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Synthesis of some New Tetracyclic Pyrimidine Derivatives Using Exocyclic α,β-unsaturated Ketone and Evaluation of their Antitumor Activities

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ABSTRACT

Thiazolopyrimidine **2** was obtained from the reaction of dihydropyrimidinone with chloroacetic acid and benzaldehyde. Thiazolopyrimidine **2** containing an α,β-unsaturated ketonic function [-CH=CH-CO-] has been used as a component of Michael addition with an equimolar amount of dinucleophiles to give a series of novel tetracyclic pyrimidine derivatives. Treatment of thiazolopyrimidine **2** with uracil, aminotriazole, cyanoacetic acid hydrazide, *o*-phenylenediamine or diaminopyridine afforded the corresponding pyridopyrimidine, triazolopyrimidine, pyrazolone, benzodiazepine and triazepine derivative, respectively. The detailed synthesis, spectroscopic data, and antitumor activity for synthesized compounds were reported.

Indexing terms/Keywords

Thiazolopyrimidine; Michael addition; uracil; annulation; dinucleophiles; benzodiazepine; triazepine; antitumor activity.

Academic Discipline And Sub-Disciplines

Organic chemistry

SUBJECT CLASSIFICATION

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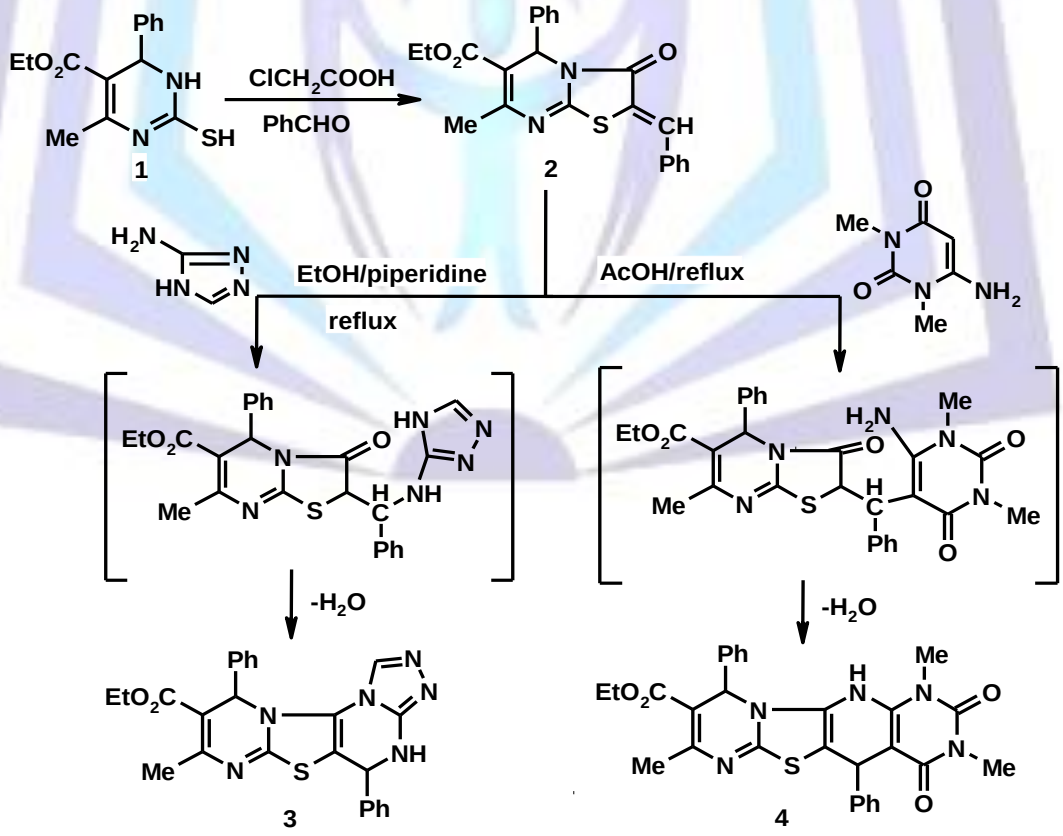
INTRODUCTION

α,β-Unsaturated ketones are versatile and convenient intermediates for the synthesis of a wide variety of heterocyclic compounds. The α,β-enone moiety of the molecule is a favorable unit for dipolar cycloaddition with numerous reagents providing heterocyclic compounds of different ring sizes with one or several heteroatoms. Their reactions with dinucleophiles usually result in the formation of polycyclic ring systems which may be the skeleton of important heterocyclic compounds [1-5]. Moreover, dihydropyrimidinones **1** (DHPMs, Biginelli compounds) appear to be a class of privileged organic compounds with medicinal significance due to their different biological and therapeutic activities [6]. In view of these reports and in continuation of our work on biologically active nitrogen and sulfur heterocycles [7-10], we have synthesized some new pyrimidine derivatives and tested their antitumor activity.

