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Synthesis and spectral characterization of some new thiazolopyrimidine derivatives

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Thiazolopyrimidnes are considered one of the most interesting classes in heterocyclic chemistry due to their pharmaceutical importance. Herein, we report the synthesis of some new heterocyclic compounds containing thiazolopyrimidine starting from compound (1) which was previously prepared in literature. The starting compound was allowed to react with different alkylating agents such as chloroacetone, chloroacetyl chloride, and phenacyl bromide to afford derivatives (2-4). Compound (5), benzylidene derivative, was obtained by the reaction of compound (2) with benzaldehyde while amino-dicarbonitrile compound (6) can be obtained by the reaction of compound (5) and malononitrile. Acetylation of amino group in compound (6) with chloroacetyl chloride led to formation of compound (7). Nucleophilic substitution of chlorine in compound (7) by aniline gave compound (8) which further subjected the Munich reaction to form compound (9). All new synthesized compounds were characterized using different elemental and spectral analysis.

1. Introduction

Fused pyrimidines continue to attract considerable attention of researchers in different countries because of their great practical usefulness, primarily, due to a very wide spectrum of their biological activities.[1-3] Thiazolopyrimidine is one of the most interesting heterocyclic scaffolds possessing structural similarity to 5-fluorouracil (5-FU)-the well-known cancer metabolite. In addition, they have been reported to possess various important potent activities such as antimicrobial, antipsychotic, anti-inflammatory, anti-Parkinson's, analgesic, antidepressant, anti-HIV, and anticancer activities.[4-12] Besides, thiazolopyrimidine have been known with their bioactivities as transient receptor potential vanilloid–receptor 1 (TRPV1) modulators,[13,14] antioxidants,[15,16] pesticides,[17] phosphate inhibitors,[18,19] acetylcholinesterase inhibitors,[20,21] and antimicrobial activities.[22-24] Accordingly, and in continuation of our ongoing interest regarding the synthesis of biologically active molecules containing nitrogen and

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sulphur heteroatom,[25-51] we report here a convenient and efficient method for the synthesis of several novel derivatives including pyrimidine building block.

2. Results and Discussion

As shown in **Fig. 1**, in the alkylation of compound 1, which prepared according to reported procedure,[52] with different alkylating agents such as chloroacetyl chloride, chloroacetone and phenacyl bromide, the alkylation of mercapto group was occurred to produce the *S*-alkylated products **2-4**. The structure of the new obtained compounds was confirmed by the elemental and spectral analysis where the IR spectrum of compound **2** showed two C=O groups 1663, 1655 cm^{-1} while the ^1H NMR spectrum showed singlet signal at 4.37 ppm characteristic for CH_2 group. In addition, the ^1H NMR spectrum of compound **4** showed multiplet signals at **7-8** ppm, which proved the introduction of additional phenyl rings.

