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Synthesis of pyrazole, 1,3-dithiolan and thiophene derivatives pendant to thiazolo[2,3-c]-1,2,4-triazole moiety

Samia Mohamed Sayed, Mohamed Ali Khalil and Mohamed Abd-Elmonem Raslan *

Chemistry Department, Faculty of Science, Aswan University, 81528 Aswan, Egypt

**Corresponding author at: Chemistry Department, Faculty of Science, Aswan University, 81528 Aswan, Egypt.*
Tel.: +2.097.2319197. Fax: +2.097.3480450. E-mail address: raslanma47@yahoo.com (M.A. Raslan).

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ABSTRACT

Coupling of 5-acetyl-2-amino-4-methylthaizole diazonium sulphate (**1**) with 3-chloro-pentane-2,4-dione (**2**) afforded the thiazolo[2,3-*c*]-1,2,4-triazole derivative, (**5**). Bormination of compound (**5**) followed by reaction with potassium cyanide afforded *bis*-3-oxo-propanenitrile derivative (**7**) which, reacts with CS_2/NaH/CH_3I to afford the ketene *S*,*S*-dithioacetal, (**8**). Synthesis of 1,3-dithiolane (**11**) and thiophene (**15**) derivatives have been reported.

1. Introduction

Heterocycles are widely used in the development of modern pharmaceuticals; this is being one of the reasons why continuous efforts are placed towards the design of amenable synthetic approaches for the synthesis of new heterocyclic systems. Thiazole ring systems are known to possess various pharmacological properties such as anti-tubercular, antifungal, analgesic and anticancer activities [1-4].

1,2,4-Triazole and their derivatives are found to be associated with various biological activities such as anticonvulsant [5-7], antifungal [8-10], anticancer [11-14], anti-inflammatory [15-17] and antibacterial properties [18-21]. In addition, compounds incorporating 1,2,4-triazole and 1,3-thiazole have been attracting widespread attention due to their diverse pharmacological such as antimicrobial, anti-inflammatory and antitumor activities [22,23].

Also, pyrazoles have emerged as a group of compounds possessing a broad spectrum of useful medicinal such as herbicide, fungicide and analgesic activities [24-26]. On the other hand many thiophene containing compounds including annulated compounds, exhibit biological activities [27-29].

Based on the above observations, we expected that incorporation of the above various nuclei will yield compounds with enhanced biological activities and as a part of our research program aimed at developing simple and efficient synthetic approaches for fused ring systems with bridgehead nitrogen atom, utilizing the inexpensive and readily obtainable starting materials like 5-acety-2-amino-4-methylthaizole [30-35], we report here on the utility of the highly versatile, multifunctional intermediates **6** and **7** as building blocks for the synthesis of the title compounds.

2. Experimental

2.1. Instrumentation

Melting points were determined on a Gallenkamp apparatus and are uncorrected. The IR spectra were recorded on Shimadzu FT-IR 8101 PC infrared spectrophotometer. The ^{1}H and ^{13}C NMR spectra were determined in DMSO-d_6 at 300 and 75 MHz, respectively, on a Varian Mercury VX 300 NMR spectrometer using TMS as an internal standard. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University.

2.2. Synthesis

2.2.1. Synthesis of N'-(5-acetyl-4-methylthiazol-2-yl)-2-oxo propanehydrazonoyl chloride (3)

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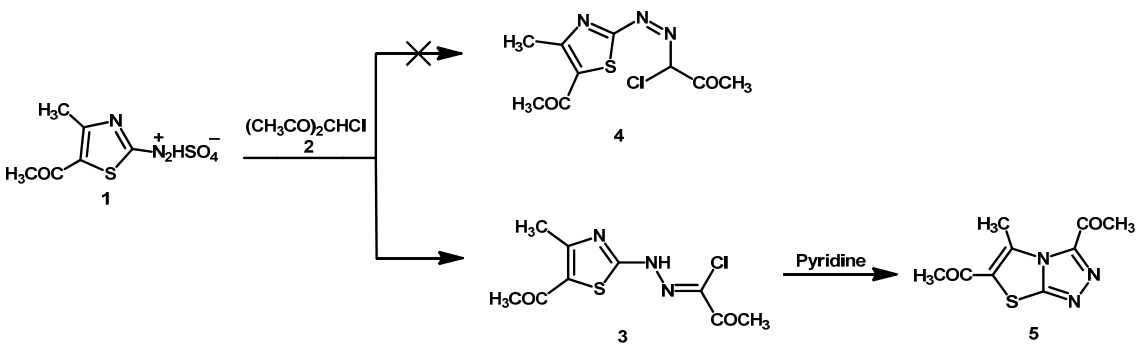