RESULTS AND DISCUSSION

In the present work we report the synthesis of several thiazolopyrimidine derivatives based on ethyl 2-benzylidene-7-methyl-3-oxo-5-phenyl-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (**2**) [11], which was prepared from ethyl 2-mercaprto-4-methyl-6-phenyl-1,6-dihydropyrimidine-5-carboxylate (**1**) [12], as starting material. Reaction of arylidene derivative **2** with aminotriazole as potential precursor for the synthesis of tetacyclic system was investigated. Thus, compound **2** was refluxed with aminotriazole in ethanol containing a catalytic amount of piperidine to afford the corresponding triazole derivative **3**. The formation of compound **3** is assumed to take place *via* a Michael type addition of NH_2 function group of triazole to the activated ethylenic double bond [13], of compound **2** to form the non-isolable intermediate which readily undergo intramolecular cyclization followed by loss of water molecule to form the target compound **3** (Scheme 1).

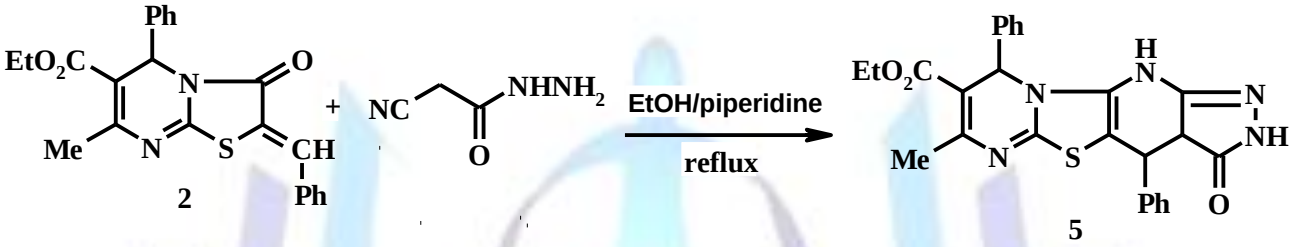
Further, annulation of compound **2** with an uracil moiety fused to C^2-C^3 of the pyridine ring was achieved, through alkylation of 6-amino-1,3-dimethyluracil with thiazolopyrimidine **2**. The problem of C and *N*-alkylation of enamines has been investigated by Troschutz et al. [14], who revealed that the β-carbon center is more nucleophilic than the amino group. No attention has been paid to the similar reaction with 6-amino-1,3-dimethyluracil, which can be used as a key intermediate for the building of a pyridopyrimidine moiety fused with the thiazolopyrimidine system. Thus, reaction of compound **2** with 6-amino-1,3-dimethyluracil in presence of glacial acetic acid gave the adduct **4**, through formation of the nonisolable intermediate which underwent intramolecular cyclization through elimination of water molecule to afford the final product **4** (Scheme 1).



Scheme 1. Synthetic pathway for the formation of triazole 3 and pyridine 4.

The ^{1}H NMR spectrum of compound **3** revealed a triplet signal at *δ* 1.07 ppm (*J* 6.9 Hz) due to CH_3 protons, a quartet signal at *δ* 4.02 ppm (*J* 6.9 Hz) due to CH_2 protons, two signals at *δ* 5.75 and 6.04 due to CH-9, CH-4 protons, respectively. It showed also D_2O-exchangeable signal at *δ* 7.61 ppm corresponding to NH proton, in addition to an aromatic multiplet in the region 7.28-7.78 ppm. The mass spectrum of compound **3** showed the molecular ion peak at m/z 470 which is coincident with the molecular weight (470.54) as supports the identity of the structure. While, the ^{1}H NMR spectrum of compound **4** showed signals at *δ* 2.28, 3.36 and 3.54 ppm assigned to the three CH_3 groups. It showed also D_2O-exchangeable signal at *δ* 12.33 ppm corresponding to NH proton, in addition to an aromatic multiplet in the region *δ* 6.87-8.12 ppm. The mass spectrum of compound **4** revealed the molecular ion peak at m/z 541 corresponding to the molecular formula $C_{29}H_{27}N_5O_4S$, which agree well with the molecular weight (541.62) and supports the identity of the structure.

