ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

Synthesis of some new purine and mercaptopurine analogues as antimetabolites

Sayed A. Ahmed[1] and Hussein S. Elgendy[2]

1,2 Department of Chemistry, Faculty of Science, Beni-Suef University, Beni-Suef 62514, Egypt.

Manuscript Info

Manuscript History:

Received: 25 March 2014
Final Accepted: 21 April 2014
Published Online: May 2014

Key words:
Isothiazole Thiadiazoles Mercaptopurine Aminopyrazoles Pyrazolopyrimidines *Sodium-3-oxo-3-phenylprop-1-en-1-olate*

Corresponding Author

Dr. Sayed A. Ahmed

Abstract

The 7-aryl-3-(methylthio)isothiazole[5',4':3,4]pyrazolo[1,5-a] pyrimidine **7** was synthesized by the reaction of Sodium 3- arylprop-3- oxo-1-en-1-olate **5** with 3-(methylthio)-5H-pyrazolo[4,3-d]isothiazol-4-amine **4**. Reaction of 5-amino-1,3,4-thiadiazol-2-thiol **9** with Sodium 3- arylprop-3- oxo-1-en-1-olate **5** to form 1-Aryl-2-[(5-mercapto-[1,3,4]-thiadiazole-2-yl)imino]ethanone,**10**. Reduction of 5-amino-[1,3,4]-thiadiazol-2-thiol **9** produced 5-amino-1,3,4-thiadiazolidine-2-thiol **12** which reacted with Sodium 3- arylprop-3- oxo-1-en-1-olate **5** to form 5-aryl-3,5-dihydro-2H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-2-thiol **13** then alkylation to give 5-aryl-2-(methylthio)-3,5-dihydro-2H-[1,3,4]thiadiazolo[3,2-a]pyrimidin **15**. Treatment of 5-amino-3-(cyanomethyl)-1H-pyrazole-4-carbonitrile **16** with Sodium 3- arylprop-3- oxo-1-en-1-olate **5** to form 7-aryl-2-(cyanomethyl)arylpyrazolo[1,5-a]pyrimidine-3-carbonitrile **18**.

INTRODUCTION

Pyrazolopyrimidines are purine analogues and have useful properties as antimetabolites in purine biochemical reactions [1,2]. Compounds of this class have attracted a wide pharmaceutical interest because of their anti-trypanosomal and antischistosomal activity [3], These interesting biological properties [4-11], initiated activities to develop new and efficient procedures for the synthesis of purine, mercaptopurine analogues and other antimetabolites [12-14]. We have recently reported different successful approaches for synthesis of purine analogues and pyrimidines [15-17] using sodium salt of cycloalkanones [18,19]. In view of these reports and in continuation with the previous work, we have herein synthesized new derivatives of pyrazolopyrimidines.

Material and Methods

Instrumentation

All melting points are uncorrected. IR spectra were obtained (KBr disk) on a Perkin Elmer 11650 FT-IR spectrophotometer. The ^{1}H NMR spectra were measured on a Varian 400 MHz spectrometer for solutions in $(CD_3)_2SO$ using TMS as an internal standard. Mass spectra were recorded on a Varian MAT 112 spectrometer. Analytical data were obtained from the Micro analytical Center at Cairo University.

Synthesis
(methylthio)-5H-pyrazolo[4,3-d]isothiazol-4-amine (4)

A solution of (1,7gm, 0.01 mol) 3,5-bis(methylsulphonyl)isothiazole-4-carbonitrile **3**, (0.01 mol) hydrazine hydrate in 30 ml ethyl alcohol, the mixture was refluxed for 3 hrs. left to cool, then poured on ice\water. The solid product was filtered off and recrystallized from ethanol.

Color: White, Yield: 60%, M.p.: 160^{o}C, FT-IR (KBr, ν, cm^{-1}): 3520,3410 (NH2),^{1}H NMR (400 MHz, DMSO, δ, ppm): 2.55 (s, 3H, SCH_3), 4.22 (s, 2H, NH_2), 8.99 (s, br., 1H, NH). MS (m/z (%)): 186, Anal. calcd. for $C_5H_6N_4S_2$: C, 32.24; H, 3.25; N, 30.08; S, 34.43% . Found: C, 32.33; H, 3.14; N, 30.23; S, 34.30 %.

Sodium 3- arylprop-3- oxo-1-en-1-olate [5]

In a three necked flask containing [0.01 mol] of sodium methoxide and 20 ml ether, [0.01 mol] of acetophenone with [0.01 mol] of ethyl formate was poured over it through separating funnel with efficient stirring. The solid product was collected at the pump and used directly in the reactions.

7-aryl-3-(methylthio)isothiazole[5',4':3,4]pyrazolo[1,5-a] pyrimidine (7a-d)

A solution of (1.86gm, 0.01 mol) 3-(methylsulphonyl)-5H pyrazolo[4,3-d]isothiazol-4- amine **4**, (0.01 mol) Sodium 3-arylprop-3- oxo-1-en-1-olate **5**, (1ml) piperidine acetate and (3 ml) H_2O was heated for 15 minutes. Acetic acid (1.5 ml) was added to the hot solution. The solid product was filtered off and recrystallized from ethanol.

7a:- 3-(methylthio)-7-phenylisothiazole[5',4':3,4]pyrazolo[1,5-a] pyrimidine

Color: Yellow, Yield: 67%, M.p.: 210^{o}C, FT-IR (KBr, ν, cm^{-1}): 1350 (CH_3), ^{1}H NMR (400 MHz, DMSO, δ, ppm): 2.43 (s, 3H, SCH_3), 7.32-7.85 (m, 5H, aromatic protons), 8.15 (d, 1H, J = 7.3 Hz, N=CH), 8.77 (d, 1H, J = 7.3 Hz, N=CH), MS (m/z (%)): 298. Anal. calcd. for $C_{14}H_{10}N_4S_2$: C, 56.35; H,3.38; N, 18.78; S, 21.49 %. Found: C, 56.23; H, 3.64; N, 18.53; S, 21.51 %.

7b:- 7-(4-chlorophenyl)-3-(methylthio)isothiazole[5',4':3,4]pyrazolo[1,5-a]pyrimidine

Color: Yellow, Yield: 72%, M.p.: 235^{o}C, FT-IR (KBr, ν, cm^{-1}): 1350 (CH_3), ^{1}H NMR (400 MHz, DMSO, δ, ppm): 2.43 (s, 3H, SCH_3), 7.55-8.11 (dd, 4H, J = 7.6 Hz, aromatic protons), 8.19 (d, 1H, J = 7.5 Hz, N=CH), 8.79(d, 1H, J = 7.5 Hz, N=CH), MS (m/z (%)): 332, Anal. calcd. for $C_{14}H_9ClN_4S_2$: C, 50.52; H, 2.73; Cl, 10.65; N, 16.83; S, 19.27% Found: C, 50.32; H, 2.91; Cl, 10.82; N, 16.64; S, 19.55 %.