Scheme 1

5-Acetyl-2-amino-4-methylthiazole salt (**1**) was prepared according to the reported literature [36]. The freshly diazonium salt **1** (10 mmol) was added portionwise with stirring to a cold solution (0-5 °C) of 3-chloropentane-2,4-dione (**2**) (10 mmol) in ethanol (50 mL) in the presence of AcONa.3H2O (2 g) over period of 30 min. The reaction mixture was stirred for further 2 h, at 0-10 °C then kept in an ice box for 24 h. The precipitate product was filtered off, washed with water, dried and finally recrystallized from dioxane to afford of the hydrazone **3** (Scheme 1). Yield: 55%. M.p.: 205-207 °C. FT-IR (KBr, ν, cm-1): 3340, 3150 (NH), 1693, 1686 (2C=O). 1H NMR (300 MHz, DMSO-*d6*, δ, ppm): 2.32 (s, 3H, CH3), 2.63 (s, 3H, CH3), 2.74 (s, 3H, CH3), 9.88 (s, 1H, NH). MS (EI, *m/z* (%)): 259 (M+), 261 (M++2). Anal. calcd. for $C_9H_{10}N_3O_2SCl$: C, 41.62; H, 3.88; N, 16.18; S, 12.32. Found: C, 41.56; H, 3.85; N, 16.20; S, 12.31%.

2.2.2. Synthesis of 3,6-diacetyl-5-methylthiazolo[2,3-c]-1,2,4-triazole (5)

A solution of the hydrazone **3** (10 mmol) in pyridine (20 mL) was heated under reflux for 4 h, then left to cool, then dilute with ice water containing few drops of hydrochloric acid. The separated solid was collected by filtration, washed with water, dried and finally recrystallized from DMF to afford of compound **5** (Scheme 1). Yield: 46%. M.p.: 287-289 °C. FT-IR (KBr, ν, cm-1): 1698, 1687 (2C=O). 1H NMR (300 MHz, DMSO-*d6*, δ, ppm): 2.31 (s, 3H, CH3), 2.62 (s, 3H, CH3), 2.71 (s, 3H, CH3). 13C NMR (75 MHz, DMSO-*d6*, δ, ppm): 192.3, 190.9 (2CO), 167.3 (C-3), 159.8 (C-7a), 126.7 (C-5), 124.8 (C-6), 25.5, 23.5, 16.4 (3CH3). MS (EI, *m/z* (%)): 223 (M+). Anal. calcd. for $C_9H_9N_3O_2S$: C, 48.42; H, 4.06; N, 18.82; S, 14.36. Found: C, 48.38; H, 4.10; N, 18.86; S, 14.32%.

2.2.3. Synthesis of 1,1'-(5-methylthiazolo[2,3-c]-1,2,4-triazole-3,6-diyl)bis((2-bromo)ethanone) (6)

A solution of the 3,6-diacetyl-5-methylthiazolo[2,3-*c*]-1,2,4-triazole **5** (20 mmol) in AcOH (50 mL) was heated at 90-100 °C with stirring. To the hot solution, bromine (40 mmol) in AcOH (20 mL) was added dropwise over a period of 30 min with stirring, maintaining the temperature at 90-100 °C. After complete addition, the mixture was stirred vigorously at room temperature for further 1 h, until evolution of hydrogen bromide ceased. The reaction mixture was allowed to cool and the precipitated solid was filtered off, washed with water, dried and finally recrystallized from ethanol to afford of compound **6** (Scheme 2). Yield: 52%. M.p.: 213-215 °C. FT-IR (KBr, ν, cm-1): 1684, 1692 (2C=O). 1H NMR (300 MHz, DMSO-*d6*, δ, ppm): 2.32 (s, 3H, CH3), 4.29 (s, 2H, CH2), 4.38 (s, 2H, CH2). MS (EI, *m/z* (%)): 381 (M+). Anal. calcd. for $C_9H_7N_3O_2SBr_2$: C, 28.37; H, 1.85; N, 11.03; S, 8.42. Found: C, 28.41; H, 1.89; N, 11.10; S, 8.38%.

2.2.4. Synthesis of 3,3'-(5-methylthiazolo[2,3-c]-1,2,4-triazole-3,6-diyl)bis(3-oxopropanenitrile) (7)

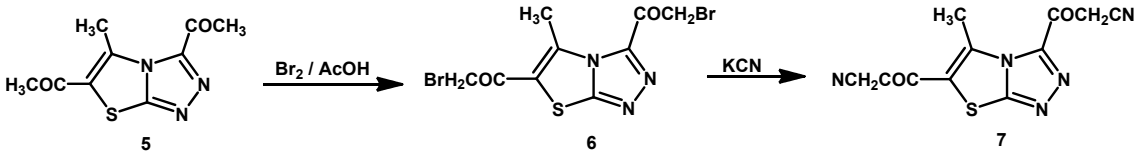
To a solution of compound **6** (15 mmol) in absolute ethanol (50 mL) was added a solution of KCN (30 mmol in 15 mL H2O) with stirring. The reaction mixture was heated on a boiling water bath. The reaction mixture was left at room temperature for 24 h, with stirring, then diluted with H2O. The solid that precipitated was filtered off, washed with water, dried and finally recrystallized from EtOH to afford of compound **7** (Scheme 2). Yield: 48%. M.p.: 228-230 °C. FT-IR (KBr, ν, cm-1): 1685, 1695 (2C=O), 2213, 2223 (2CN). 1H NMR (300 MHz, DMSO-*d6*, δ, ppm): 2.32 (s, 3H, CH3), 4.50 (s, 2H, CH2), 4.59 (s, 2H, CH2). 13C NMR (75 MHz, DMSO-*d6*, δ, ppm): 196.1, 197.3 (2C=O), 166.5 (C-3), 158.2 (C-7a), 126.4 (C-5), 123.7 (C-6), 116.4 (2CN), 26.1, 23.5 (2CH2), 16.8 (CH3). MS (EI, *m/z* (%)): 273 (M+). Anal. calcd. for $C_{11}H_7N_5O_2S$: C, 48.35; H, 2.58; N, 25.63; S, 11.73. Found: C, 48.42; H, 2.60; N, 25.61; S, 11.68%.

