Antioxidant Activity of Novel Fused Heterocyclic Compounds Derived from Tetrahydropyrimidine Derivative

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Abstract

Pyrimidines are of great importance in fundamental metabolism, being an integral part of DNA and RNA, found in the three bases uracil, thymine and cytosine of the six present in the nucleotides. They are found to possess diverse biological properties as bactericides, fungicides, viricides, insecticide, and mecticides. Many derivatives of pyrimidines have been used as therapeutic agents. Several triazolo and pyrazolopyrimidine derivatives are found to possess antifungal and antileishmanial activity. Certain pyrimidine derivatives are known to display antimalarial antifilarial activities and also potent inhibitors of cancer cell proliferation. Antifilarial activity of pyrimidines is the key starting material for design and synthesis of fused novel heterocyclic systems such as pyrimidines, tetrazolopyrimidine, pyrimidothiazolopyrimidine, pyrimidothiazolotriazine and pyrrolothiazolopyrimidine derivatives. The newly synthesized compounds were characterized by IR, 1H-NMR, 13C-NMR, and mass spectral data. Antioxidant activities of all synthesized compounds were investigated.

Key words: arylidene; tetrahydropyrimidine; thiazolo[3,2-a]pyrimidine; antioxidant activity

Results and Discussion

Chemistry When tetrahydropyrimidine 1 was submitted to react with bromomalonalonitrile in aqueous alcoholic potassium carbonate solution enamino nitride 2 was obtained. The structural features of enamino nitride 2 were identified on the basis of coupling band exhibited at ν 3391 and 3291 cm⁻¹ due to the amino NH₂ functionality and disappearance of νC=S. 1H-NMR spectrum revealed D₂O-exchangeable singlet at δ 8.48 ppm due to amino group.

Thiazolopyrimidine derivative 3 can be obtained via reaction of tetrahydropyrimidine 1 with chloroacetamide. The structural features of thiazolopyrimidine derivative 3 were established by elemental analysis as well as spectral data. The structure of compound 3 also confirmed chemically via condensation reaction with substituted aromatic aldehydes namely, 4-chlorobenzaldehyde and/or 4-methoxybenzaldehyde to afford the corresponding benzylidene derivatives 4a and 4b, respectively.

Chlorination of tetrahydropyrimidine 1 with a mixture of phosphorus pentachloride and phosphorus oxychloride as a chlorinating reagent gave the chloropyrimidine derivative 5. The structure of compound 5 was assigned from its spectroscopic data, a qualitative and quantitative elemental analysis which indicates the presence of chlorine. A chemical evidence for the structure assignment of compound 5 is the reaction with glycine, sodium azide and/or anthranilic acid to afford dihydropyrimidine 6, tetrazolopyrimidine 7 and pyrimidoquinazolinone 8, respectively. The IR spectrum of the dihydropyrimidine 6 showed a broad peak centered at 3206 cm⁻¹ due to νOH and νNH and the carbonyl band of a carboxylic acid at 1700 cm⁻¹. This spectrum pattern reveals the possibility of two interconvertible forms for the product 6 via 1,3-proton shift.

Alkylation of tetrahydropyrimidine 1 with ethyl iodide in the presence of sodium ethoxide furnished 5-alkylated product 9, which has been chlorinated via reaction with phosphorus pentachloride in the presence of phosphorus oxychloride to afford the chlorinated product 10. Pyrimidine derivative 10 underwent thiation under the effect of thiourea to give thioxodihydropyrimidine 11. The IR spectrum of thioxodihydropyrimidine 11 displayed the appearance of νNH and νC=S at 3194 and 1240, respectively. 1H-NMR of compound 11 showed D₂O-exchangeable signal at 13.02 ppm due to NH proton. Alkaline hydrolysis of tetrahydropyrimidine 1 using 10% alcoholic sodium hydroxide solution gave dioxotetrahydropyrimidine derivative 12 (cf. Chart 1).

Enaminonitrile 2 is the key starting material for design and synthesis of fused novel heterocyclic systems such as pyrimidothiazolopyrimidine derivatives 13 and 14 and pyrimidothiazolotriazine 15. Thus, when enamino nitride 2 was allowed to react with formamide, formic acid and/or sodium nitrite, it afforded pyrimidothiazolopyrimidine derivatives 13 and 14 and...
Treatment of enaminonitrile 2 with ethyl chloroacetate and/or carbon disulfide in pyridine furnished ethyl-2-(7-(benzo[d][1,3] dioxol-5-yl)-2,6-dicyano-5-oxo-5H-thiazolo[3,2-a] pyrimidin-3-ylamino) acetate (16) and/or (7-(benzo[d][1,3] dioxol-5-yl)-2,6-dicyano-5-oxo-5H-thiazolo[3,2-a] pyrimidin-3-yl) carbamodithioic acid (17), respectively (cf. Chart 2).