7c:- 3-(methylthio)-7-(p-tolyl)isothiazole[5',4':3,4]pyrazolo[1,5-a]pyrimidine

Color: Yellow, Yield: 77%, M.p.: 255^{o}C, FT-IR (KBr, ν, cm^{-1}): 1350 (CH_3), ^{1}H NMR (400 MHz, DMSO, δ, ppm): 2.03 (s, 3H, CH_3), 2.50 (s, 3H, SCH_3), 7.29-8.01 (m, 4H, aromatic protons), 8.25 (d, 1H, J = 7.4 Hz, N=CH), 8.89(d, 1H, J = 7.4 Hz, N=CH), MS (m/z (%)): 312, Anal. calcd. for $C_{15}H_{12}N_4S_2$: C, 57.67; H, 3.87; N, 17.93; S, 20.53 %. Found: C, 57.44; H, 3.74; N, 17.99; S, 20.31 %.

7d: - 7-(4-methoxyphenyl)-3-(methylthio)isothiazole[5',4':3,4]pyrazolo[1,5-a]pyrimidine

Color: Yellow, Yield: 81%, M.p.: 280^{o}C, FT-IR (KBr, ν, cm^{-1}): 1355(CH_3), ^{1}H NMR (400 MHz, DMSO, δ, ppm): 2.53 (s, 3H, SCH_3), 3.93 (s, 3H, OCH_3), 7.09-8.10 (dd, 4H, J = 7.5 Hz, aromatic protons), 8.29 (d, 1H, J = 7.4 Hz, N=CH), 8.80(d, 1H, J = 7.4 Hz, N=CH), MS (m/z (%)): 328, Anal. calcd. for $C_{15}H_{12}ON_4S_2$:C, 54.86; H,3.68; N, 17.06; S, 19.53 %. Found: C, 54.64; H, 3.64; N, 17.29; S, 19.71 %.

1-Aryl-2-[(5-mercapto-[1,3,4]-thiadiazole-2-yl)imino]ethanone (10a-d)

A solution of (1.32gm, 0.01 mol) 5-amino-1,3,4-thiadiazol-2-thiol **9**, (0.01 mol) Sodium 3- arylprop-3- oxo-1-en-1-olate 5, (1ml) piperidine acetate and (3 ml) H_2O was heated for 15 minutes. Acetic acid (1.5 ml) was added to the hot solution. The solid product was filtered off and recrystallized from ethanol.

10a:- 3-[(5-mercapto-[1,3,4]-thiadiazole-2-yl)imino]-1-phenylpropan-1-one

Color: White, Yield: 65%, M.p.: 170^{o}C, FT-IR (KBr, ν, cm^{-1}): 3049 (CH=). 2450 (SH); 1705 (C=O), 1610 (HC=N). ^{1}H NMR (400 MHz, DMSO, δ, ppm): 3.01 (d, 2H, J = 6.9 Hz, CH_2), 3.55 (s, 1H, SH), 7.22 (t, 1H, J = 6.1 Hz, N=CH-CH_2), 7.5-8.2 (m, 5H, aromatic protons), MS (m/z (%)): 263, Anal. calcd. for $C_{11}H_9ON_3S_2$: C, 50.17; H, 3.44; O, 6.08; N, 15.96; S, 24.35 %. Found: C, 50.42; H, 3.41; O, 6.12 N, 15.75; S, 24.22 %.

10b:- 1-(4-chlorophenyl)-3-[(5-mercapto-[1,3,4]-thiadiazole-2-yl)imino]-1-phenylpropan-1-one

Color: White, Yield: 74%, M.p.: 185^{o}C, FT-IR (KBr, ν, cm^{-1}): 3055 (CH=). 2400 (SH); 1713 (C=O), 1590 (HC=N). ^{1}H NMR (400 MHz, DMSO, δ, ppm): 2.95 (d, 2H, J = 7.00 Hz, CH_2) 3.55 (s, 1H, SH), 7.22 (t, 1H, J = 6.1 Hz, N=CH-CH_2), 7.5-8.2 (m, 4H, J = 7.4 Hz, aromatic protons), MS (m/z (%)): 297, Anal. calcd. for $C_{11}H_8ON_3S_2Cl$: C, 44.37; H, 2.71; Cl, 11.91; O, 5.37 N, 14.11; S, 21.54 %. Found: C, 44.22; H, 2.49; Cl, 11.88; O, 5.74; N, 14.46; S, 21.29 %.

10c:- 3-[(5-mercapto-[1,3,4]-thiadiazole-2-yl)imino]-1-(p-tolyl)-1-phenylpropan-1-one

Color: White, Yield: 63%, M.p.: 190^{o}C, FT-IR (KBr, ν, cm^{-1}): 3035 (CH=). 2470 (SH); 1710 (C=O), 1598 (HC=N). ^{1}H NMR (400 MHz, DMSO, δ, ppm):2.23 (s, 3H, CH_3), 2.99 (d, 2H, J = 7.01 Hz, CH_2), 3.95 (s, 1H, SH), 6.52 (t, 1H, J = 6.09 Hz, N=CH-CH_2), 7.33-7.92 (m, 4H, aromatic protons), MS (m/z (%)): 277. Anal. calcd. for $C_{12}H_{11}ON_3S_2$: C, 51.96; H,4.00; O, 5.77; N, 15.15; S, 23.12 %. Found: C, 51.81; H, 4.29; O; 5.15; N, 15.76; S, 23.50%.

10d: - 3-[(5-mercapto-[1,3,4]-thiadiazole-2-yl)imino]-1-(p-methoxyphenyl)-1-phenylpropan-1-one

Color: White, Yield: 75%., M.p.: 205^{o}C, FT-IR (KBr, ν, cm^{-1}): 3055 (CH=). 2560 (SH); 1719(C=O), 1588 (HC=N). ^{1}H NMR (400 MHz, DMSO, δ, ppm):3.03 (d, 2H, J = 7.03 Hz, CH_2), 3.93 (s, 3H, OCH_3), 3.75 (s, 1H, SH), 7.12 (t, 1H, J = 6.1 Hz, N=CH-CH_2), 7.15-7.99 (m, 4H, aromatic protons), MS (m/z (%)): 293. Anal. calcd. for $C_{12}H_{11}O_2N_3S_2$: C, 49.13; H, 3.78; N, 14.32; S, 21.86 %. Found: C, 49.11; H, 3.29; N, 14.76; S, 21.50%.

5-amino-1,3,4-thiadiazolidine-2-thiol (12):-

A solution of compound (1.33 gm , 0.01 mol) 5-amino-1,3,4-thiadiazol-2-thiol **9** in hydrochloric acid and [0.5 gm] of zinc dust, was refluxed for 3 h. The reaction mixture was allowed to cool to room temperature and was poured into cold water (100 mL). The solid formed was collected by filtration, dried and crystallized from ethanol and used directly in the reactions. (white powder).