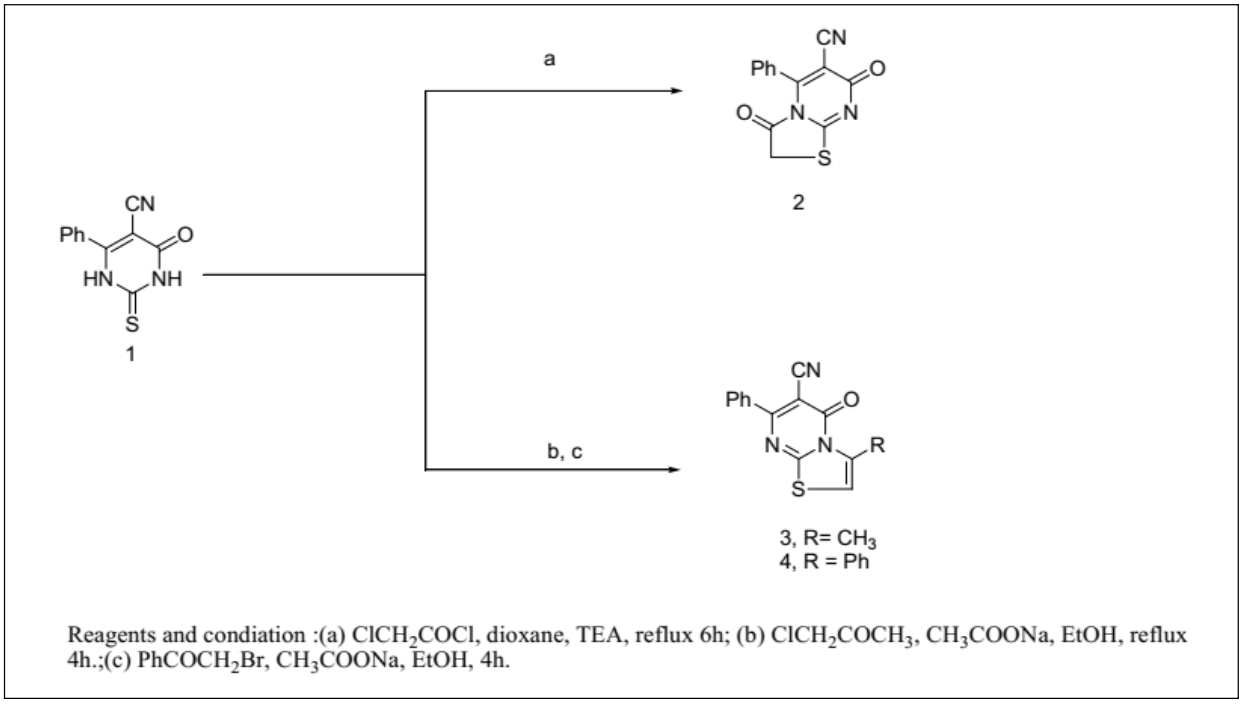

Fig. 1. Synthesis of compounds **2**-**4**.

As shown in **Fig. 2**, condensation of compound **2** with benzaldehyde gave a cyclic chalcone derivative **5** which in turn reacted with malononitrile to give the amino-dicarbonitrile compound **6**. After that, acetylation of the amino group in compound **6** with chloroacetyl chloride led to the formation of 2-Chloro-N-(3,8-dicyano-7-oxo-4,9-diphenyl-5a,6-dihydro-4H,7H-pyrano[2',3':4,5]thiazolo[3,2-a]pyrimidin-2-yl)acetamide compound (**7**). When the latter compound was allowed to react with aniline, nucleophilic substitution occurred to produce compound **8**, which reacted with formaldehyde under Munich condition to give compound **9**. The structure of the obtained compounds was easily confirmed by the spectral analysis where the ^1H NMR spectrum of compound **5** showed two singlet signals at 3.88 and 5.93 ppm characteristic for CH=CH protons as well as increasing the aromatic protons by 5H. Also, the IR spectrum of compound **6** showed the appearance of two bands at 3321, 3245 cm^{-1} characteristics for amino groups whereas the ^1H NMR spectrum exhibited singlet signal at 6.64 ppm characteristics for NH_2 group. Finally, the structure of Munich product **9** was proved by the spectral analysis, where its ^1H NMR spectrum showed two singlet signals at 4.22 and 4.56 ppm characteristics for 2 CH_2 groups.