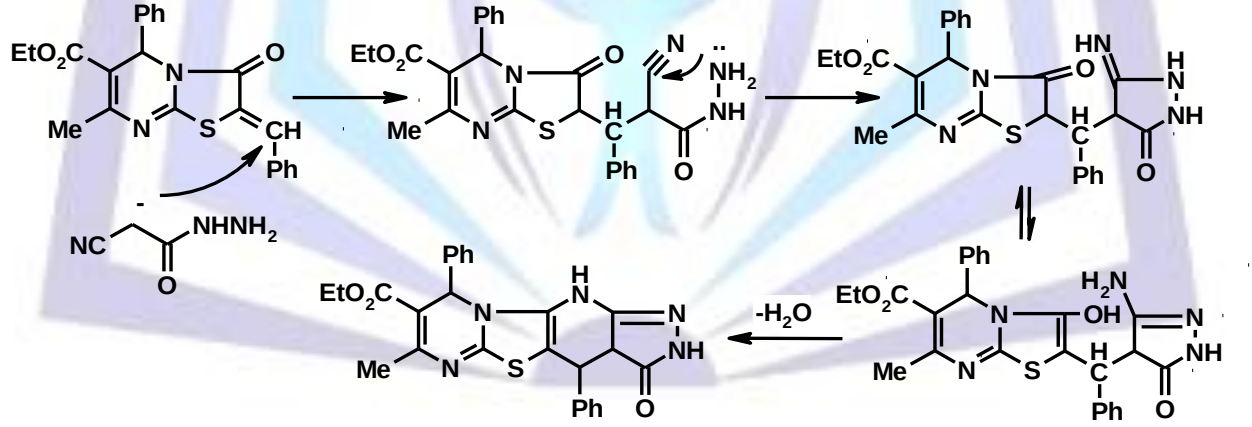
Furthermore, the reaction of α,β-unsaturated ketone with cyanoacetic acid hydrazide in the presence of a base gave pyrazolone derivative. Thus, reaction of compound **2** with cyanoacetic acid hydrazide in ethanol containing a catalytic amount of piperidine gave pyrazolone derivative **5** (Scheme 2).



2 5

Scheme 2. Synthetic pathway for the formation of pyrazolone 5.

The mechanism of formation of pyrazolone **5** involves a cyclocondensation reaction, which is depict in Scheme 3. The reaction proceeds by a Michael addition/elimination on the β-carbon atom of the enone [15], by the more nucleophilic function of the cyanoacetic acid hydrazide [16]. The intermediate formed undergoes cyclization by the addition of NH_2 function to the cyano group to provide enaminoketone intermediate which followed by loss of water molecule to form the target compound **5**.



