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Anticancer Activity of New Substituted Pyrimidines, Their Thioglycosides and Thiazolopyrimidine Derivatives

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ABSTRACT

Novel functionalized pyrimidine, thioxopyrimidine, iminopyrimidine derivatives and their derived bicyclic thiazolopyrimidine compounds were synthesized. The substituted arylidine derivatives of the thiazolopyrimidine compounds were also prepared. Glycosylation of the thiopyrimidine derivative resulted in formation of the acetylated thioglycosides which were deacetylated to the free hydroxythioglycosides. The synthesized compounds were studied for their anticancer activity against hepatocellular carcinoma HepG-2, human prostate adenocarcinoma PC-3 and human colorectal carcinoma HCT-116 cell lines. Compounds **7c, 8a** and **12a** showed high activity against PC-3 cancer cells while compounds **11b** and **12a** revealed higher activity against HCT-116 cell line.

INTRODUCTION

The chemistry and biological research on pyrimidines and their derivatives have attracted great attention because such ring system represents the main skeleton in alkaloids and nucleic bases in addition to their interesting potent biological activities. The anticancer (Abdel Mohsen *et al*., 2010; El-Sayed *et al*. 2009), antiviral (El-Sayed *et al*., 2009; 2008), antibacterial (El-Sayed and Abdel-Rahman, 2010; Ramez *et al*., 2010) antifungal (Gholap *et al*., 2008), anti-inflammatory (Da *et al*., 2006) and central nervous activities (Gillespie *et al*., 2009) properties of many pyrimidine derivatives are well reported. New 4,6-diarylpyrimidine compounds have been found to exhibit anti-tubercular, antibacterial and antiviral activity (Siddiqui *et al*., 2007). Pyrimidinedione derivatives have been reported to possess antibacterial and anticancer activities (Haiba *et al*., 2013; Singh and Paul, 2006). Thiazolopyrimidenes represent an important class of fused pyrimidine compounds due to their inhibition activity of 2-methylerythritol-2,4-cyclodiphosphate synthase (Geist *et al*., 2010). Such type of compounds have been shown to hav antiparkinsonian, analgesic (Amr *et al*., 2008), anticancer (Flefel *et al*., 2007; Said *et al*., 2004) and antimicrobial (Rashad *et al*., 2010) agents, in addition to activity as phosphate (Kolb *et al*., 2009) and acetylcholinesterase inhibitors (Zhi *et al*., 2008). Aromatic thiophenes have attracted much attention as target molecules due to the wide spectrum of its biological activities. These compounds exhibit potent antitumor (Brault *et al*., 2005) and antibacterial effects (Alagarsamy *et al*., 2006). On the other hand, extensive interest has been gained to the chemistry and biological properties of glycosyl heterocycles incorporating modified sugar and/or and heterocyclic constituents as biological inhibitors (El Ashry *et al*., 2007; El-Sayed *et al*., 2016; 2017). Interestingly, the possible potential hydrogen bond donors and acceptors as a result of presence of polyhydroxyl chain in thioglycosides are expected to promote their affinity toward protein and nucleic acid (Kumar *et al*., 2015).