2.2.5. Synthesis of 3,3'-(5-methylthiazolo[2,3-c]-1,2,4-triazole-3,6-diyl)bis(2-(bis(methylthio)methylene)-3-oxo propanenitrile) (8)

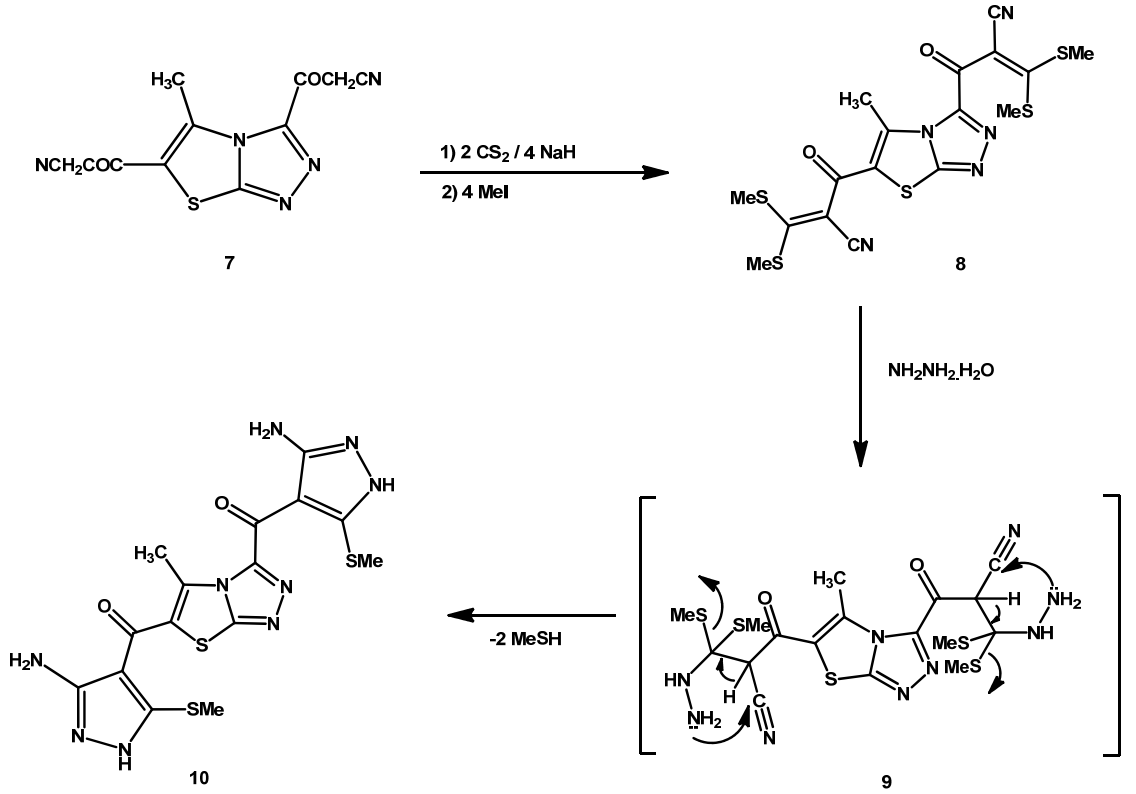
To a stirred solution of sodium hydride (40 mmol) in DMSO (20 mL), compound **7** (10 mmol) was added. The resulting mixture was stirred for 1 h, and then CS2 (20 mmol) was added and the stirring was continued for additional 6 h, and then CH3I (20 mmol) was added dropwise. Stirring continued for additional 6 h. The resulting reaction mixture was then poured onto crushed ice and the solid product was filtered off, washed with water, dried and finally recrystallized from EtOH to afford of compound **8** (Scheme 3). Yield: 62%. M.p.: 206-208 °C. FT-IR (KBr, ν, cm-1): 1683, 1692 (2C=O); 2216, 2220 (2CN). 1H NMR (300 MHz, DMSO-*d6*, δ, ppm): 2.35 (s, 3H, CH3), 2.63 (s, 6H, SCH3) 2.79 (s, 6H, SCH3). 13C NMR (75 MHz, DMSO-*d6*, δ, ppm): 187.9, 186.7 (2C=O), 187.9, 186.1 (=CSMe), 165.3 (C-3), 157.2 (C-7a), 127.2 (C-5), 137.6 (C-6), 115.9 (CN), 107.2, 92.4 (=CCN), 17.5 (SCH3), 17.1 (CH3). MS (EI, *m/z* (%)): 483 (M++2). Anal. calcd. for $C_{17}H_{15}N_5O_2S_5$: C, 42.39; H, 3.14; N, 14.54; S, 33.29. Found: C, 42.34; H, 3.18; N, 14.58; S, 33.36%.