In one of our previous publications, it has been reported that the effect of boiling triethyl orthoformate on enaminonitrile resulted in ethyl formamide derivative such as 18. In the present work, reaction of neat triethyl orthoformate with enaminonitrile 2 under reflux gave pyrrolothiazolopyrimidine derivative 19 indicating that cyclization on the cyano functionality takes place after the nucleophilic attack of the amino group on the electronically deficient carbon atom of triethyl orthoformate.

Treatment of enaminonitrile 2 with diethyl malonate in ethanolic solution of sodium ethoxide afforded N-(7-(benzo[d][1,3] dioxol-5-yl)-2,6-dicyano-5-oxo-5H-thiazolo[3,2-a] pyrimidin-3-yl)acetamide (20). As –NH is more acidic than C–H bond, the basic ethoxide ion abstracts a proton from NH2 groups to generate N− which attacks the carbonyl carbon of the ester group through tetrahedral mechanism leading to departure of the good leaving ethoxide group (cf. Chart 3).

**Pharmacology**

**Antioxidant Evaluation**

The antioxidant activities of the synthesized compounds were determined and listed in Table 1 and Fig. 1. The results revealed that all compounds were found to be potent. Moreover, the results showed that nearly three compounds 1, 6 and 9 were found to be the most potent levels of activity. Additionally, compounds 2, 4b, 8, 11, 14, 17, 19 and 20 were found to have moderate activity.

The following points were noticed. On comparison between the compounds 1, 6 and 9, it was noticed that compound 6 indicating that the presence of COOH group was more effective than the tetrahydropyrimidine 1, while conversion of the C=S group in tertrahydropyrimidine 1 to -C-S-Et group in compound 9, resulted in low activity of 9. Chloropyrimidine 5 is less active than tetrahydropyrimidine 1 but more active than pyrimidoquinazoline 8. Compound 19 is more potent antioxidant than compounds 14, 17 and 20 that is due...
to the presence of =NH group.

Experimental

All melting points were measured on a Gallenkamp electric melting point apparatus and are uncorrected. The infrared spectra were recorded using potassium bromide disks on a Pye Unicam SP-3–300 infrared spectrophotometer. $^1$H- and $^{13}$C-NMR experiments were run at 300 MHz on a Varian Mercury VX-300 NMR spectrometer using tetramethylsilane (TMS) as internal standard in deuterated chloroform or dimethylsulphoxide. Chemical shifts are quoted as δ. The mass spectra were recorded on Shimadzu GCMS-QP-1000EX mass spectrometers at 70 eV. All the spectral measurements as well as the elemental analyses were carried out at the Micro analytical Center of Cairo University. All the newly synthesized compounds gave satisfactory elemental analyses. The reactions and the purity of all new compounds were monitored by TLC.

Synthesis

3-Amino-7-(benzo[d][1,3]dioxol-5-yl)-5-oxo-5H-thiazolo[3,2-a]pyrimidine-2,6-dicarbonitrile (2)

A mixture of tetrahydropyrimidine 1 (2.73 g, 0.01 mol), bromomalononitrile (1.44 g, 0.01 mol) and potassium carbonate (1.38 g, 0.01 mol/25 mL H$_2$O) in ethanol (25 mL) was heated under reflux for 2h, cooled and then poured onto ice with stirring. The resulted solid product was filtered, dried and recrystallized from ethanol to give enamionitrile 2 as orange crystals. mp 260–262°C, yield 60%. FT-IR (KBr, cm$^{-1}$): 3391, 3291 $\nu_{NH_2}$, 3081 $\nu_{CH}$ aromatic, 2909 $\nu_{CH}$ aliphatic,

