,777, (1991).
[18] Engman L. and Cava M. P. Bis(P- methoxyphenyl)-telluroxide, a novel organotellurium aldol catalyst, *Tetrahedron Lett*., **22**(52),5251-5252(1981). https://doi.org/10.1016/S0040-4039(01)92472-4
[19] Vincent J.G., Vincent H.W., and Morton J., Filter Paper Disc Modification of the Oxford Cup Penicillin Determination. *Proc. Soc. Exp. Biol. Med*., **55**(3), 162-164 (1944), https://doi.org/10.3181/00379727-55-14502

.

.