2.2.6. Synthesis of (5-methylthiazolo[2,3-c][1,2,4]triazole-3,6-diyl)bis((3-amino-5-(methylthio)-1H-pyrazol-4-yl)methanone) (10)

To a solution of compound **8** (10 mmol) in EtOH (25 mL), hydrazine hydrate (80%, 20 mmol) was added and the reaction mixture was refluxed for 4 h, and then left to cool. The solid product so formed was filtered off, washed with EtOH, dried and finally recrystallized from DMF:H2O (1:1, *v:v*) to afford of compound **10** (Scheme 3). Yield: 52%. M.p.: 312-314 °C.



Scheme 2



Scheme 3

FT-IR (KBr, ν, cm^{-1}): 3421, 3356, 3291, 3228 (NH and NH_2), 1685, 1692 (2C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.35 (s, 3H, CH_3), 2.61 (s, 3H, SCH_3), 2.72 (s, 3H, SCH_3) 5.93 (brs, 4H, NH_2, D_2O-exchangeable), 8.36 (brs, 2H, NH, D_2O-exchangeable). MS (EI, *m/z* (%)): 451 (M^++2). Anal. calcd. for $C_{15}H_{15}N_9O_2S_3$: C, 40.08; H, 3.36; N, 28.04; S, 21.40. Found: C, 40.12; H, 3.31; N, 27.98; S, 21.46%.

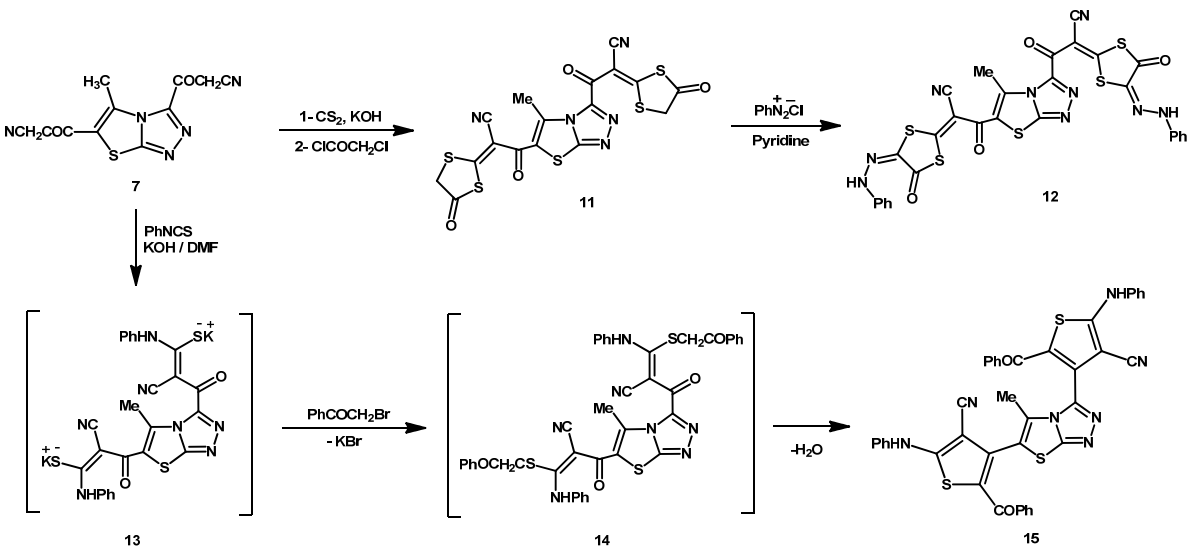
2.2.7. Synthesis of 3,3'-(5-methylthiazolo[2,3-c]-1,2,4-triazole-3,6-diyl)bis(2-(4-oxo-1,3-dithiolan-2-ylidene)-3-oxopropanenitrile) (11)

To a stirred solution of KOH (10 mmol) in DMF (30 mL), compound **7** (5 mmol) was added, after stirring for 1 h, CS_2 (10 mmol) was added to the resulting mixture. Stirring was continued for 12 h, and then chloroacetyl chloride (10 mmol) was added dropwise. Stirring was continued for additional 8 h, then the reaction mixture was poured onto ice water. The solid product that formed was filtered off, dried and finally recrystallized from EtOH afford of compound **11** (Scheme 4). Yield: 64%. M.p.: 295-297 °C. FT-IR (KBr, ν, cm^{-1}): 2196, 2202 (2CN), 1716, 1698, 1668 (C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.35 (s, 3H, CH_3), 3.63 (brs, 4H, CH_2). MS (EI, *m/z* (%)): 505 (M^+). Anal. calcd. for $C_{17}H_7N_5O_4S_5$: C, 40.38; H, 1.40; N, 13.85; S, 31.71. Found: C, 40.45; H, 1.48; N, 13.81; S, 31.76%.