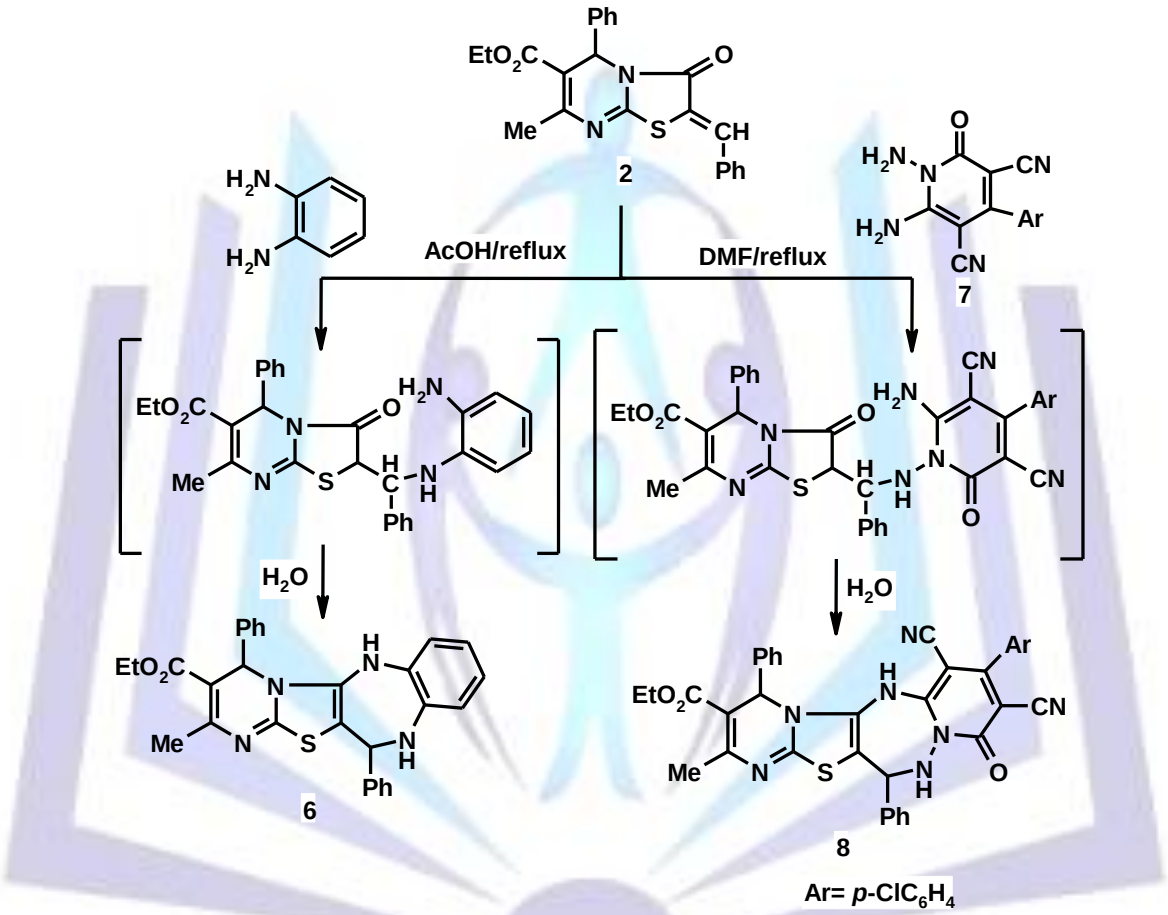
5

Scheme 3. The proposed mechanism for the formation of pyrazolone 5.

The IR spectrum of compound **5** revealed absorption bands at 1711 and 1680 cm^{-1} corresponding to two C=O groups. Its ^{1}H NMR spectrum revealed a triplet signal at *δ* 1.12 ppm (*J* 7.2 Hz) due to CH_3 protons, a quartet signal at *δ* 4.08 ppm (*J* 7.2 Hz) due to CH_2 protons. It showed also two D_2O-exchangeable signals at *δ* 9.70 and 10.35 ppm assigned to two NH protons, in addition to an aromatic multiplet in the region 6.82-7.63 ppm. The mass spectrum of compound **5** showed the molecular ion peak at m/z 485 corresponding to the molecular formula $C_{26}H_{23}N_5O_3S$.

Moreover, the reaction of aromatic or heteroaromatic 1,2-diamines with α,β-unsaturated ketones is a useful method for the preparation of condensed 1,4-diazepine systems [17]. Thus, reaction of 1,2-diamines with α,β-unsaturated ketones gave different products depending on the experimental conditions. Thiazolopyrimidine **2** was reacted with *o*-phenylenediamine in refluxing glacial acetic acid affording the corresponding diazepine derivative **6**. Formation of compound **6** is believed to take place by the addition of the diamine on the ethylenic double bond of compound **2** followed by interamolecular condensation of the amino group with the carbonyl function affording compound **6** as the final product

(Scheme 4). Finally, the chalcone **2** was treated with 1,6-diamino-4-(4-chlorophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**7**) [18], in dimethylformamide to give triazepine **8**. Due to the presence of non-equivalent amino groups at the *ortho*-position, regioisomeric cyclization products could be expected. However, the formation of a single product was observed, possibly because of the electronic effect of the nitrogen atom which enhances the nucleophilicity of the amino group on N-1 [19]. Therefore, the reaction proceeds initially via a Michael type addition by the more nucleophilic amino group (*N*-NH_2) of pyridine **7** to the activated ethylenic double bond of compound **2** to form the non-isolable intermediate which followed by ring closure through loss of water molecule to produce the desired product **8** (Scheme 4). The structures of compounds **6** and **8** were determined from spectroscopic as well as elemental analytical data. The ^{1}H NMR spectrum of compound **6** revealed signals at *δ* 5.58 ppm due to CH-4 proton and two D_2O-exchangeable signals at 12.58 ppm corresponding to two NH protons, in addition to an aromatic multiplet in the region *δ* 7.00-7.85 ppm, while the ^{1}H NMR spectrum of compound **8** showed signals at *δ* 5.67 and 6.04 ppm due to CH-4, CH-13 protons, respectively. It showed also D_2O-exchangeable signal at *δ* 8.52 ppm corresponding to two NH protons, in addition to an aromatic multiplet in the region *δ* 7.29-7.79 ppm.