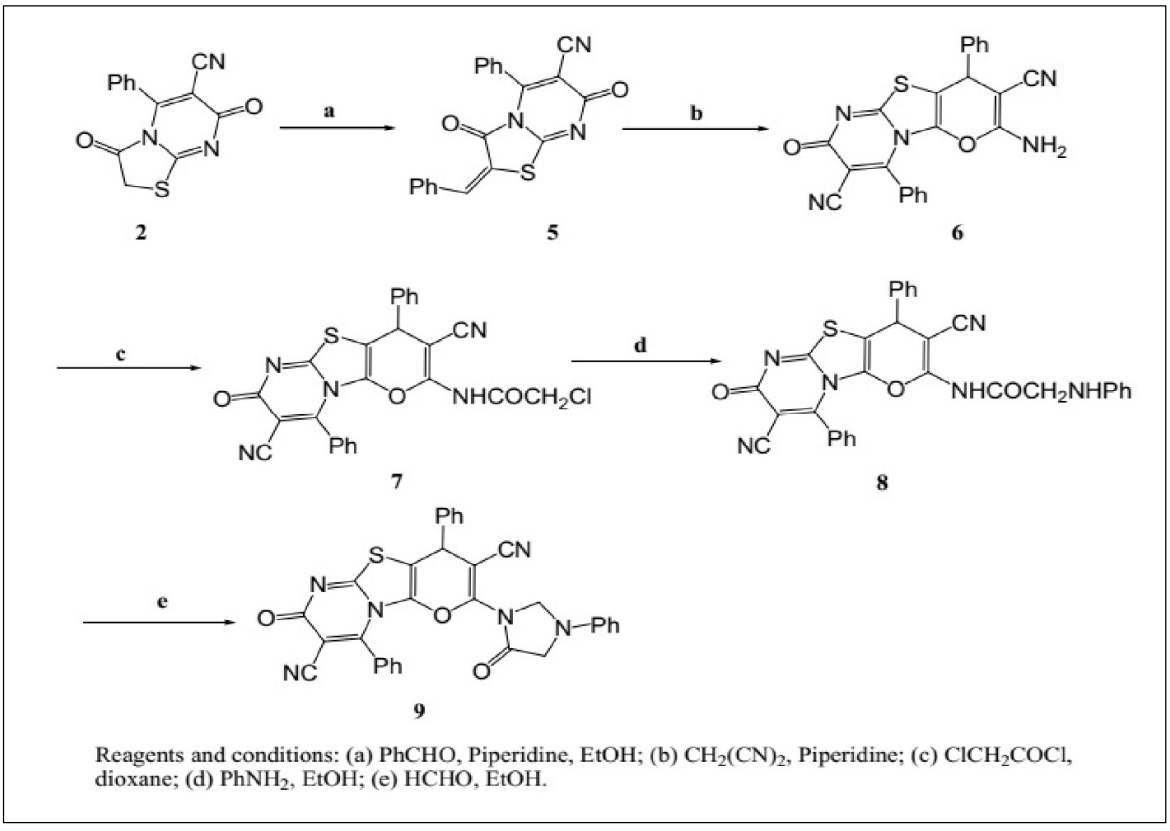

Fig. 2. Synthesis of compounds **5-9**

3. Conclusion

In the present work, we introduced a synthetic route for the synthesis of some new heterocyclic compounds containing thiazolopyrimidine moiety. Since, the compound 4-oxo-6-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (**1**) was prepared according to the reported procedure and used as a precursor for synthesizing the target compounds. In addition, all the synthesized compounds were characterized using spectroscopic data and elemental analyses.

4. Experimental

4.1 Materials and methods

All melting points are uncorrected and measured on a Fisher-John apparatus. Elemental analysis was determined on an elementar analysensysteme GmbH - vario EL III elemental analyzer in the central lab of Assiut University. Their results were found to be in good agreement (±0.2%) with the calculated values. IR spectra were recorded on a Pye-Unicam Sp-100 spectrophotometer using KBr wafer technique. ^{1}H NMR spectra were obtained on BRUKER 400 MHz spectrometers in a suitable deuterated solvent using tetramethylsilane as an internal standard (chemical shifts in ppm), otherwise stated. Mass spectra were obtained on JEOL JMS-600 apparatus. Preparative and analytical TLC were carried out on silica gel plates (Fluka 70643-50EA. SIGMA-ALDRICH, Germany) using UV light All reactions were carried out under an air atmosphere. 4-oxo-6-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (**1**) was prepared according to the reported procedure.[52]

4.2 Synthetic procedure for 3,7-Dioxo-5-phenyl-2,3-dihydro-7H-thiazolo[3,2-a]pyrimidine-6-carbonitrile (2).

To a solution of compound (1) (0.75 g, 3 mmol) in dioxane (10 mL) containing triethyl amine (0.3 mL, 3 mmol), chloroacetyl chloride (0.38 mL, 3 mmol) was added in small portions with continuous cooling and stirring, the mixture was heated at reflux in a water bath for 6 h. The solid obtained was filtered off and recrystallized from benzene as orange crystals in 66 % yield, m.p.268-270 ºC. FT-IR (KBr), υ (cm^{-1}), 3040 (CH aromatic) 1663, 1655 (2C=O), 2204 (CN). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 4.37 (s, 2H, CH_2), 8.55 (m, 5H, Ar-H). Elemental Analysis Calculated for $C_{13}H_7N_3O_2S$ (%) C, 57.99; H, 2.62; N, 15.61; S, 11.91. Found (%): C, 57.77; H, 2.70; N, 15.57; S, 11.88.