2.2.8. Synthesis of 3,3'-(5-methylthiazolo[2,3-c]-1,2,4-triazole-3,6-diyl)bis(2-(4-oxo-(5-phenylhydrazono)-1,3-dithiolan-2-ylidene)-3-oxopropanenitrile) (12)

To a solution of **11** (5 mmol) in pyridine (20 mL), an ice-cooled solution of the aniline diazonium salt (15 mmol) was added dropwise with stirring for 30 min, after which water was added and the precipitate product was filtered off, washed with water several times, dried and finally recrystallized from DMF: H_2O (1:1, *v:v*) to give of compound **12** (Scheme 4). Yield: 53%. M.p.: 264-266 °C. FT-IR (KBr, ν, cm^{-1}): 3317, 3237 (NH), 2221, 2235 (CN), 1698, 1684, 1676 (C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.34 (s, 3H, CH_3), 7.23-7.86 (m, 10H, Ar), 11.91 (brs, 2H, NH, D_2O-exchangeable). Anal. calcd. for $C_{29}H_{15}N_9O_4S_5$: C, 48.80; H, 2.12; N, 17.66; S, 22.46. Found: C, 48.86; H, 2.15; N, 17.61; S, 22.49%.

2.2.9. Synthesis of 4,4'-(5-methylthiazolo[2,3-c]-1,2,4-triazole-3,6-diyl)bis(5-benzoyl-2-(phenyl-amino)thiophene-3-carbonitrile) (15)



Scheme 4

To a stirred solution of KOH (10 mmol) in DMF (30 mL), compound **7** (10 mmol) was added, after stirring for 1 h, phenyl isothiocyanate (20 mmol) was added to the resulting mixture. The reaction was stirred for additional 6 h, during which the 2-bromo-1-phenylethanone went into solution and a yellow product precipitated. The solid product was filtered off, washed with water, dried and finally recrystallized from DMF: EtOH (1:2, *v*:*v*) afforded of compound **15** (Scheme 4). Yield: 59%. M.p.: > 330 °C. FT-IR (KBr, ν, cm^{-1}): 3298, 3218 (NH), 2218, 2224 (CN), 1665, 1669 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.35 (s, 3H, CH_3), 7.21-7.83 (m, 20H, ArH), 10.93 (brs, 2H, NH, D_2O-exchangeable). Anal. calcd. for $C_{41}H_{25}N_7O_2S_3$: C, 66.20; H, 3.39; N, 13.18; S, 12.93. Found: C, 66.17; H, 3.45; N, 13.11; S, 12.88%.

2.2.10. Synthesis of 2,2'-(5-methylthiazolo[2,3-c][1,2,4] triazole-3,6-dicarbonyl)bis(3-(methylthio)-3-(phenyl amino)acrylonitrile) **(16)**

To a stirred solution of KOH (20 mmol) in DMF (30 mL) was added compound **7** (10 mmol). After stirring for 1 h, phenyl isothiocyanate (20 mmol) was added to the resulting mixture. Stirring continued for additional 6 h and then CH_3I (20 mmol) was added, stirring continued for additional 5 h. Then, the reaction mixture was poured onto ice water. The solid product that formed was filtered off, washed with ethanol, dried and finally recrystallized from DMF: EtOH (1:2, *v*:*v*) to afford of compound **16** (Scheme 5). Yield: 63%. M.p.: 312-314 °C. FT-IR (KBr, ν, cm^{-1}): 3392, 3268 (NH), 2223, 2198 (CN), 1698, 1694 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.34 (s, 3H, CH_3), 2.83 (s, 3H, SCH_3), 2.89 (s, 3H, SCH_3), 7.23-7.96 (m, 10H, ArH), 9.87 (brs, 2H, NH, D_2O-exchangeable). MS (EI, *m/z* (%)): 572 (M^++1). Anal. calcd. for $C_{27}H_{21}N_7O_2S_3$: C, 56.72; H, 3.70; N, 17.15; S, 16.83. Found: C, 56.66; H, 3.74; N, 17.09; S, 16.80%.

2.2.11. Synthesis of (5-methylthiazolo[2,3-c]-1,2,4-triazole-3,6-diyl)bis((3-amino-5-(phenylamino)-1H-pyrazol-4-yl) methanone) **(17)**