Scheme 4. Synthetic pathway for the formation of benzodiazepine 6 and triazepine 8.

Antitumor activity

The antitumor activity of the newly synthesized compounds was investigated against Ehrlich ascites carcinoma cells (EAC). The antitumor efficacy of the compounds against EAC cell lines was demonstrated compared to doxorubicin. The obtained results revealed that compounds **1** and **2** exhibited IC_{50} values less than the used standard drug (doxorubicin). Diazepine derivative **6** was declared active. Further, compound **3** shows promising cytotoxic effect against EAC cell lines. While, compounds **4**, **5**, and **8** were essentially inactive (Table 1).

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Table 1. Tumor cell growth inhibition expressed as inhibitory concentration IC_{50} (IC_{50} the molar concentration that inhibits tumor cell growth to 50%):

Compound No.	IC_{50} (µg mL^{-1})
1	38.8
2	28.1
3	48.1
4	–
5	–
6	45.2
8	–
Doxorubicin	39.5

EXPERIMENTAL PROCEDURE

Melting points are uncorrected and were recorded in open capillary tubes on a Stuart SMP3 melting point apparatus. Infrared spectra were recorded on FT-IR Bruker Vector 22 spectrophotometer using a KBr wafer technique. The ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ on Gemini spectrometer (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) and the chemical shift in δ downfield from TMS as an internal standard. Elemental microanalyses were performed at the Main Laboratories of the War Chemical. Mass spectra were obtained using gas chromatography GCMS qp-2010 plus and on a Schimadzu instrument mass spectrometer (70 eV) at the Cairo University Microanalytical Center. Ethyl 2-benzylidene-7-methyl-3-oxo-5-phenyl-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (**2**) [11], and ethyl 2-mercaprto-4-methyl-6-phenyl-1,6-dihydropyrimidine-5-carboxylate (**1**) [12], were prepared following the literature procedures.

Ethyl 4,9-diphenyl-7-methyl-4,9-dihydro-3*H*-[1,2,4]triazolo[3',4':2'',3'']pyrimido[4'',5'':4',5'][1,3]thiazolo[3,2-*a*] pyrimidine-8-carboxylate (3)

A mixture of compound **2** (0.404 g, 1 mmol) and 3-aminotriazole (0.084 g, 1 mmol) in EtOH (10 mL) and few drops of piperidine is refluxed for 6h. The solid thus obtained is filtered off and recrystallized from EtOH to give compound **3** as yellow crystals, yield 68%, mp 147-148 °C. IR spectrum (KBr) ν_{max}/cm^{-1}: 3040 ($CH_{arom.}$), 2990 ($CH_{aliph.}$), 1715 ($C{=}O_{ester}$); ^{1}H NMR spectrum (300 MHz, DMSO-d_6) *δ* 1.07 (t, 3H, *J* 6.9 Hz, $CH_2\mathit{CH_3}$), 2.20 (s, 3H, CH_3), 4.02 (q, 2H, *J* 6.9 Hz, $\mathit{CH_2}CH_3$), 5.75 (s, 1H, pyrimidine-H9), 6.04 (s, 1H, dihydropyrimidine-H4), 7.28-7.78 (m, 11H, Ar-H), 7.61 (s, 1H, D_2O-exchangeable, NH); MS *m/z* (%): 470 $[M]^+$ (9.3), 404 (36.3), 327 (100), 306 (16.1), 271 (40), 228 (35.3), 149 (52.5), 113 (41); Anal. Calc. for $C_{25}H_{22}N_6O_2S$ (470.54): C, 63.81; H, 4.71; N, 17.86; S, 6.81. Found: C, 63.80; H, 4.71; N, 17.88; S, 6.80%.