Table 1. Total Antioxidant Capacity of the Synthesized Compounds

| Compound | Total antioxidant capacity (mg AAE/g compound) |
|----------|------------------------------------------------|
| 1        | 308.33±1.25                                    |
| 2        | 132.54±1.65                                    |
| 3        | 69.01±2.55                                     |
| 4a       | 20.38±1.85                                     |
| 4b       | 102.74±1.35                                    |
| 5        | 112.15±2.40                                    |
| 6        | 436.85±2.25                                    |
| 7        | 97.25±2.75                                     |
| 8        | 109.01±1.15                                    |
| 9        | 225.87±1.50                                    |
| 10       | 82.34±2.45                                     |
| 11       | 176.46±1.60                                    |
| 12       | 56.46±1.30                                     |
| 13       | 76.07±1.95                                     |
| 14       | 163.91±2.80                                    |
| 15       | 95.68±1.20                                     |
| 16       | 81.56±2.45                                     |
| 17       | 123.91±2.45                                    |
| 19       | 176.46±1.75                                    |
| 20       | 145.88±3.30                                    |

Results are (mean±S.D.) ($n$=3) and AAE.
2.42; Cl, 8.24; N, 9.73; S, 7.27.

57.87; H, 2.31; Cl, 8.13; N, 9.64; S, 7.36. Found: C, 57.75; H, 2.08; N, 19.76; S, 9.71. These data are satisfied and convincing for both forms of compound 6:

MS ν<sub>C</sub> = 127.99, 129.26, 147.67, 150.83, 151.28, 161.35, 165.19 (C=C=O).

Fig. 1. Total Antioxidant Capacity of the Synthesized Compounds

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2-(4-Methoxybenzylidene)-7-(benzo[d][1,3]dioxol-5-yl)-3,5-dioxo-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carbonitrile (4b)

White crystals, mp >300°C, yield 72%, FT-IR (KBr, cm<sup>-1</sup>): 3141 ν<sub>CH</sub> aromatic, 2980 ν<sub>CH</sub> aliphatic, 2205 ν<sub>C=O</sub>, 1713 and 1662 ν<sub>C=O</sub> ν<sub>CH</sub> (300 MHz, DMSO-d<sub>6</sub>): 9.87 (s, 1H, –CH=–C=–S), 7.31–6.94 (m, 7H, Ar-H), 6.07 (s, 2H, O–CH=–O) and 3.87 (s, 3H, –OCH<sub>3</sub>). 13C-NMR (75 MHz, DMSO-d<sub>6</sub>): 77.89 (OCH<sub>3</sub>), 101.26 (O–CH=–O), 107.42, 107.49, 108.33, 108.42, 120.15, 122.49, 122.51, 132.64, 147.82, 148.37, 158.55, 165.86 (2C=O, C=C=C). MS m/z: 431 (M<sup>+</sup> ). Anal. Calcd for C<sub>25</sub>H<sub>17</sub>N<sub>5</sub>O<sub>5</sub>S: C, 58.42; H, 2.81; N, 11.65; S, 9.42.

6-(Benzo[d][1,3]dioxol-5-yl)-4-chloro-2-thioxo-1,2-dihydropyrimidine-5-carbonitrile (5)

A mixture of tetrahydropyrimidine 1 (2.73 g, 0.01 mol) and phosphorus pentachloride (2.5 g, 0.01 mol) in phosphorus oxychloride (7 mL, 0.01 mol) was heated on a water bath for 8 h.

1H-NMR (300 MHz, DMSO-d<sub>6</sub>): 13.07 (s, 3H, Ar-H) and 6.14 (s, 2H, O–CH=–O) and 4.13 (s, 2H, S–CH=–C=–O). MS m/z: 313 (M<sup>+</sup> ).

Reaction of 4-(Chlorobenzylidene)-7-(benzo[d][1,3]dioxol-5-yl)-3,5-dioxo-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carbonitrile (4a)

Yellow crystals, mp 270–272°C, yield 68%, FT-IR (KBr, cm<sup>-1</sup>): 3127 ν<sub>CH</sub> aromatic, 2828 ν<sub>CH</sub> aliphatic, 2227 ν<sub>C=O</sub>, 1721, 1665 ν<sub>CH</sub> (300 MHz, DMSO-d<sub>6</sub>): 7.26–7.08 (m, 7H, Ar-H), and 6.19–6.11 (m, 3H, O–CH=–O, –CH=–C=–S). MS m/z: 435 (M<sup>+</sup> ).