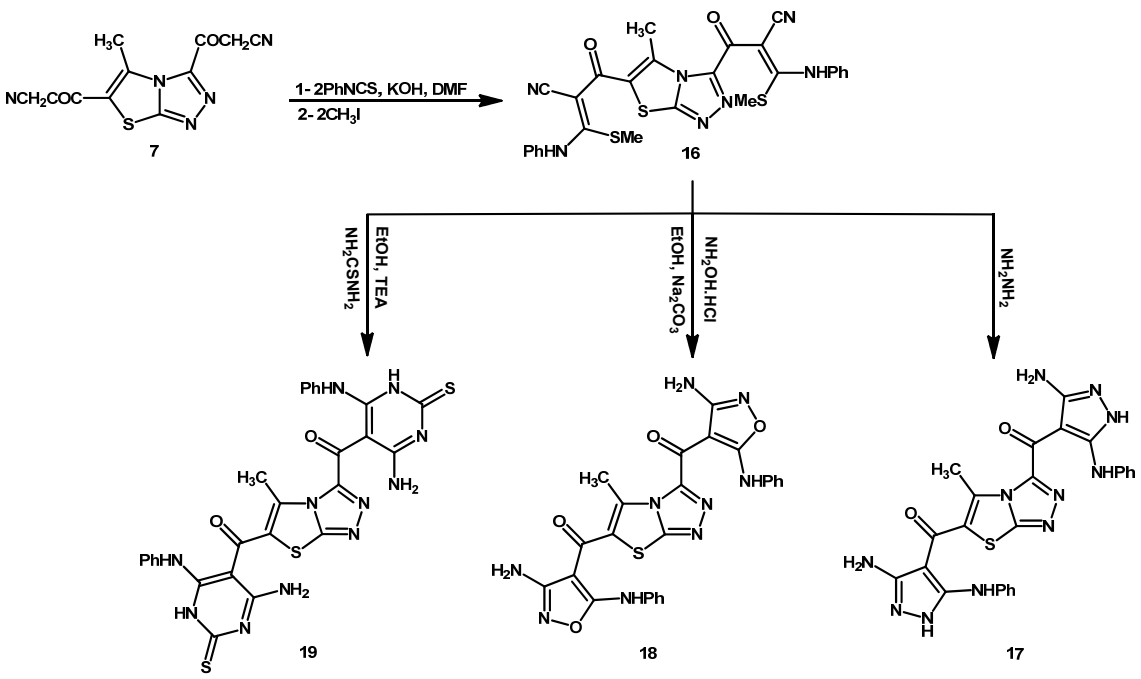
A mixture of **16** (10 mmol) and hydrazine hydrate 80%, (25 mmol) was heated on boiling water bath for 4h., then left to cool. The reaction mixture was triturated with ethanol and the resulting solid was filtered off, washed with EtOH, dried and finally recrystallized from DMF: EtOH (1:2, *v*:*v*) to afford of compound **17** (Scheme 5). Yield: 62%. M.p.: 262-264 °C. FT-IR (KBr, ν, cm^{-1}): 3473, 3376 (NH_2), 3285, 3258, 3225 (NH), 1686, 1693 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.35 (s, 3H, CH_3), 7.28-7.79 (m, 10H, Ar), 6.12 (brs, 4H, NH_2, D_2O-exchangeable); 8.74 (brs, 2H, NH, D_2O-exchangeable), 9.25 (brs, 2H, NH, D_2O-exchangeable). ^{13}C NMR (75 *MHz*, DMSO-d_6, δ, ppm): 187.8, 185.6 (2CO), 166.3 (C-3), 156.9 (C-7a), 156.1 (2C-5 pyrazole), 153.3 (2C-3 pyrazole), 144.2 (2C-ArNH), 129.9-116.9 (Ar-C), 129.7 (C-5), 123.7 (C-6), 99.2 (2C-4 pyrazole), 17.1 (CH_3). MS (EI, *m/z* (%)): 539 (M^+). Anal. calcd. for $C_{25}H_{21}N_{11}O_2S$: C, 55.65; H, 3.92; N, 28.55; S, 5.94. Found: C, 55.61; H, 3.87; N, 28.59; S, 5.99%.

2.2.12. Synthesis of (5-methylthiazolo[2,3-c]-1,2,4-triazole-3,6-diyl)bis((3-amino-5-(phenylamino)-isoxazol-4-yl) methanone) **(18)**

A solution of **15** (10 mmol) in ethanol (30 mL) was treated with hydroxylamine hydrochloride (20 mmol) and sodium carbonate. The reaction mixture was heated under reflux 6 h, then left to cool. The reaction solid product was collected by filtration, washed with water several times, dried and finally recrystallized from DMF:H_2O (1:1, *v*:*v*) to afford of compound **18** (Scheme 5). Yield: 59%. M.p.: 308-309 °C. FT-IR (KBr, ν, cm^{-1}): 3445, 3351 (NH_2), 3331, 3241 (NH), 1689, 1682 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.35 (s, 3H, CH_3), 7.25-7.76 (m, 10H, Ar), 5.71 (brs, 4H, NH_2, D_2O-exchangeable); 9.29 (brs, 2H, NH, D_2O-exchangeable). MS (EI, *m/z* (%)): 541 (M^+). Anal. calcd. for $C_{25}H_{19}N_9O_4S$: C, 55.45; H, 3.54; N, 23.28; S, 5.92. Found: C, 55.40; H, 3.57; N, 23.22; S, 5.87%.

2.2.13. Synthesis of (5-methylthiazolo[2,3-c]-1,2,4-triazole-3,6-diyl)bis(1-(4-amino-1,2-dihydro-6-(phenylamino)-2-thioxopyrimidin-5-yl)methanone) **(19)**

A solution of compound **15** (10 mmol) in EtOH (30 mL) containing Et_3N (1 mL) was treated with solution of thiourea (20 mmol) in ethanol (15 mL). The reaction mixture was heated under reflux 16 h, then the reaction was poured onto ice water. The solid product that for was filtered off, dried and finally recrystallized from DMF to afford of compound **19** (Scheme 5). Yield: 61%. M.p.: > 332 °C. FT-IR (KBr, ν, cm^{-1}): 3336, 3320 (NH_2), 3261, 3158, 3117 (NH), 1678 (C=O).