Ethyl 1,3-dimethyl-2,4-dioxo-5,10-diphenyl-8-methyl-2,3,4,5,10,12-hexahydro-1*H*-pyrimido[4',5':2'',3'']pyrido [6'',5'':4',5'][1,3]thiazolo[3,2-*a*]pyrimidne-9-carboxylate (4)

A solution of compound **2** (0.404 g, 1 mmol) and 6-aminouracil (0.155 g, 1 mmol) in glacial acetic acid (10 mL) is refluxed for 10 h. The reaction mixture is cooled, then poured into ice water and basified with ammonia solution. The solid obtained is filtered off and recrystallized from MeOH to give compound **4** as brown crystals, yield 72%, mp 156-157 °C. IR spectrum (KBr) ν_{max}/cm^{-1}: 3027 ($CH_{arom.}$), 2985 ($CH_{aliph.}$), 1715 ($C{=}O_{ester}$), 1700, 1691 ($C{=}O_{uracil}$); ^{1}H NMR spectrum (300 MHz, DMSO-d_6) *δ* 1.14 (t, 3H, *J* 7.2 Hz, $CH_2\mathit{CH_3}$), 2.28 (s, 3H, CH_3), 3.36 (s, 3H, CH_3), 3.54 (s, 3H, CH_3), 4.04 (q, 2H, *J* 7.2 Hz, $\mathit{CH_2}CH_3$), 5.24 (s, 1H, pyrimidine-H10), 6.05 (s, 1H, dihydropyridine-H5), 6.87-8.12 (m, 10H, Ar-H), 12.33 (s, 1H, D_2O-exchangeable, NH); MS *m/z* (%): 541 $[M]^+$ (1.7), 525 (41.9), 450 (100), 327 (85.2), 199 (52.9), 173 (54.6), 131 (92.8), 103 (70.8); Anal. Calc. for $C_{29}H_{27}N_5O_4S$ (541.62): C, 64.31; H, 5.02; N, 12.93; S, 5.92. Found: C, 64.32; H, 5.02; N, 12.94; S, 5.94%.

Ethyl 3-oxo-4,9-diphenyl-7-methyl-2,3a,4,9-tetrahydro-11*H*-pyrazolo[3',4':2'',3'']pyrido[5'',6'':5',4'][1,3]thiazolo[3,2-*a*] pyrimidine-8-carboxylate (5)

A mixture of compound **2** (0.404 g, 1 mmol) and cyanoacetic acid hydrazide (0.099 g, 1 mmol) in EtOH (10 mL) and few drops of piperidine is refluxed for 6h. The solid thus obtained is filtered off and recrystallized from MeOH to give compound **5** as brown crystals, yield 63%, mp 211-212 °C. IR spectrum (KBr) ν_{max}/cm^{-1}: 3200 (NH), 3030 ($CH_{arom.}$), 2970 ($CH_{aliph.}$), 1711 ($C{=}O_{ester}$), 1680 ($C{=}O_{pyrazolone}$); ^{1}H NMR spectrum (300 MHz, DMSO-d_6) *δ* 1.12 (t, 3H, *J* 7.2 Hz, $CH_2\mathit{CH_3}$), 2.28 (s, 3H, CH_3), 4.08 (q, 2H, *J* 7.2 Hz, $\mathit{CH_2}CH_3$), 5.16 (s, 1H, pyrimidine-H9), 5.50 (d, 1H, pyrazolone-H3a), 6.09 (d, 1H, dihydropyridine-H4), 6.82-7.63 (m, 10H, Ar-H), 9.70 (s, 1H, D_2O-exchangeable, pyrazolone-NH), 10.35 (s, 1H, D_2O-exchangeable, pyridine-NH); MS *m/z* (%): 485 $[M]^+$ (12.6), 396 (58.2), 307 (46.9), 233 (44), 221 (70.6), 207 (35.5), 167

(100), 87 (43.9); Anal. Calc. for $C_{26}H_{23}N_5O_3S$ (485.55): C, 64.31; H, 4.77; N, 14.42; S, 6.60. Found: C, 64.30; H, 4.77; N, 14.40; S, 6.62%.