2-(4-Chlorobenzylidene)-7-(benzo[d][1,3]dioxol-5-yl)-3,5-dioxo-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carbonitrile (4a)

White crystals, mp 240–242°C, yield 86%. FT-IR (KBr, cm<sup>-1</sup>): 3102 ν<sub>CH</sub> aromatic, 2987 ν<sub>CH</sub> aliphatic, 2225 ν<sub>C=O</sub>, 1652 ν<sub>C=O</sub> ν<sub>CH</sub> (300 MHz, DMSO-d<sub>6</sub>): 13.07 (s, 3H, Ar-H) and 6.14 (s, 2H, O–CH=–O). MS m/z: 291 (M<sup>+</sup> ). Anal. Calcd for C<sub>25</sub>H<sub>17</sub>N<sub>5</sub>O<sub>5</sub>S: C, 58.42; H, 2.81; N, 11.65; S, 9.42.

A mixture of tetrahydropyrimidine 1 (2.73 g, 0.01 mol), and glycine (0.75 g, 0.01 mol) in acetic anhydride (10 mL) was refluxed for 6 h, cooled and The solid formed was collected by filtration, dried and recrystallized from ethanol to yield compound 6 as beige crystals, mp >300°C, yield 86%. FT-IR (KBr, cm<sup>-1</sup>): 3202 ν<sub>NH</sub>, 3151 ν<sub>CH</sub> aromatic, 2987 ν<sub>CH</sub> aliphatic, 2225 ν<sub>C=O</sub>, 1652 ν<sub>C=O</sub>, 1220 ν<sub>C=O</sub> ν<sub>CH</sub> (300 MHz, DMSO-d<sub>6</sub>): 13.07 (s, 3H, Ar-H) and 6.14 (s, 2H, O–CH=–O). MS m/z: 291 (M<sup>+</sup> ).

2-(6-(Benzo[d][1,3]dioxol-5-yl)-4-chloro-2-thioxo-1,2-dihydropyrimidin-5-carbonitrile (5)

A mixture of tetrahydropyrimidine 1 (2.73 g, 0.01 mol), and phosphorus pentachloride (2.5 g, 0.01 mol) in phosphorus oxychloride (7 mL, 0.01 mol) was heated on a water bath for 8 h. The reaction mixture was cooled then poured onto crushed ice, collect the product by filtration, dried and recrystallized from ethanol to afford thioxodihydropyrimidine derivative 5 as beige crystals, mp >300°C, yield 86%. FT-IR (KBr, cm<sup>-1</sup>): 3202 ν<sub>NH</sub>, 3151 ν<sub>CH</sub> aromatic, 2987 ν<sub>CH</sub> aliphatic, 2225 ν<sub>C=O</sub>, 1652 ν<sub>C=O</sub>, 1220 ν<sub>C=O</sub> ν<sub>CH</sub> (300 MHz, DMSO-d<sub>6</sub>): 13.07 (s, 3H, Ar-H) and 6.14 (s, 2H, O–CH=–O). MS m/z: 291 (M<sup>+</sup> ). Anal. Calcd for C<sub>25</sub>H<sub>17</sub>N<sub>5</sub>O<sub>5</sub>S: C, 58.42; H, 2.81; N, 11.65; S, 9.42.

A mixture of thioxodihydropyrimidine 1 (2.73 g, 0.01 mol), and phosphorus pentachloride (2.5 g, 0.01 mol) in phosphorus oxychloride (7 mL, 0.01 mol) was heated on a water bath for 8 h. The reaction mixture was cooled then poured onto crushed ice, collect the product by filtration, dried and recrystallized from ethanol to give thioxodihydropyrimidine derivative 5 as beige crystals, mp >300°C, yield 86%. FT-IR (KBr, cm<sup>-1</sup>): 3202 ν<sub>NH</sub>, 3151 ν<sub>CH</sub> aromatic, 2987 ν<sub>CH</sub> aliphatic, 2225 ν<sub>C=O</sub>, 1652 ν<sub>C=O</sub>, 1220 ν<sub>C=O</sub> ν<sub>CH</sub> (300 MHz, DMSO-d<sub>6</sub>): 13.07 (s, 3H, Ar-H) and 6.14 (s, 2H, O–CH=–O). MS m/z: 291 (M<sup>+</sup> ).