Scheme 5

^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.34 (s, 3H, CH_3), 7.28-7.75 (m, 10H, Ar), 5.37 (brs, 4H, NH_2, D_2O-exchangeable); 8.89 (brs, 2H, NH, D_2O-exchangeable), 9.74 (brs, 2H, NH, D_2O-exchangeable). MS (EI, *m/z* (%)): 627 (M^+). Anal. calcd. for $C_{27}H_{21}N_{11}O_2S_3$: C, 51.66; H, 3.37; N, 24.54; S, 15.32. Found: C, 51.70; H, 3.34; N, 24.58; S, 15.28%.

3. Results and discussion

It has been found that a buffered solution of 5-acetyl-2-amino-4-methylthiazole diazonium sulfate (**1**) couple smoothly and in moderate yield with 3-chloropentane-2,4-dione (**2**) followed by Japp-Klingemann rearrangement to afford the corresponding hydrazine, (**3**) [37,38]. The structure of the latter product was established on the basis of its elemental analyses and spectral data. Its ^{1}H NMR spectrum revealed D_2O-exchangeable broad singlet signal at δ 9.88 ppm assignable to hydrazone NH proton. The absence of any other CH signal in the ^{1}H NMR spectrum of compound **3** excludes the presence of the azo tautomer (**4**).

Compound **3** undergoes a facile intramolecular cyclisation to the corresponding 3,6-diacetyl-5-methylthiazolo[2,3-*c*]-1,2,4-triazole (**5**) upon refluxing in pyridine via loss of hydrogen chloride [37,38] (Scheme 1). The product **5** gave analytical and spectral data consist with its assigned structure. Its IR spectra showed the disappearance of NH absorption and revealed absorption bands at 1687 and 1698 cm^{-1} assignable to two carbonyl groups. Its ^{1}H NMR spectrum revealed two singlet signals at δ 2.62 and 2.71 ppm assignable to two acetyl protons, respectively.

Bormination of compound **5** afforded 1,1'-(5-methyl thiazolo[2,3-*c*]-1,2,4-triazole-3,6-diyl)*bis*((2-bromo)ethanone) (**6**). The structure of compound **6** was established on the basis of elemental and spectral data. Its IR showed absorption bands at 1684 and 1692 cm^{-1} for two carbonyl groups. The ^{1}H NMR spectrum revealed absorption bands at δ 4.29 and 4.38 ppm assignable to methylene protons.

Treatment of compound **6** with ethanolic potassium cyanide solution furnished 3,3'-(5-methylthiazolo[2,3-*c*]-1,2,4-triazole-3,6-diyl)*bis*(3-oxopropanenitrile) (**7**). Its IR spectrum revealed absorption bands at 2213 and 2223 cm^{-1} for two cyano functions and absorption bands at 1689 and 1696 cm^{-1} for two carbonyl groups. Its ^{1}H NMR spectrum revealed two singlet signals at δ 4.50 and 4.59 ppm assignable to methylene protons (Scheme 2).

The ketene *S,S*-dithioacetals (**8**) was prepared by the reaction of 3,3'-(5-methylthiazolo[2,3-*c*]-1,2,4-triazole-3,6-diyl) *bis*(3-oxopropanenitrile) **7** with sodium hydride and carbon disulfide followed by alkylation with methyl iodide afforded 3,3'-(5-methylthiazolo[2,3-*c*]-1,2,4-triazole-3,6-diyl)*bis*(2-(*bis* (methylthio)methylene)-3-oxopropanenitrile), **8**.

The structure of compound **8** was elucidated on the basis of its elemental analysis and spectral data. The IR spectrum showed the appearance of absorption bands at 2216, 2220 cm^{-1} and 1692, 1683 cm^{-1} for cyano and carbonyl functions, respectively. Its ^{1}H NMR spectrum revealed two singlet signals at δ 2.63 and 2.79 ppm assignable to methyl protons while the singlet signal for the methylene protons of compound **7** was disappeared.

Reaction of compound **8** with hydrazine hydrate gave (5-methyl-thiazolo[2,3-*c*]-1,2,4-triazole-3,6-diyl)*bis*(3-amino-5-(methylthio)-1*H*-pyrazol-4-yl)methanone, (**10**). The structure of compound **10** was elucidated on the basis of the elemental analysis and spectral data. The IR spectrum displayed stretching absorption bands at 3421 and 3356 cm^{-1} due to the two formed NH_2 and two NH functions at 3291 and 3228 cm^{-1}, while carbonyl absorption band appeared at 1685 and 1692 cm^{-1}. Its ^{1}H NMR spectrum revealed two signals at δ 2.61 and 2.72 ppm assigned for SCH_3 protons, in addition to D_2O-exchangeable signals at δ 5.93 and 8.36 ppm due to NH_2 and NH protons, respectively (Scheme 3).

Reaction of compound **7** with carbon disulfide in DMF containing potassium hydroxide followed by addition of chloroacetyl chloride afforded 3,3'-(5-methylthiazolo[2,3-*c*]-1,2,4-triazole-3,6-diyl)*bis*(2-(4-oxo-1,3-dithiolan-2-ylidene)-3-oxopropanenitrile, (**11**). The IR spectrum of compound **11** displayed absorption bands for CN at 2196, 2202 cm^{-1} and at 1716, 1698, 1668 cm^{-1} for carbonyl functions. Its ^{1}H NMR

spectrum displayed singlet signal at δ 3.63 ppm assignable for the newly methylene protons.