Ethyl 4,12-diphenyl-2-methyl-4,6,11,12-tetrahydropyrimido[2',1':2,3][1,3]thiazolo[4,5-*b*][1,5]benzodiazepine-3-carboxylate (6)

A mixture of **2** (0.404 g, 1 mmol) and *o*-phenylenediamine (0.108 g, 1 mmol) is dissolved in glacial acetic acid (10 mL). The reaction mixture is heated at reflux for 10 h. After cooling, the reaction mixture is cooled and poured gradually onto crushed ice and basified with ammonia solution. The solid obtained is filtered off and recrystallized from MeOH to give compound **6** as brown crystals, yield 74%, mp 218-219 °C. IR spectrum (KBr) ν_{max}/cm^{-1}: 3196 (NH), 3050 ($CH_{arom.}$), 2982, 2937 ($CH_{aliph.}$), 1715 ($C{=}O_{ester}$); ^{1}H NMR spectrum (300 MHz, DMSO-d_6) δ 1.17 (t, 3H, *J* 6.3 Hz, $CH_2\mathit{CH_3}$), 2.28 (s, 3H, CH_3), 4.01 (q, 2H, *J* 6.3 Hz, $\mathit{CH_2}CH_3$), 5.58 (s, 1H, pyrimidine-H4), 6.05 (s, 1H, diazepine-H12), 7.00-7.85 (m, 14H, Ar-H), 12.58 (s, 2H, D_2O-exchangeable, 2NH); ^{13}C NMR spectrum (75 MHz, $CDCl_3$) δ 17.5, 39.9, 40.2 (aliphatic), 121.9, 123.5, 129.2, 129.9, 130.3, 131.6, 132.9, 144.6, 145.2 (aromatic), 167.8 (C=O); MS *m/z* (%): 495 $[M+1]^+$ (12.3), 494 $[M]^+$ (2.4), 460 (36.4), 292 (100), 259 (50.8), 162 (54.5), 103 (40.8), 77 (36); Anal. Calc. for $C_{29}H_{26}N_4O_2S$ (494.60): C, 70.42; H, 5.30; N, 11.33; S, 6.48. Found: C, 70.40; H, 5.30; N, 11.34; S, 6.46%.

Ethyl 8-(4-chlorophenyl)-7,9-dicyano-4,13-diphenyl-2-methyl-10-oxo-4,6,10,13-tetrahydro-12*H*-pyrido[1,2-*b*] pyrimido[2',1':2,3][1,3]thiazolo[4,5-*e*][1,2,4]triazepine-3-carboxylate (8)

A mixture of compound **2** (0.404 g, 1 mmol) and diaminopyridine **7** (0.285 g, 1 mmol) is dissolved in DMF (10 mL). The reaction mixture is heated at reflux for 10 h. After cooling, the reaction mixture is cooled and poured gradually onto crushed ice. The solid obtained is filtered off and recrystallized from EtOH to give compound **8** as brown crystals, yield 85%, mp 276-277 °C. IR spectrum (KBr) ν_{max}/cm^{-1}: 3190 (NH), 3020 ($CH_{arom.}$), 2980 ($CH_{aliph.}$), 2225, 2220 (C≡N), 1710 ($C{=}O_{ester}$), 1653 ($C{=}O_{pyridone}$); ^{1}H NMR spectrum (300 MHz, DMSO-d_6) δ 1.11 (t, 3H, *J* 6.9 Hz, $CH_2\mathit{CH_3}$), 2.38 (s, 3H, CH_3), 4.04 (q, 2H, *J* 6 Hz, $\mathit{CH_2}CH_3$), 5.67 (s, 1H, pyrimidine-H4), 6.04 (s, 1H, triazepine-H13), 7.29-7.79 (m, 14H, Ar-H); 8.52 (s, 2H, D_2O-exchangeable, 2NH); ^{13}C NMR spectrum (75 MHz, $CDCl_3$) δ 13.8, 39.9, 40.2 (aliphatic), 115.2, 116.4 (C≡N), 127.3, 128.6, 129.3, 129.9, 130.2, 131.6, 132.4, 132.9, 133.3, 134.9, 156.5, 158.2 (aromatic), 164.8, 165.1 (C=O); Anal. Calc. for $C_{36}H_{26}ClN_7O_3S$ (672.15): C, 64.33; H, 3.90; N, 14.59; S, 4.77. Found: C, 64.34; H, 3.90; N, 14.60; S, 4.78%.

CONCLUSIONS

In summary, the thiazolopyrimidine **2** has proved to be a versatile precursor for the synthesis of tetracyclic pyrimidine derivatives. The present investigation offers procedures for the synthesis of the poly-condensed new heterocyclic ring systems. These compounds were also screened for their antituomer activity.

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