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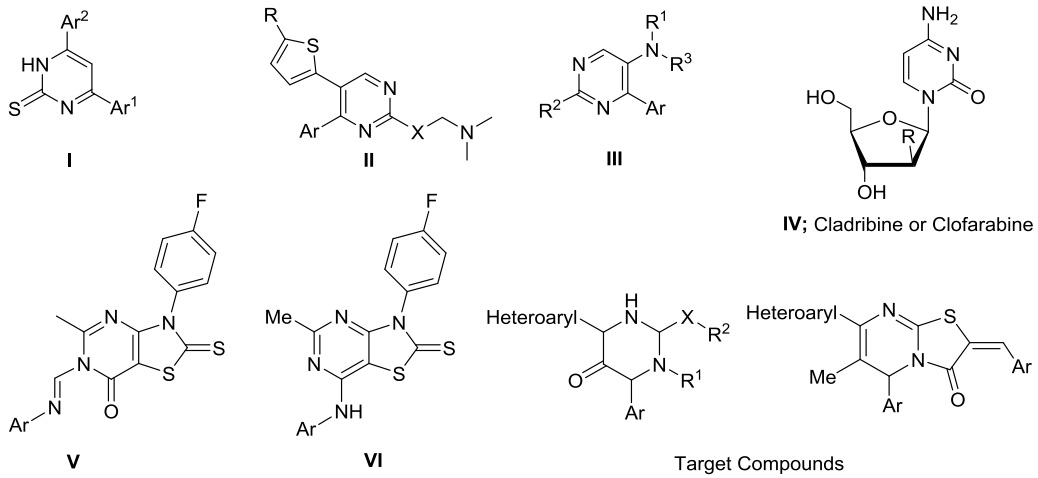


Fig. 1: Anticancer Disubstituted pyrimidines, thiazolopyrimidines and pyrimidine sugar Derivatives.

Many pyrimidine nucleosides and analogues have been synthesized and studied for anticancer behaviour, and two are in general clinical use. A number of nucleosides and 5-fluorouracil were applied orderly for remediation of breast cancer, gastrointestinal tract tumours in addition to other solid tumours (MacCoss and Robins, 1990). Nucleosides bearing pyranosyl rings have been evaluated for their potential antiviral (Ostrowski *et al*. 1998; Maurinsh *et al*., 1997), antioxidant (Spanou *et al*., 2007) and antibiotic (Haouz *et al*., 2003) properties and as building blocks in nucleic acid synthesis (Vastmans *et al*., 2001).

Furthermore, a number of pyrimidine thioglycosides have been shown to have antischistosomal activity (Srour *et al*., 2009). Compounds **I-VI** (Abdel Mohsen *et al*., 2010; Chou *et al*., 1999; Alagarsamy *et al*., 2013; Jordheim *et al*., 2013; Fahmy *et al*., 2003) (fig. 1) represents examples of reported disubstituted pyrimidine, thiazolopyrimidine and pyrimidinyl sugar derivatives with their anticancer activity. In the same direction and following our program aiming for the synthesis of glycosylthio five and six membered heterocycles, with anticancer, antiviral and antimicrobial activity properties (El-Sayed *et al*., 2008; 2017; Flefel *et al*., 2017) we report the synthesis of novel disubstituted pyrimidines, their bicyclic derivatives and their derived thioglycosides with cytotoxic activity evaluation.

MATERIALS AND METHODS

Instruments and reagents

All melting points were measured by Electro-thermal IA 9100 apparatus (Shimadzu, Tokyo, Japan) and are uncorrected. Infra-red spectra were investigated (KBr) by means of a Perkin-Elmer 1650 spectrophotometer (Norwalk, CT, USA). Nuclear Magnetic Resonance (^{1}H and ^{13}C NMR) of prepared compounds was carried out on a Jeol-Ex-400 NMR spectrometer (Jeol, Tokyo, Japan) at 25 ºC and chemical shifts were expressed as part per million; ppm (δ values) with respect to TMS as internal standard. Mass spectrometry was performed using VG 2AM-3F spectrometer (Thermo electron corporation, USA). Microanalyses were determined using Mario El Mentar apparatus. Following up the reactions and checking the purity of the compounds were performed by means of TLC which was implemented by aluminum plates pre-coated with silica gel 60 or 60 F254 (Merck) and visualized using UV light (254 nm).

All chemicals which have been used were of reagent grade and used as provided directly unless otherwise stated. Synthesis of compounds **1a-c** and **2a** was performed according to reported procedure (Ramesh and Rao, 2010; Greiner-Bechert and Otto, 1991; Qiang *et al*., 2013).