5-aryl-3,5-dihydro-2H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-2-thiol (13a-d):-

A solution of (1.37gm, 0.01 mol) 5-amino-1,3,4-thiadiazolidine-2-thiol **12**, (0.01 mol) Sodium-3-arylprop-3- oxo-1-en-1-olate **5** (1.7gm, 0.01 mol) , (1 ml) piperidine acetate and (3 ml) H_2O was heated for 15 minutes. Acetic acid (1.5 ml) was added to the hot solution. The solid product was filtered off and recrystallized from ethanol.

13a:- 5-phenyl-3,5-dihydro-2H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-2-thiol

Color: Yellow, Yield: 66%, M.p.: 220^{o}C, FT-IR (KBr, ν, cm^{-1}): 3355(NH), 2450 (SH), ^{1}H NMR (400 MHz, DMSO, δ, ppm):1.53 (s, 1H, SH), 2.95 (s, 1H, NH), 4.12 (s, 1H, CH), 5.01 (d, 1H, J = 1.5 Hz, CH); 6.11 (t, 1H, J = 6.2 Hz, CH); 7.15 (d, 1H, J = 10.1 Hz, CH); 7.23-7.52 (m, 5H, aromatic protons), MS (m/z (%)): 249. Anal. calcd. for $C_{11}H_{11}N_3S_2$: C, 52.99 ;H,4.45; N, 16.85; S, 25.71 %. Found: C, 52.11; H, 4.29; N, 16.96; S, 25.50%.

13b:- 5-(4-chlorophenyl)-3,5-dihydro-2H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-2-thiol

Color: Yellow, Yield: 70%, M.p.: 244^{o}C, FT-IR (KBr, ν, cm^{-1}): 3400(NH), 2430 (SH). ^{1}H NMR (400 MHz, DMSO, δ, ppm): 1.61 (s, 1H, SH), 2.83 (s, 1H, NH), 4.33 (s, 1H, CH), 5.22 (d, 1H, J = 1.6 Hz, CH); 6.34 (t, 1H, J = 6.3 Hz, CH); 7.09 (d, 1H, J = 10.5 Hz, CH); 7.44-7.92 (dd, 4H, aromatic protons), MS (m/z (%)): 283. Anal. calcd. for $C_{11}H_{10}N_3S_2Cl$: C, 46.55; H,3.55; Cl, 12.49; N, 14.81; S, 22.60 %. Found: C, 46.11; H, 3.29; Cl, 12,64; N, 14.96; S, 22.70%.

13c:- 5-(p-tolyl)-3,5-dihydro-2H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-2-thiol

Color: Yellow, Yield: 69%, M.p.: 268^{o}C, FT-IR (KBr, ν, cm^{-1}): 3398 (NH), 2438 (SH), ^{1}H NMR (400 MHz, DMSO, δ, ppm):1.53 (s, 1H, SH), 2.62 (s, 1H, NH), 2.87 (s, 3H, CH_3), 4.13 (s, 1H, CH), 5.03 (d, 1H, J = 1.5 Hz, CH); 6.14 (t, 1H, J = 6.2 Hz, CH); 6.89 (d, 1H, J = 10.7 Hz, CH); 7.20-7.44 (m, 4H, aromatic protons), MS (m/z (%)): 263. Anal. calcd. for $C_{12}H_{13}N_3S_2$: C, 54.72; H, 4.97; N, 15.95; S, 24.35 %. Found: C, 54.41; H, 4.29; N, 15.99; S, 24.70%.

13d:- 5-(4-methoxyphenyl)-3,5-dihydro-2H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-2-thiol

Color: Yellow, Yield: 62%, M.p.: 290^{o}C, FT-IR (KBr, ν, cm^{-1}): 3400 (NH), 2450 (SH),^{1}H NMR (400 MHz, DMSO, δ, ppm):1.57 (s, 1H, SH), 2.22 (s, 1H, NH), 3.98 (s, 3H, OCH_3), 4.23 (s, 1H, J = 1.6 Hz, CH), 5.00 (d, 1H, J = 1.4 Hz, CH); 6.25 (t, 1H, J = 6.3 Hz, CH); 7.89 (d, 1H, J = 10.7 Hz, CH); 6.94-7.35 (dd, 4H, J = 7.6 Hz, aromatic protons), MS (m/z (%)): 279. Anal. calcd. for $C_{12}H_{13}ON_3S_2$: C, 51.59; H, 4.69; N, 15.04; S, 22.95 %. Found: C, 51.91; H, 4.55; N, 15.39; S, 22.50%.

5-aryl-2-(methylthio)-3,5-dihydro-2H-[1,3,4]thiadiazolo[3,2-a]pyrimidin (15a-d):-

A solution of (0.57gm, 0.01mol.) potassium hydroxide in 20 ml methanol, stirring for completely soluble then add (2.49gm, 0.01mol.) of 5-aryl-2,3-dihydro-5H-[1,3,4]-thiadiazolo[3,2-a]pyrimidine2-thiol **13** was Left stirring until completely soluble then added (1,26ml, 0.01mol.) dimethylsulfate drop by drop with stirring, the mixture was left stirrer over night and poured on ice/water, The solid product was filtered off and recrystallized from ethanol.

15a:- 2-(methylthio)-5-phenyl-3,5-dihydro-2H-[1,3,4]thiadiazolo[3,2-a]pyrimidin

Color: Colorless, Yield: 71%, M.p.: 130^{o}C, FT-IR (KBr, ν, cm^{-1}): 3355(NH), 1360 (CH_3), ^{1}H NMR (400 MHz, DMSO, δ, ppm): 2.15 (s, 1H, NH), 2.35 (s, 3H, SCH_3), 4.42 (s, 1H, CH), 5.25 (d, 1H, J = 1.5 Hz, CH); 6.01 (t, 1H, J = 6.3 Hz, CH); 7.35 (d, 1H, J = 10.2 Hz, CH); 7.40-7.62 (m, 5H, aromatic protons), MS (m/z (%)): 263. Anal. calcd. for $C_{12}H_{13}N_3S_2$: C, 54.72; H,4.97; N, 15.95; S, 24.35 %. Found: C, 54.54; H, 4.49; N, 15.99; S, 24.50%.

15b:- 5-(4-chlorophenyl)-2-(methylthio) -3,5-dihydro-2H-[1,3,4]thiadiazolo[3,2-a]pyrimidin

Color: Colorless, Yield: 74%, M.p.: 168^{o}C, FT-IR (KBr, ν, cm^{-1}): 3355(NH), 1365 (CH_3), ^{1}H NMR (400 MHz, DMSO, δ, ppm): 1.89 (s, 1H, NH), 2.15 (s, 3H, SCH_3), 4.35 (s, 1H, CH), 5.55 (d, 1H, J = 1.7 Hz, CH); 6.41 (t, 1H, J = 6.5 Hz, CH); 7.33 (d, 1H, J = 10.4 Hz, CH); 7.45-7.82 (dd, 4H, J = 7.6 Hz, aromatic protons), MS (m/z (%)): 297 Anal. calcd. for $C_{12}H_{12}N_3S_2Cl$: C, 48.39; H, 4.06; Cl, 11.90; N, 14.11; S, 21.53 %. Found: C, 48.22; H, 4.62; Cl, 11,79; N, 14.44; S, 21.30%.