2-(6-(Benzo[d][1,3]dioxol-5-yl)-4-chloro-2-thioxo-1,2-dihydropyrimidin-5-carbonitrile (5)
7-(Benzo[d][1,3]dioxol-5-yl)-5-thioxo-5,6-dihydrotetrazolo[1,5-f]-pyrimidine-8-carbonitrile (7)

To a solution of thioxodihydropyrimidine derivative 5 (2.92 g, 0.01 mol) in glacial acetic acid (30 mL), sodium azide (0.65 g, 0.01 mol), was added. The reaction mixture was refluxed for 5 h and allowed to cool. The solid formed was collected, dried and recrystallized from ethanol to give compound 7 as brown crystals, mp >300°C, yield 63%. FT-IR (KBr, cm⁻¹): 3217 ν\textsubscript{NH}, 2216 ν\textsubscript{CN}, 1612 ν\textsubscript{CN}. ¹H-NMR (300 MHz, DMSO-d₆): 7.77–7.07 (m, 3H, Ar-H), 6.13 (s, 2H, O–CH=O) and 3.40 (brs, 1H, –NH, D₂O-exchangeable). MS m/z: 298 (M⁺). Anal. Calcd for C₁₉H₁₀N₄O₃S (374.37): C, 60.96; H, 2.69; N, 14.97; S, 8.56.

A mixture of thioxodihydropyrimidine derivative 5 (2.92 g, 0.01 mol), and anthranilic acid (1.37 g, 0.01 mol) in ethanol (50 mL) was refluxed for 6 h, cooled, filtered, dried and recrystallized from ethanol to afford compound 8 as pale brown crystals, mp 270–272°C, yield 68%. FT-IR (KBr, cm⁻¹): 3346, 3209 ν\textsubscript{NH}, 2216 ν\textsubscript{CN}, 1645 ν\textsubscript{CN} = pyrimidine, 1605 ν\textsubscript{CN}. ¹H-NMR (300 MHz, DMSO-d₆): 8.10 (brs, 1H, –NH, D₂O-exchangeable), 7.50–7.13 (m, 7H, Ar-H), 6.17 (s, 2H, O–CH=O). MS m/z: 374 (M⁺). Anal. Calcd for C₁₉H₁₂N₄O₄S (376.39): C, 60.96%; H, 2.69%; N, 14.97%; S, 8.56.

3-(Benzo[d][1,3]dioxol-5-yl)-10-oxo-1-thioxo-2,10-dihydro-1H-pyrimido[6,1-h]quinazoline-4-carbonitrile (8)

A mixture of thioxodihydropyrimidine derivative 5 (2.92 g, 0.01 mol), and antrhanic acid (1.37 g, 0.01 mol) in ethanol (50 mL) was refluxed for 6 h, cooled, filtered, dried and recrystallized from ethanol to give compound 8 as brown crystals, mp 234–236°C, yield 70%. FT-IR (KBr, cm⁻¹): 3340 ν\textsubscript{NH}, 2232 ν\textsubscript{CN}, 1702 ν\textsubscript{CO̶O}, 1660 ν\textsubscript{CN}. ¹H-NMR (300 MHz, DMSO-d₆): 13.09 (s, 2H, –NH, D₂O-exchangeable), 7.25–7.09 (m, 3H, Ar-H), 6.17 (s, 2H, O–CH=O). MS m/z: 257 (M⁺). Anal. Calcd for C₁₉H₁₂N₄O₄S (376.39): C, 56.04%; H, 2.74%; N, 16.34. Found: C, 55.98%; H, 2.63%; N, 16.22.

A solution of tetrahydropyrimidin 1 (2.73 g, 0.01 mol) in ethanol solution of sodium ethoxide (20 mL), ethyl iodide (1.82 g, 0.01 mol), was added then refluxed for 6 h. Left to cool, the solid was filtered, dried and recrystallized from ethanol to give compound 9 as yellow crystals, mp 274–275°C, yield 55%. FT-IR (KBr, cm⁻¹): 3167 ν\textsubscript{VOH}, 3082 ν\textsubscript{CH}, aromatic, 2969 ν\textsubscript{CO̶O}, aliphatic, 2234 ν\textsubscript{CN}, 1705 ν\textsubscript{CN} = pyrimidine, 1672 ν\textsubscript{CN} = NH-NMR (300 MHz, DMSO-d₆): 13.10 (s, 1H, –NH, D₂O-exchangeable), 7.24–7.10 (m, 3H, Ar-H), 6.17 (s, 2H, O–CH=O), 3.45 (q, 2H, –CH₂CH₃, J=6.0 Hz) and 1.55 (t, 3H, –CH₂CH₃, J=6.0 Hz). ¹C-NMR (75 MHz, DMSO-d₆): 14.30, 14.57, 62.78, 100.08, 102.54, 109.84, 103.94, 126.21, 129.97, 154.42, 154.80, 178.65. MS m/z: 301 (M⁺). Anal. Calcd for C₁₉H₁₂N₄O₄S (376.39): C, 55.80%; H, 3.68%; N, 13.95%; S, 10.64. Found: C, 55.68%; H, 3.75%; N, 13.78%; S, 10.60.