General procedure for preparation of compounds 2b,c

To a solution of enone derivatives **1b,c** (10 mmole) in dry acetone (40 mL)/methanol (15 mL) mixture, H_2O_2 (20%, 15 mL) and anhydrous NaOH (2 g) were added portion-wise. The resulting mixture was stirred in an ice bath until the yellow color is disappeared, then, the temperature was allowed to raise to 30-40 °C for 45 minutes until white clear solution was achieved, then stirring was continued at room temperature for 3 h. Crushed ice-water mixture was added and the resulting solid substance was filtered and re-crystallized from ethanol affording the oxirane **2b,c**.

(3-(3,4-Dimethoxyphenyl)oxiran-2-yl)(thiophen-2-yl)methanone (2b)

Yield: 61%, m.p. 123-125 °C, yellow powder. IR (KBr) υ, cm^{-1}: 1697 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.75, 3.77 (2s, 6H, $2OCH_3$), 3.79 (d, 1H, *J* = 7.2 Hz, oxirane H-2), 3.92 (d, 1H, *J* = 7.2 Hz, oxirane H-3), 6.80-6.84 (m, 2H, Ar-H), 7.26 (d, 1H, *J* = 7.2 Hz, Ar-H), 7.52-7.55 (m, 1H, thiophene-H), 7.68 (d, 1H, *J* = 7.5 Hz, thiophene-H), 7.92 (d, 1H, *J* = 7.8 Hz, thiophene-H). Anal. calcd. for $C_{15}H_{14}O_4S$ (290.33): C, 62.05; H, 4.86. Found: C, 62.25; H, 4.94.

Thiophen-2-yl(3-(3,4,5-trimethoxyphenyl)oxiran-2-yl)methanone (2c)

Yield 73%, m.p. 153-155°C, yellow powder. IR (KBr) υ, cm^{-1}: 1710 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.83 (s, 3H, OCH_3), 3.85 (s, 6H, $2OCH_3$), 3.90 (d, 1H, *J* = 7.2 Hz, oxirane H-2), 4.02 (d, 1H, *J* = 7.2 Hz, oxirane H-3), 7.18 (s, 2H, Ar-H), 7.26-7.28 (m, 1H, thiophene-H), 7.74 (d, 1H, *J* = 7.5 Hz, thiophene-H), 8.00 (d, 1H, *J* = 7.5 Hz, thiophene-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_c 56.2 ($2CH_3O$), 59.6 (CH_3O), 60.9 (oxirane-C), 68.9 (oxirane-C), 109.5, 110.7, 120.9, 128.2, 128.5, 130.8, 131.7, 133.6 (Ar-C and thiophene-C), 186.3 (C=O). MS, *m/z* (%) (320.35, 2.49 %, M^+). Anal. calcd. for $C_{16}H_{16}O_5S$ (320.36): C, 59.99; H, 5.03. Found: C, 59.77; H, 4.86.

General method for preparation of dihydropyrimidines 3a-c

Thiourea (10 mmole) was added to a stirred mixture of chalcone derivatives **1a-c** (10 mmole) and anhydrous sodium hydroxide (1.5 g) in absolute ethanol (10 mL) then the reaction mixture was heated under reflux till completion of reaction (TLC; Pet ether/ethyl acetate: 3:1). The resulting mixture was poured onto hydrochloric acid solution (5%, 15 mL) in an ice bath resulting in a yellowish precipitate which was filtered and re-crystallized to afford substituted dihydropyrimidine **3a-c**, respectively.