15c:- 2-(methylthio)-5-(p-tolyl)-3,5-dihydro-2H-[1,3,4]thiadiazolo[3,2-a]pyrimidin

Color: Colorless, Yield: 71%, M.p.: 195^{o}C,FT-IR (KBr, ν, cm^{-1}): 3350 (NH), 1365 (CH_3), ^{1}H NMR (400 MHz, DMSO, δ, ppm): 1.99 (s, 1H, NH), 2.25 (s, 3H, SCH_3), 2.45 (s, 3H, CH3), 4.45 (s, 1H, CH), 5.33 (d, 1H , J = 1.7 Hz, CH); 6.64 (t, 1H, J = 6.6 Hz, CH); 7.01(d, 1H, J = 10.8 Hz, CH); 7.13-7.29(m, 4H, aromatic protons), MS (m/z (%)): 277. Anal. calcd. for $C_{13}H_{15}N_3S_2$: C, 56.28; H, 5.45; N, 15.15; S, 23.12 %. Found: C, 56.56; H, 5.24; N, 15.26; S, 23.30%.

15d:- 5-(4-methoxyphenyl)-2-(methylthio)-3,5-dihydro-2H-[1,3,4]thiadiazolo[3,2-a]pyrimidin

Color: Colorless, Yield: 69%, M.p.: 215^{o}C, FT-IR (KBr, ν, cm^{-1}): 3450 (NH), 1355(CH_3), ^{1}H NMR (400 MHz, DMSO, δ, ppm): 2.01 (s, 1H, NH), 2.05 (s, 3H, SCH_3), 3.99 (s, 3H, OCH3), 4.40 (s, 1H, CH), 5.25 (d, 1H, J = 1.5 Hz, CH); 6.71 (t, 1H, J = 6.5 Hz, CH); 6.99 (d, 1H, J = 10.4 Hz, CH); 7.11-7.23(dd, 4H, J = 7.5 Hz aromatic protons), MS (m/z (%)): 293. Anal. calcd. for $C_{13}H_{15}ON_3S_2$: C, 53.22; H, 5.15; N, 14.32; S, 21.86%. Found: C, 53.94; H, 5.53; N, 14.29; S, 21.90%.

7-aryl-2-(cyanomethyl) arylpyrazolo[1,5-a]pyrimidine-3-carbonitrile (18a-d)

A solution of (1.47gm, 0.01 mol) 5-amino-3-(cyanomethyl)-1H-pyrazole-4-carbonitrile 16, (0.01 mol) Sodium 3-arylprop-3- oxo-1-en-1-olate 5, (1ml) piperidine acetate and (3 ml) H_2O was heated for 15 minutes. Acetic acid (1.5 ml) was added to the hot solution. The solid product was filtered off and recrystallized from ethanol.

18a:- 2-(cyanomethyl)-7-phenylpyrazolo[1,5-a]pyrimidine-3-carbonitrile

Color: White, Yield: 75%, M.p.: 215^{o}C, FT-IR (KBr, ν, cm^{-1}): 2220(CN), 1450 (CH_2), ^{1}H NMR (400 MHz, DMSO, δ, ppm): 3.77 (s, 2H, CH_2), 7.32-7.85 (m, 5H, aromatic protons), 8.09 (d, 1H, J = 7.6 Hz, N=CH), 8.33 (d, 1H, J = 7.4 Hz, N=CH), MS (m/z (%)): 259. Anal. calcd. for $C_{15}H_9N_5$: C, 69.49; H, 3.50; N, 27.01%. Found: C, 69.34; H, 3.22; N, 27.32%.

18b:- 7-(chlorophenyl)-2-(cyanomethyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile

Color: Pale yellow, Yield: 72%., M.p.: 240^{o}C, FT-IR (KBr, ν, cm^{-1}): 2215(CN), 1465 (CH_2), ^{1}H NMR (400 MHz, DMSO, δ, ppm): 3.87 (s, 2H, CH_2), 7.57-7.95 (dd, J = 7.6 Hz 4H, aromatic protons), 8.19 (d, 1H, J = 7.5 Hz N=CH), 8.65 (d, J = 7.5 Hz 1H, N=CH), MS (m/z (%)): 293. Anal. calcd. for $C_{15}H_8N_5Cl$: C, 61.34; H, 2.75; Cl, 12,07; N, 23.84%. Found: C, 61.14; H, 2.64; Cl, 12.21; N, 23.76%.

18c:- 2-(cyanomethyl)-7-(p-tolyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile

Color: White, Yield: 70%, M.p.: 250^{o}C, FT-IR (KBr, ν, cm^{-1}): 2225(CN), 1460 (CH_2), ^{1}H NMR (400 MHz, DMSO, δ, ppm: 2.15 (s, 3H, CH_3), 3.65 (s, 2H, CH_2), 7.25-7.62 (m, 4H, aromatic protons), 8.22 (d, 1H, J = 7.6 Hz, N=CH), 8.51 (d, 1H, J = 7.5 Hz, N=CH), MS (m/z (%)): 273. Anal. calcd. for $C_{16}H_{11}N_3S_2$: C, 70.32; H, 4.06; N, 25.63%. Found: C, 70.24; H, 4.01; N, 25.51%.