The active methylene group in 3,3'-(5-methylthiazolo[2,3-*c*]-1,2,4-triazole-3,6-diyl)*bis*(2-(4-oxo-1,3-dithiolan-2-ylidene)-3-oxopropanenitrile **11** coupled smoothly with benzene diazonium salt yielded 3,3'-(5-methylthiazolo[2,3-*c*]-1,2,4-triazole-3,6-diyl)*bis*(2-(4-oxo-(5-phenylhydrazono)-1,3-dithiolan-2-ylidene)-3-oxopropanenitrile, (**12**). The structure of compound **12** was elucidated on the basis of spectral data. The IR spectrum showed absorption bands at 3317, 3237 cm^{-1} due to NH, at 2221, 2235 cm^{-1} due to CN and at 1698, 1684, 1668 cm^{-1} due to carbonyl functions. Its ^1H NMR spectrum showed the absence of a singlet signal assignable for methylene protons, while showed a new signal at δ 11.91 ppm for hydrazo protons.

The nucleophilic addition of 3,3'-(5-methylthiazolo[2,3-*c*]-1,2,4-triazole-3,6-diyl)*bis*(3-oxopropanenitrile) **7** to phenyl isothiocayante in DMF in the presence of KOH afforded the corresponding potassium salt, (**13**). Heterocyclization of the intermediate **13** with an equimolar amount of the phenacyl bromide furnished one isolable product. The reaction product was identified as 4,4'-(5-methylthiazolo[2,3-*c*]-1,2,4-triazole-3,6-diyl)*bis*(5-benzoyl-2-(phenylamino)thiophene-3-carbonitrile), (**15**). Its IR displayed absorption bands at 3298, 3218 due to NH function and absorption bands at 2218, 2224 cm^{-1} due to CN. Its ^1H NMR spectrum showed singlet signal at δ 10.93 ppm D_2O-exchangeable peak due to two NH protons, in addition to an aromatic multiplet in the region δ 7.21-7.83 ppm. The aforementioned results indicate that the reaction of the intermediate **13** with phenacyl bromide proceed via loss of two water molecules from the non-isolable intermediate **14** (Scheme 4).

Polarized cyanoketene *N,S*-acetal are versatile starting materials for the synthesis of a wide variety of fused heterocycles [39]. So, further reaction of compound **7** with phenyl isothiocyanate in DMF containing KOH followed by addition of methyl iodide to afford 2,2'-(5-methylthiazolo[2,3-c][1,2,4]triazole-3,6-dicarbonyl)*bis*(3-(methylthio)-3-(phenylamino)acrylonitrile), (**16**).

The assignment of the structure **16** was based on elemental analysis and spectral data. Its IR spectrum showed absorption bands at 3392 and 3268 cm^{-1} for NH functions, absorption band at 2198, 2223 cm^{-1} for nitrile groups and two strong absorption bands at 1694 and 1698 cm^{-1} for two carbonyl groups. Its ^1H NMR spectrum displayed no signal for methylene protons, while a strong singlet signal at δ 2.83 and 2.89 ppm for two methylthio protons and a broad signal at δ 9.87 ppm were appeared for NH protons.

Compound **16** was utilized as a starting material for the preparation of wide variety of fused heterocyclic compounds by reaction with bifunctional nucleophilic reagents. Refluxing of **16** with hydrazine hydrate afforded (5-methylthiazolo[2,3-*c*]-1,2,4-triazole-3,6-diyl) *bis*((3-amino-5-(phenylamino)-1*H*-pyrazol-4-yl)methanone), (**17**). The structure of compound **17** was elucidated on the basis of the elemental analysis and spectral data.

Refluxing of compound **16** with hydroxyl amine hydrochloride in ethanolic sodium carbonate afforded (5-methylthiazolo[2,3-*c*]-1,2,4-triazole-3,6-diyl) *bis*((3-amino-5-(phenyl-amino)isoxazole-4-yl)methanone), (**18**). The structure of compound **18** was elucidated on the basis of the elemental analysis and spectral data. The IR spectrum displayed stretching absorption bands at 3445, 3351 cm^{-1} due to the formed amino groups and absorption bands for NH functions at 3331, 3241 cm^{-1}, while carbonyl absorption band appeared at 1682 cm^{-1}

Treatment of compound **16** with thiourea in ethanol containing catalytic amount of triethylamine as a basic catalyst afforded the (5-methylthiazolo[2,3-*c*]-1,2,4-triazole-3,6-diyl)*bis*(1-(4-amino-1,2-dihydro-6-(phenylamino)-2-thioxopyrimidin-5-yl)methanone), (**19**). The structure of compound **19** was elucidated on the basis of the elemental analysis and spectral data. Its ^1H NMR spectrum exhibited appearance of a broad signal at δ 5.37 ppm assignable for two newly formed amino protons, a broad signal at δ 8.89 ppm and δ 9.74 ppm for NH and NH protons, respectively, in addition to an aromatic multiplet in the region δ 7.28-7.75 ppm (Scheme 5).

4. Conclusion

A series of novel thiazolo[2,3-c]-1,2,4-triazole were prepared with good to moderate yields could be considered as good candidates for future research to develop high potency anti-inflammatory agents.

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