A mixture of S-alkylated pyrimidine 9 (3.01 g, 0.01 mol), was heated under reflux in phosphorous oxychloride (7 mL, 0.01 mol) and phosphorous pentachloride (2.5 g, 0.01 mol) for 8 h, cooled and poured onto ice. The precipitated solid was filtered off, dried and recrystallized from ethanol to give compound 10 as brown crystals, mp 220–222°C, yield 73%. FT-IR (KBr, cm⁻¹): 3205 ν\textsubscript{VCH} aromatic, 2914 ν\textsubscript{VCH} aliphatic, 2222 ν\textsubscript{CN}, 1655 ν\textsubscript{CN}. ¹H-NMR (300 MHz, DMSO-d₆): 7.30–6.95 (m, 3H, Ar-H), 6.17 (s, 2H, O–CH=O), 3.43 (q, 2H, –CH₂CH₃, J=7.5 Hz), 1.06 (t, 3H, –CH₂CH₃, J=7.5 Hz). MS m/z: 319 (M⁺). Anal. Calcd for C₁₆H₁₇Cl₂N₄O₃S (397.77): C, 52.59%; H, 3.15%; Cl, 11.09%; N, 13.14; S, 10.03. Found: C, 52.45%; H, 3.03%; Cl, 11.00; N, 13.02; S, 10.14.
acid (30 mL) and conc. HCl (15 mL). After completion of the addition the ice bath was removed and stirring continued for an additional 2 h. The crude product was filtered, dried then recrystallized from ethanol to afford 15 as brown crystals, mp 92–94°C, yield 78%. FT-IR (KBr, cm⁻¹): 3389, 3211, 2215, 2192 (2 vC=O), 1673 vC≡O pyrimidinone, 1621 vC=O ester, 1668 vC≡O pyrimidinone, 1635 vC≡O pyrimidinone (300 MHz, DMSO-d₆), 8.38–6.91 (m, 3H, Ar-H), 6.21 (s, 2H, O–CH₂–O). MS m/z: 385 (M⁺+1), 384 (M⁺). Anal. Calcd for C₁₉H₁₇N₃O₃S: C, 57.34; H, 4.79; N, 12.41; S, 18.46. Found: C, 57.36; H, 4.75; N, 12.39; S, 18.50.

A mixture of enaminonitrile 2 (1.69 g, 0.005 mol) in pyridine (7 mL), carbon disulfide (10 mL) was added. The reaction mixture was refluxed for 8 h, left to cool, acidified with cold dilute hydrochloric acid, filtered, dried and recrystallized from ethanol to give compound 16 as black crystals, mp 255–257°C, yield 80%. FT-IR (KBr, cm⁻¹): 3338 νNH, 2470 νC≡O, 1730 νC=O ester, 1668 νC≡O pyrimidinone, 1635 νC≡O pyrimidinone (300 MHz, DMSO-d₆), 8.72–7.28 (m, 4H, Ar-H, –NH, D₃O-exchangeable), 6.13 (s, 2H, O–CH₂–O), 4.63 (q, 2H, –CH₂CH₃), J=7.2 Hz), 2.47 (m, 2H, NN–CH₂–CO), 1.55 (t, 3H, –CH₂CH₃), J=7.2 Hz). MS m/z: 423 (M⁺). Anal. Calcd for C₁₆H₁₇N₅O₃S: C, 53.90; H, 3.09; N, 16.54; S, 7.57. Found: C, 53.78; H, 2.99; N, 16.45; S, 7.48.