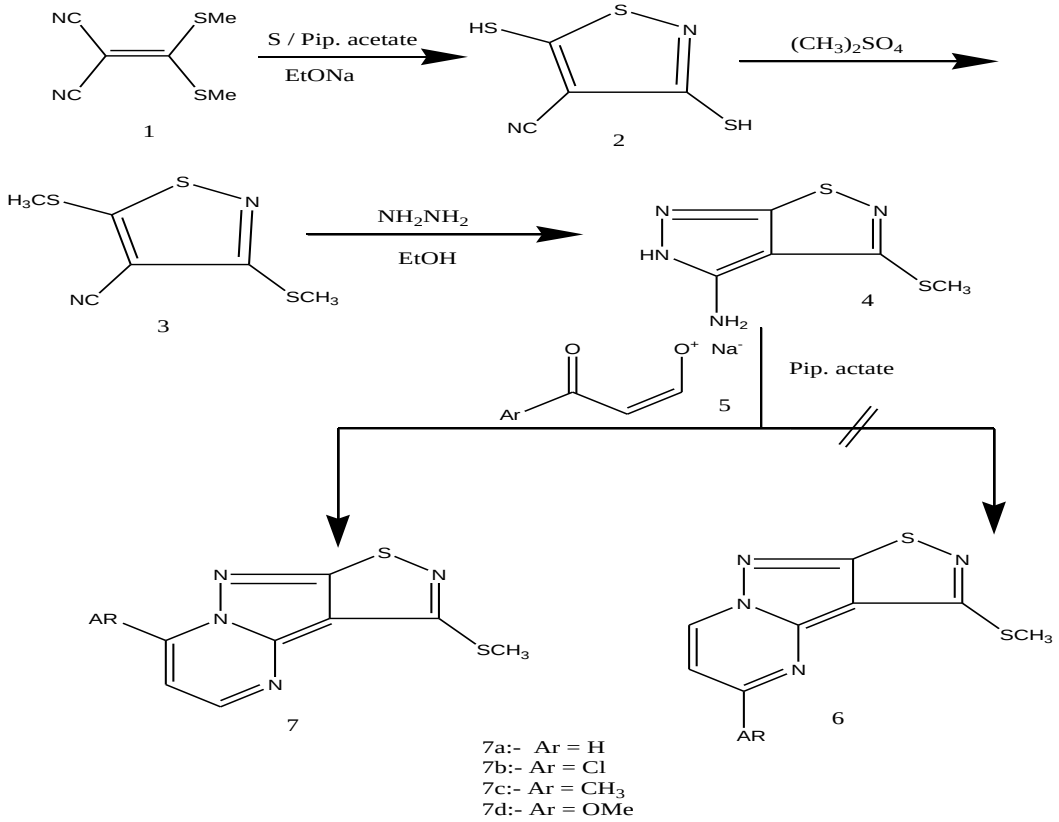
18d: - 2-(cyanomethyl)-7-(methoxyphenyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile

Color: Pale yellow, Yield: 77%, M.p.: 280^{o}C, FT-IR (KBr, ν, cm^{-1}): 2220(CN), 1470 (CH_2), ^{1}H NMR (400 MHz, DMSO, δ, ppm): 3.65 (s, 2H, CH_2), 3.90 (s, 3H, OCH_3), 7.11-7.45 (dd, J = 7.5 Hz 4H, aromatic protons), 8.19 (d,

1H, J = 7.4 Hz N=CH), 8.43 (d, J = 7.6 Hz, 1H, N=CH), MS (m/z (%)): 289. Anal. calcd. for $C_{16}H_{11}ON_5$: C, 66.43; H, 3.83; N, 24.21. Found: C, 66.21; H, 3.77; N, 24.30.

Result and Discussion

Treatment of (bis(methylthio)methylene)malanonitrile **1** [20] with sulphur metal in presence of sodium ethoxide and piperidine acetate to form 3,5-dimercaptoisothiazole-4-carbonitrile **2** which alkylation by dimethylsulphate in presence of sodium methoxide and potassium hydroxide afforded 3,5-bis(methylthio)isothiazole-4-carbonitrile **3** [21,22]. The product was cyclized to form 3-(methylthio)-5H-pyrazolo[4,3-d]isothiazol-4-amine **4**, structure of 4 was established by elemental analysis and spectral data. Thus, compound **4** is supported by its mass spectrum, which showed a molecular formula $C_5H_6N_4S_2$ (M^+ 186). ^{1}H NMR (400 MHz, DMSO, δ, ppm): 2.55 (s, 3H, SCH_3), 4.22 (s, 2H, NH_2), 8.99 (s, br., 1H, NH) **[Scheme 1].**

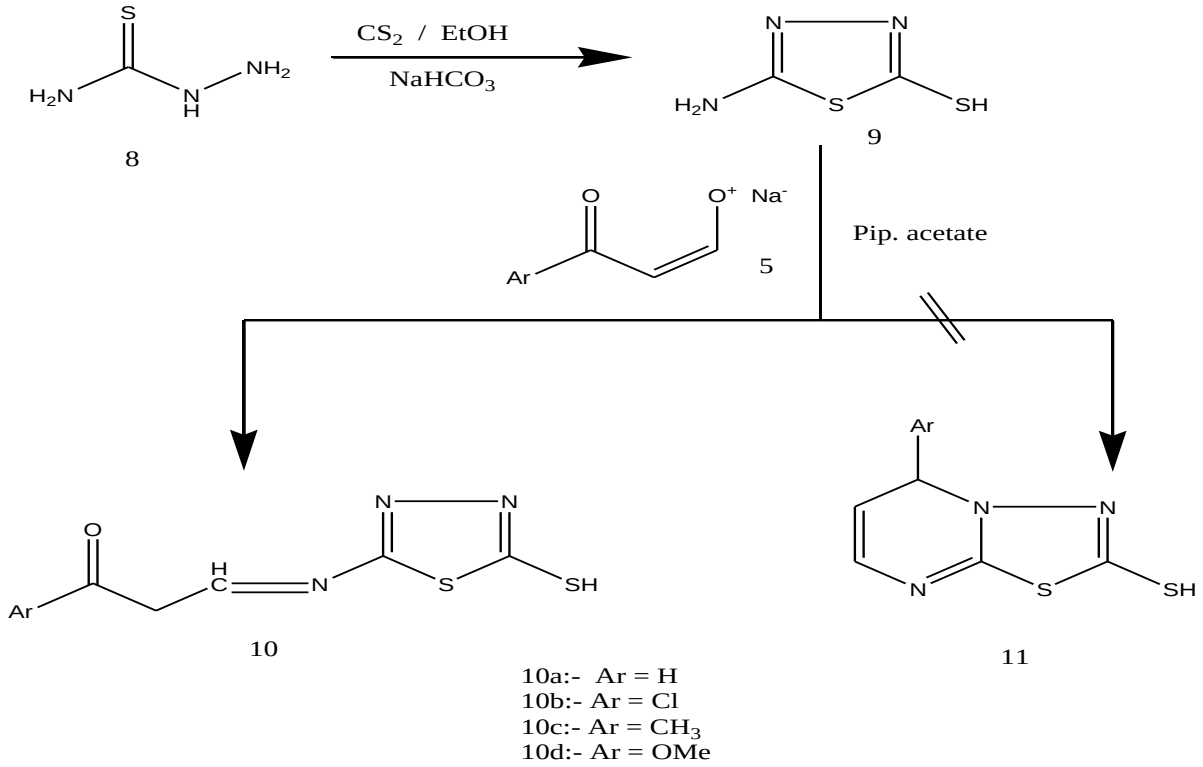


Scheme (1).