4.3 Synthetic procedure for 3-Methyl-5-oxo-7-phenyl-5H-thiazolo[3,2-a]pyrimidine-6-carbonitrile (3).

A mixture of compound (1) (0.50g, 2 mmol), chloroacetone (0.2 ml, 2mmol) and fused sodium acetate (0.49g, 5mmol) were added to ethanol, the resultant mixture was heated at reflux for 4h. the sodium salt obtained after cooling was filtered off and dissolved in water then neutralized with HCl to give reddish brown precipitate then filtered off, dried and recrystallized from ethanol: dioxane mixture (1:1) as pale brown crystals in 72 % yield, m.p.302-304 ºC. FT-IR (KBr), υ (cm^{-1}): 3056 (CH aromatic), 2936 (CH aliphatic), 1655 (C=O), 2207 (CN). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.67 (s, 3H, CH_3), 6.73 (s, 1H, CH), 7.16-8.45 (m, 5H, Ar-H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 16.35, 104.66, 111.75, 118.76, 124.63, 127.67, 128.56, 134.45, 143.55, 156.67, 160.32, 165.34. Elemental Analysis Calculated for $C_{14}H_9N_3OS$ (%) C, 62.91; H, 3.39; N, 15.72; S, 11.99 % Found (%) C, 62.87; H, 3.35; N, 15.76; S, 11.96.

4.4 Synthetic procedure for 5-Oxo-3,7-diphenyl-5H-thiazolo[3,2-a]pyrimidine-6-carbonitrile (4).

A mixture of compound (1) (0.50 g, 2 mmol), phenacyl bromide (0.4 g, 2 mmol) and fused sodium acetate (0.4 g, 5 mmol) were added to ethanol, the resultant mixture was refluxed for 4 h. The reaction mixture was cooled and poured into water solution. The solid obtained after neutralization with HCl was filtered off, dried and crystallized from ethanol:dioxane (2:1) as pale yellow crystals in 88% yield, m.p.322-324ºC. FT-IR (KBr), υ (cm^{-1}): 3045 (CH aromatic), 1664 (C=O), 2213 (CN). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 6.65 (s, 1H, CH), 7.15-8.67 (m, 10H, Ar-H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 102.34, 109.63, 117.23, 126.55, 127.16, 127.96, 128.45, 128.87, 129.17, 129.46, 129.68, 137.65, 143.31, 158.56 165.4,168.66. Elemental Analysis Calculated for $C_{19}H_{11}N_3OS$ (%) C, 69.29; H, 3.37; N, 12.76; S, 9.73 % Found (%) C, 69.33; H, 3.34; N, 12.72; S, 9.76.

4.5 Synthetic procedure for (E)-2-Benzylidene-3,7-dioxo-5-phenyl-2,3-dihydro-7H-thiazolo[3,2-a]pyrimidine-6-carbonitrile (5).

A mixture of compound (2) (0.50 g, 1.8 mmol), benzaldehyde (2 mmol) and piperidine (2 mL) were added to ethanol, the resultant mixture was refluxed for 5 h, The solid obtained during heating was collected, filtered off, dried and crystallized from ethanol: dioxane (2:1) as yellow crystals in 74% yield, m.p.277-279 ºC. FT-IR (KBr), υ (cm^{-1}): 3042 (CH aromatic), 1678 (C=O), 1664 (C=O), 2213 (CN). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 7.16-8.68 (m, 10 H, Ar-H), 9.45 (s, 1H, CH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 79.65, 83.81, 116.74, 123.87, 127.98, 128.16, 128.56, 128.98, 129.65, 129.87, 131.13, 132.76, 136.45, 138.78, 158.15, 164.18, 168.32. Elemental Analysis Calculated for $C_{20}H_{11}N_3O_2S$ (%) C, 67.22; H, 3.10; N, 11.76; S, 8.97 Found (%): C, 67.31; H, 3.01; N, 11.64; S, 9.02.

4.6 Synthetic procedure for 2-Amino-7-oxo-4,9-diphenyl-4H,7H-pyrano[2',3':4,5]thiazolo[3,2-a]pyrimidine-3,8-dicarbonitrile (6).

A mixture of compound (5) (0.45 g, 1.25 mmol), malononitrile (0.3 g, 4.54 mmol) and piperidine (1 mL) were added to ethanol, the resultant mixture was heated under reflux for 3 h. The solid obtained after cooling was collected, filtered off, dried and crystallized from dioxane brown crystals in 46 % yield, m.p.302-304 ºC. FT-IR (KBr), υ (cm^{-1}): 3321, 3245 (NH_2, NH), 3052 (CH aromatic), 1669 (C=O), 2213, 2204 (2CN). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 5.93 (s, 1H, CH), 6.64 (s, 2H, NH_2), 7.12-8.89 (m, 10 H, Ar-H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 72.55, 77.78, 85.45, 89.49,

117.57, 118.22, 123.26, 124.55, 128.01, 128.45, 128.98, 129,44, 129.67, 129.81, 130.15, 132,55, 136,23, 141.32, 148.45, 157,56, 165,33. Elemental Analysis Calculated for $C_{23}H_{13}N_5O_2S$ (%) C, 65.24; H, 3.09; N, 16.54; S, 7.57 Found (%): C, 65.32; H, 2.99; N, 16.62; S, 7.43.