(7-(Benzo[d][1,3]dioxol-5-yl)-2,6-dicyano-5-oxo-5H-thiazolo[3,2-a]pyrimidin-3-yl)-acetamide (19)

A solution of enaminonitrile 2 (1.69 g, 0.005 mol) in triethyl orthoformate (10 mL), was heated under reflux for 8h, excess of triethyl orthoformate was removed by distillation under reduced pressure. The solid formed was filtered, dried then recrystallized from ethanol to give compound 19 as brown crystals, mp 170–174°C, yield 69%. FT-IR (KBr, cm⁻¹): 3344 νNH, 2199 νC=O, 1710 νC≡O pyrimidinone, 1624 νC≡O pyrimidinone (300 MHz, DMSO-d₆), 7.69–7.12 (m, 3H, Ar-H), 6.11 (s, 2H, O–CH₂–O), 4.52 (s, 1H, –NH, D₃O-exchangeable), 4.30 (q, 2H, –CH₂CH₃), J=6.9 Hz), 1.27 (t, 3H, –CH₂CH₃), J=6.9 Hz). MS m/z: 393 (M⁺). Anal. Calcd for C₁₅H₇N₅O₃S: C, 51.73; H, 2.82; N, 17.80; S, 18.15. Found: C, 51.85; H, 2.74; N, 17.68; S, 8.00.

N-(7-(Benzo[d][1,3]dioxol-5-yl)-2,6-dicyano-5-oxo-5H-thiazolo[3,2-a]pyrimidin-3-yl)acetamide (20)

A mixture of enaminonitrile 2 (1.69 g, 0.005 mol), diethyl malonate (0.01 mol) in solution of sodium ethoxide (0.05 g sodium in 30 mL absolute ethanol) was heated under reflux for 6 h, cooled and acidified with cold dilute hydrochloric acid, filtered, dried and recrystallized from ethanol to give compound 15 as brown crystals, mp 280–282°C, yield 81%. FT-IR (KBr, cm⁻¹): 3389, 3211, 2215, 2192 (2 vC=O), 1673 vC≡O pyrimidinone, 1628 vC≡O amide, 1618 νC=O pyrimidinone (300 MHz, DMSO-d₆), 8.48 (brs, 1H, –NH, D₃O-exchangeable), 7.62–7.11 (m, 3H, Ar-H), 6.17 (s, 2H, O–CH₂–O) and 1.26 (s, 3H, –CH₃). MS m/z: 381 (M⁺+2)⁺, 380 (M⁺+1)⁺, 379 (M⁺). Anal. Calcd for C₁₉H₁₇N₃O₃S: C, 53.82; H, 2.39; N, 18.46; S, 8.45. Found: C, 53.69; H, 2.24; N, 18.38; S, 8.31.

**Determination of Total Antioxidant Capacity (TAC)**

The antioxidant activity (AOA) of a compound was determined according to phosphomolybdenum method using ascorbic acid as standard. This assay is based on the reduction of Mo VI to Mo V by the sample analyte and subsequent formation of a green colored [MoO₄²⁻=MoV] complex at acidic pH. In this method, 0.5 mL of the compound (100 μg/mL) in methanol was combined in dried vial with 5 mL of reagent solution (0.6 m sulfuric acid, 28 mM sodium phosphate and 4 mM ammonium molybdate solutions). The vials containing the reaction mixture were capped and incubated in a thermal block at 95°C for 90 min. After the samples had cooled at room temperature, the absorbance was measured at 695 nm against a blank. The blank consisted of all reagents and solvents without the sample and it was incubated under the same conditions. All experiments were carried out in triplicate. The antioxidant activity of the sample was expressed as the number of ascorbic acid equivalent (AAE). The phosphomolybdenum assay is based on the reduction of Mo VI to Mo V by antioxidant compounds and the formation of a green phosphate/Mo V complex with a maximal absorption at 695 nm.

**Statistical Analysis**

All data were presented as mean±standard deviation (S.D.) using SPSS 13.0 program.

**Conclusion**

A variety of fused and non fused heterocyclic systems containing pyrimidine nucleus have been synthesized from the reaction of tetrahydropyrimidine with different reagents. All the synthesized pyrimidines are potent antioxidants. In particular the tetrahydropyrimidine 6, dihydropyrimidine 1, and S-alkylated product 9 showed the most antioxidant activity (AOA) expressed in 308.33±1.25, 436.85±2.25 and 225.87±1.50 mg AAE/g compound (AAE) using ascorbic acid as standard.

**Acknowledgment**

The authors gratefully thank Dr. Mosad Ahmed Ghareeb and his colleagues in Biochemistry and Medicinal Chemistry Department, Theodor Bilharz Research Institute (TBRI) for performing antioxidant screening of the synthesized compounds.

**Conflict of Interest**

The authors declare no conflict of interest.

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