Compound **4** is subjected to react with Sodium 3- arylprop-3- oxo-1-en-1-olate **5** [23-25] in presence of piperidine actate afforded 5-aryl-3-(methylthio)isothiazole[5$^-$,4$^-$:3,4]pyrazolo[1,5-a]pyrimidine **6** or isomeric 7-aryl-3-(methylthio)isothiazole[5',4':3,4]pyrazolo[1,5-a] pyrimidine **7.** The two isomers and spectral data, it was found that the compound **7** is formed through initial nucleophilic attacked by the exocyclic amino group which takes place at the formyl group then Michael cyclization followed by elimination two moles of water which leads to structures **7.** The other discussed that the initial nucleophilic attacked by endo imino group takes place at the formyl group and

followed by cyclization of exocyclic amino group of ketonic group which leads to isomeric structure **6**. Really only one isomer was obtained. Thus structure **7** was established by elemental analysis and spectral data. And compound **7a** is supported by its mass spectrum, which showed a molecular formula $C_{14}H_{10}N_4S_2$ (M^+ 298). ^{1}H NMR spectrum showed signals at ^{1}H NMR (400 MHz, DMSO, δ, ppm): 2.43 (s, 3H, SCH_3), 7.32-7.85 (m, 5H, aromatic protons), 8.15 (d, 1H, J = **7.3** Hz, N=CH), 8.77 (d, 1H, J = **7.3** Hz, N=CH). (Scheme 1).

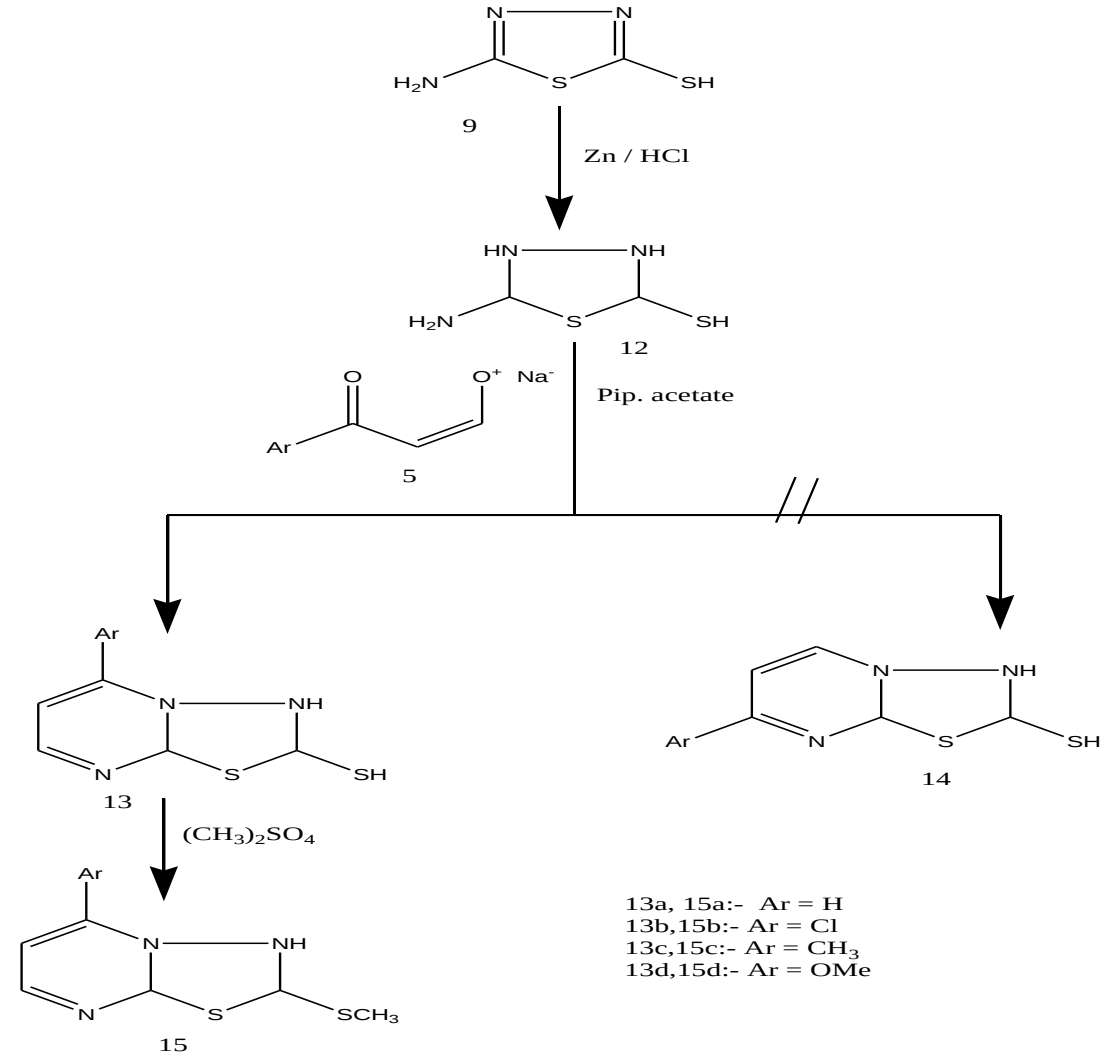
The reaction of thiosemicarbazide **8** with carbondisulphide in presence of sodiumbicarbonate and absolute alcohol produced 5-amino-1,3,4-thiadiazol-2-thiol **9** [26]. The product reacted with sodium 3-arylprop-3-oxo-1-en-1-olate **5** in presence of piperidine acetate to give the open structure 1-Aryl-2-[(5-mercapto-[1,3,4]-thiadiazole-2-yl)imino]ethanone **10**. Or isomeric cyclic structure 5-aryl-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-2-thiol **11**. Compound **10** was confirmed by the elemental analysis and spectral data. Thus compound **10a** is supported by its mass spectrum, which showed a molecular formula $C_{11}H_9ON_3S_2$ (M^+ 263). ^{1}H NMR spectrum showed signals at ^{1}H NMR (400 MHz, DMSO, δ, ppm): 3.01 (d, 2H, J = 6.9 Hz, CH_2), 3.55 (s, 1H, SH), 7.22 (t, 1H, J = 6.1 Hz, N=CH-CH_2), 7.5-8.2 (m, 5H, aromatic protons). [Scheme 2**]**



Scheme (2).

Reduction of 5-amino-1,3,4-thiadiazol-2-thiol **9** in presence of zinc dust and hydrochloric acid produced 5-amino-1,3,4-thiadiazolidine-2-thiol **12** which reacted with sodium 3-arylprop-3-oxo-1-en-1-olate **5** in presence of piperidine acetate to produce 7-aryl-3,5-dihydro-2H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-2-thiol **13** or isomeric structure 7-aryl -3,5-dihydro-2H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-2-thiol **14** but the elemental analysis and spectral data confirm that the obtained structure is 5-aryl -2,3-dihydro-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-2-

thiol 13. Thus, compound 13a is supported by its mass spectrum, which showed a molecular formula $C_{11}H_{11}N_3S_2$ (M^+ 249). ^{1}H NMR (400 MHz, DMSO, δ, ppm):1.53 (s, 1H, SH), 2.95 (s, 1H, NH), 4.12 (s, 1H, CH), 5.01 (d, 1H, J = **1.5** Hz, CH); 6.11 (t, 1H, J = **6.2** Hz, CH); 7.15 (d, 1H, J = 10.1 Hz, CH); 7.23-7.52 (m, 5H, aromatic protons). [Scheme 3].