4.7 Synthetic procedure for 2-Chloro-N-(3,8-dicyano-7-oxo-4,9-diphenyl-4H,7H-pyrano[2',3':4,5]thiazolo[3,2-a]pyrimidin-2-yl)acetamide (7).

A mixture compound 6 (0.75 g, 1.7 mmol), and chloroacetylchloride (0.45 mL, 3.9 mmol) in dioxane (20 mL) was heated on steam bath for 3 hours. After cooling, the mixture was poured onto water and neutralized with diluted sodium carbonate solution The solid thus formed was filtered, washed with water, dried and recrystallized from ethanol-water (2:1) to afford reddish brown crystals in 56% yield; m.p. 268–270°C. FT-IR (KBr), υ (cm^{-1}): 3250 (2NH), 3055 (C-H aromatic), 2925, 2866 (C-H aliphatic), 2214, 2204 (2CN), 1668, 1678 (2CO amidic). ^{1}H NMR (300 MHz, DMSO-d_6): 4.27 (s, 2H, CH_2), 5.88 (s, 1H, CH), 7.14-8.76 (m, 10 H, Ar-H), 9.43 (s, 1H, NH). Elemental Analysis Calculated for $C_{25}H_{14}ClN_5O_3S$ (%) C, 60.06; H, 2.82; N, 14.01; S, 6.41 Found (%): C, 60.11; H, 2.90; N, 14.01; S, 6.21.

4.8 Synthetic procedure for N-(3,8-Dicyano-7-oxo-4,9-diphenyl-4H,7H-pyrano[2',3':4,5]thiazolo[3,2-a]pyrimidin-2-yl)-2-(phenylamino)acetamide (8).

A mixture of chloroacetamide derivative 7 (0.5 g, 0.99 mmol) and aniline (2 mmol) was dissolved in 20 mL ethanol and refluxed for 3 h. The solid precipitate, which was formed, filtered off, dried and recrystallized from ethanol-water (2:1) to give pale brown needles in 46% yield; m.p. 315-317 ºC. FT-IR (KBr), υ (cm^{-1}): 3265, 3167 (2NH), 3053 (C-H aromatic), 2913, 2834 (C-H aliphatic), 2217, 2203 (2CN), 1666, 1679 (2CO amidic). ^{1}H NMR (300 MHz, DMSO-d_6): 4.27 (s, 2H, CH_2), 5.11 (s, 1H, NH), 5.88 (s, 1H, CH), 7.16-8.87 (m, 15 H, Ar-H), 8.55 (s, 1H, NH). Elemental Analysis Calculated for $C_{31}H_{20}N_6O_3S$ (%) C, 66.90; H, 3.62; N, 15.10; S, 5.76. Found (%): C, 66.95; H, 3.54; N, 15.14; S, 5.73.

4.9 Synthetic procedure for 7-Oxo-2-(5-oxo-3-phenylimidazolidin-1-yl)-4,9-diphenyl-4H,7H-pyrano[2',3':4,5]thiazolo[3,2-a]pyrimidine-3,8-dicarbonitrile (9).

To a solution of compounds 8 (0.25 g, 0.44 mmol) in ethanol (10 ml) a few drops of formaldehyde (1.2 mL) was added. The solution was refluxed for 4 hrs. The solid obtained on hot, filtered off, dried and recrystallized from ethanol: dioxane (2:1) to give brown precipitate in 52% yield; m.p. 342-344 ºC. FT-IR (KBr), υ (cm^{-1}): 3265 (NH), 3054 (C-H aromatic), 2977 (C-H aliphatic), 2213, 2205 (2CN), 1663, 1671 (CO amidic). ^{1}H NMR (300 MHz, DMSO-d6): 4.22 (s, 2H, CH_2), 4.56 (s, 2H, CH_2), 6.01 (s, 1H, CH), 7.12-8.76 (m, 15 H, Ar-H). Elemental Analysis Calculated for $C_{32}H_{20}N_6O_3S$ (%) C, 67.59; H, 3.55; N, 14.78; S, 5.64. Found (%): C, 67.65; H, 3.45; N, 14.85; S, 5.57.

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