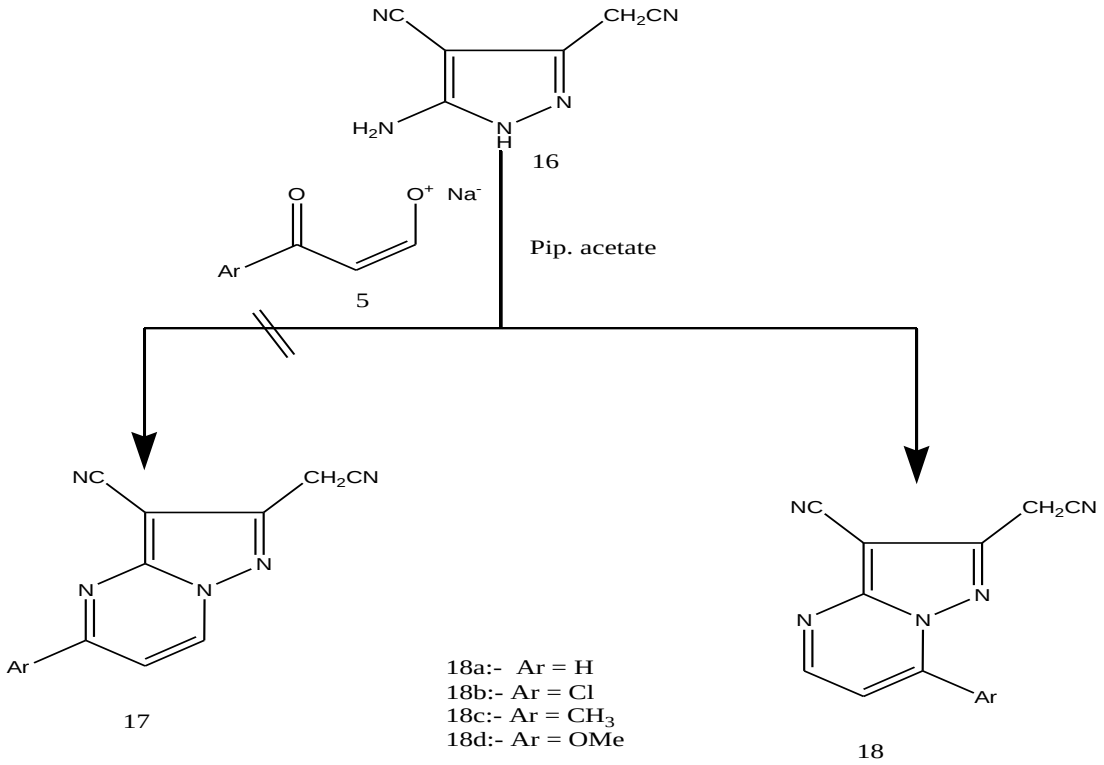


Scheme (3).

According to the mentioned mechanism, reaction of compound **12** with sodium 3-arylprop-3-oxo-1-en-1-olate **5** produced compound **13** Which was subjected to alkylation with dimethyl sulphate to yield the alkylated product **15** which confirmed by elemental analysis and spectral data. Thus compound **15a** is supported by its mass spectrum, which showed a molecular formula $C_{12}H_{13}N_3S_2$ (M^+ 263). ^{1}H NMR (400 MHz, DMSO, δ, ppm): 2.15 (s, 1H, NH),

2.35 (s, 3H, SCH_3), 4.42 (s, 1H, CH), 5.25 (d, 1H, J = 1.5 Hz, CH); 6.01 (t, 1H, J = 6.3 Hz, CH); 7.35 (d, 1H, J = 10.2 Hz, CH); 7.40-7.62 (m, 5H, aromatic protons).

Treatment of 5-amino-3-(cyanomethyl)-1H-pyrazole-4-carbonitrile **16** [27] with sodium 3-arylprop-3-oxo-1-en-1-olate **5** in presence of piperidine acetate was produced 7-aryl-2-(cyanomethyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile **18** or isomeric structure 5-aryl-2-(cyanomethyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile **17**. Structure **18** was established by elemental analysis and spectral data. Thus compound **18a** is supported by its mass spectrum, which showed a molecular formula $C_{15}H_9N_5$ (M^+ 259). ^{1}H NMR (400 MHz, DMSO, δ, ppm): 3.77 (s, 2H, CH_2), 7.32-7.85 (m, 5H, aromatic protons), 8.09 (d, 1H, J = 7.6 Hz, N=CH), 8.33 (d, 1H, J = 7.4 Hz, N=CH). [Scheme 4].



Scheme (4).

Conclusion

In summary, we have achieved a synthesis of interesting novel purine and mercaptopurine analogues utilizing the reaction of sodium salt of Acetyl derivatives with aminothiadiazoles and aminopyrazole derivatives. The compounds obtained seem promising for further chemical transformations and for biological evaluation studies.

Acknowledgements

The authors are grateful to Prof. Dr. Ahmed Hafez Hussien Elghandour and Dr. Emadeldin Mohamed Kamel for their help and valuable advice.

References

[1]. Lunxiang, Y.; Jürgen,L. (2005). **ω-Functionalized 3-Alkynylpyrazolo[1, 5-a]pyrimidines by Sonogashira Coupling**. **Synthesis. 1:131-135.**

[2]. Lunxiang, Y; Jürgen, L. (2004). **Convenient Synthesis of Substituted 3-Alkenylpyrazolo[1,5-a]pyrimidines via Heck Cross-Coupling Reaction. Synthesis. 14 : 2329-2334.**

[3]. senga, K.; Novinson, T.; Wilson, H. R., (1981). **Synthesis and antischistosomal activity of certain pyrazolo[1,5-a]pyrimidines. J. Med. Chem. 24: 610-613.**

[4]. Suzuki, M.; Iwasaki, H.; Fujikawa, Y.; Sakashita, M.;Kitahara, M.; Sakoda, R., (2001). **Synthesis and biological evaluations of condensed pyridine and condensed pyrimidine-based HMG-CoA reductase inhibitors.Bioorg. Med. Chem. Lett., 11:1285-1288.**

[5]. Almansa, C.; Arriba, A. F.; Cavalcanti, F. L.; Gomez, L. A.; Miralles, A.; Forn, (2001). **Synthesis and SAR of a new series of COX-2-selective inhibitors: pyrazolo[1,5-a]pyrimidines. J. Med. Chem., 44:350-361.**

[6]. Fraley, M. E.; Hoffman, W. F.; Rubino, R. S.; Hungate, R. W.; Tebben, A. J.; Rutledge, R. Z.; McFall, R. C.; Huckle, W. R.; Kendall, R. L.; Coll, K. E.; Thomas, K. A.; (2002). **Synthesis and initial SAR studies of 3,6-disubstituted pyrazolo[1,5-a]pyrimidines: a new class of KDR kinase inhibitors. Bioorg. Med. Chem. Lett. 12: 2767-2770.**

[7]. Wong, H; Lehman-Mckeeman, L D; Grubb, M. F; Grossman S. J; Bhaskaran V. M; Solon E. G; Shen, H. S; Gerson R. J; Car, B. D; Zhao, B; Gemzik B., (2005). **Increased Hepatobiliary Clearance of Unconjugated Thyroxine Determines DMP 904-Induced Alterations in Thyroid Hormone Homeostasis in Rats.Toxicol Sci., 84: 232-242.**

[8]. Gehan, E. A; Freireichb, E. J., (2011**). The 6-MP versus placebo clinical trial in acute leukemia. Clin Trials. 8: 288-297.**

[9]. Thijs, W.H. P; Peter, I. B; Nuno, M.M. P; Iker, O; Mariska, V; Margreet, R. de V; Marco, v. E; Jeroen Roelofsen, L. M. H; Paul, H.A. Q, Andre, B.P. K; Vivian D. W; Hans, P; Carlie, J.M. V., (2010). **6-Mercaptopurine Inhibits Atherosclerosis in Apolipoprotein E*3-Leiden Transgenic Mice Through Atheroprotective Actions on Monocytes and Macrophages. Arterioscler. Thromb. Vasc. Bio., 30: 1591-1597.**

[10]. Pires, N. M; Pols, T. W; de Vries, M. R; van Tiel, C. M; Bonta, P. I; Vos, M; Arkenbout, E. K; Pannekoek, H; Jukema, J. W; Quax, P. H; de Vries, C. J., (2007). **Activation of Nuclear Receptor Nur77 by 6-Mercaptopurine Protects Against Neointima Formation. Circulation. 115: 493-500.**

[11]. Karanik, M.; Pätzel, M.; Liebscher, (2003). **Bicyclic Aminoalkyl N-Heterocycles by Ring-Chain-Transformation of Bridged 1,3-Dicarbonyl Heteroanalogues with Aminopyrazoles and Aminotriazole. Synthesis.8: 1201-1208.**

[12]. Abdelhamid, A. O; Elghandour, A. H. H; Ahmed, S. A; and Zaki, Y. H, (2005). **Reaction of hydrazonoyl halides 49 1: Synthesis and antimicrobial activity of some new pyrimido[1,2-b][1,2,4,5]tetrazin-6-one, tetrazino[3,2-b]quinazolin-5-one, pyrimidino[1,2-b]1,2,4,5-tetrazin-5-one and triazolo[4,3-a]pyrimidine derivatives. J. Sulfur Chem., 26: 405-410.**

[13]. Abdelhamid, A. O; Elghandour, A. H. H; Ahmed, S. A; and Zaki, Y. H. (2006). **Synthesis and reactions of 2-chloro-2-(hydroximino)-1-(4-methyl-2-phenylthiazol-5-yl)ethanone J. Heterocyclic Chem., 43: 249-254.**

[14]. Zaki, Y. H; Ahmed, S. A; Hussein, A. M; and Abdelhamid A. O., (2006). **Reactions of Hydrazonoyl Halides 47 : Synthesis of Some New 2,3-dihydro-1,3,4-thiadiazoles, Triazolo[4, 3-a]pyrimidines, and Pyrazolo[3, 4-d]pyridazines with Expected Biological Activity Phosphorous Sulfur and Silicon, 181: 825-837.**

[15]. Ahmed, S. A; H; Hussein, A. M; Elghandour, A, H; Hozayen, W. G. M; Elghandour, A, H. and Abdelhamid A. O. (2007). **Synthesis of some pyrazolopyrimidines as purine analogues. J. Heterocyclic Chem., 44: 803-810.**

[16]. Elgemeie, G. H.; Mahmoud. M. A. and Jones, P. G., (2002). **N-(3-Cyano-2-oxo-2,5,6,7,8,9-hexahydro-1H-cyclohepta[b]pyridin-1-yl)-4-methylbenzenesulfonamide. Acta Cryst., E58: 01293-01295.**

[17]. Elgemeie, G. H.; and Hussain, B. A. W., (1994). **A convenient synthesis of 5-deaza nonclassical antifolates: Reaction of cyanothioacetamide with sodium salts of 2-(hydroxymethylene)-1-cycloalkanones. Tetrahedron.50: 199-204.**

[18]. Elgemeie, G. H.; and Metwally, N. H., (1999). **Novel Synthesis of 5-Amino-1-arylsulfonyl-4-pyrazolin-3-ones as a New Class of N-Sulfonylated Pyrazoles. J. Chem. Research.6: 384-385.**

[19]. Wansa, K. D; Muscat, G. E., (2005). **TRAP220 is modulated by the antineoplastic agent 6-Mercaptopurine, and mediates the activation of the NR4A subgroup of nuclear receptors.J. Mol. Endocrinol. 34: 835-848.**

[20]. Tominaga, Y.; and Matsuda, Y., (1985). **Synthesis of heterocyclic compounds using nitro ketene dithioacetal J. Heterocycl. Chem., 22: 937-949.**

[21]. Soderack, E., (1963). **Condensation of carbon disulfide with reactive methyl groups. Acta Chem. Scand., , 17: 362-376.**

[22]. Hatchard, W. R., (1964). **The Synthesis of Isothiazoles. II. 3,5-Dimercapto-4-isothiazolecarbonitrile and Its Derivatives. J. Org. Chem., 29: 665-668.**

[23]. Gordon, N. W., (1958). **Piperidine-Catalyzed Condensation of 1,3-Dicarbonyl Compounds with Ethyl β-Ketoglutarate. J. Org. Chem., 23: 34-39.**

[24]. Osama, M. A.; Mahmoud A. M.; Rasha R. A.; Sayed A. A., (2009). **Synthesis and anti-tumor activities of some new pyridines and pyrazolo[1,5-a]pyrimidines. Eur. J. Med.Chem. , 44: 3519-3523.**

[25]. Yan, C. W.; Xiao, M. Z.; Fang, Z. H. and Hua, Z. Y.(2005). **Design and Synthesis of Novel Sulfone-containing Pyrazolo[1,5-a]pyrimidines and Pyrazolo[5,1-d][1,2,3,5]tetrazine-4(3H)-ones J. Heterocyclic Chem., 42: 609-613.**

[26]. Bahar, A. and Md, Y., (2010). **Synthesis of aromatic aldhyde imine derivatives of 2-thiobenzyl-1,3,4-thiadiazole and evaluation of their anticonvulsant activity. Indian j. Chem., 49B: 241-246.**

[27]. Edward C. T.; Klaus S., (1959). **The Reaction of Malononitrile with Hydrazine. J. Am. Chem. Soc., 81: 2452-2455.**