4-Phenyl-6-(thiophen-2-yl)-3,4-dihydropyrimidine-2(1H)-thione (3a)

Yield 93%, m.p. 160-162 °C, reaction time; 1.5 hour, solvent of crystallization: ethanol/water (2:1), yellow powder. IR (KBr) υ, cm^{-1}: 3250 (NH). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 4.57 (d, 1H, *J* = 6.2 Hz, pyrimidine H-4), 6.18 (d, 1H, *J* = 6.2 Hz, pyrimidine H-5), 6.58-6.64 (m, 2H, Ar-H), 6.73 (t, 1H, *J* = 7.5 Hz, Ar-H), 6.95-7.01 (m, 3H, Ar-H and thiophene-H), 7.32 (d, 1H, *J* = 7.5 Hz, thiophene-H), 7.56 (d, 1H, *J* = 7.5 Hz, thiophene-H), 8.50 (brs, 2H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_c 59.9 (pyrimidine C-4), 102.5 (pyrimidine C-5), 120.9, 128.3, 128.6, 130.8, 132.5, 135.2, 137.8, 148.6 (Ar-C, thiophene-C and pyrimidine C-6), 176.2 (C=S). Anal. calcd. for $C_{14}H_{12}N_2S_2$ (272.38): C, 61.73; H, 4.44; N, 10.28. Found: C, 61.95; H, 4.58; N, 10.09.

4-(3,4-Dimethoxyphenyl)-6-(thiophen-2-yl)-3,4-dihydropyrimidine-2(1H)-thione (3b)

Yield 87%, m.p. 85-87 °C, reaction time; 1 hour, solvent of crystallization: ethanol, yellow needles. IR (KBr) υ, cm^{-1}: 3310 (NH). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.75, 3.77 (2s, 6H, $2OCH_3$), 4.37 (d, 1H, *J* = 6.2 Hz, pyrimidine H-4), 6.18 (d, 1H, *J* = 6.2 Hz, pyrimidine H-5), 6.53 (d, 1H, *J* = 7.5 Hz, Ar-H), 6.65-6.72 (m, 2H, Ar-H), 6.95-6.99 (m, 1H, thiophene-H), 7.21 (d, 1H, *J* = 7.5 Hz, thiophene-H), 7.42 (d, 1H, *J* = 7.5 Hz, thiophene-H), 9.81 (brs, 1H, NH), 11.15 (brs, 1H, NH). Anal. calcd. for $C_{16}H_{16}N_2O_2S_2$ (332.44): C, 57.81; H, 4.85; N, 8.43. Found: C, 57.55; H, 4.73; N, 8.58.

6-(Thiophen-2-yl)-4-(3,4,5-trimethoxyphenyl)-3,4-dihydropyrimidine-2(1H)-thione (3c)

Yield: 73%, m.p. 260-262 °C, reaction time; 1 hour, solvent of crystallization: ethanol, yellow needles. IR (KBr) υ, cm^{-1}: 3380 (NH). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.71 (s, 3H, OCH_3), 3.73 (s, 6H, $2OCH_3$), 4.01 (d, 1H, *J* = 6.2 Hz, pyrimidine H-4), 6.34 (d, 1H, *J* = 6.2 Hz, pyrimidine H-5), 6.78 (s, 2H, Ar-H), 6.86-6.89 (m, 1H, thiophene-H), 6.99 (d, 1H, *J* = 7.5 Hz, thiophene-H), 7.15 (d, 1H, *J* = 7.5 Hz, thiophene-H), 9.78 (brs, 1H, NH), 11.25 (brs, 1H, NH). MS, *m/z* (%) (362, 1.49%, M^+). Anal. calcd. for $C_{17}H_{18}N_2O_3S_2$ (362.46): C, 56.33; H, 5.01; N, 7.73. Found: C, 56.18; H, 4.85; N, 7.90.

***6-(Thiophen-2-yl)-4-(3,4,5-trimethoxyphenyl)-3,4-dihydropyrimidin-2(1H)-imine* (4c)**

A suspension of compound **1c** (10 mmole), guanidine hydrochloride (10 mmole) and anhydrous KOH (1.5 g) in ethanol-water mixture (1:1; 15 mL) was refluxed for 5 h. The obtained residue after complete evaporation the solvent was acidified drop-wise with cold HCl (12 mL) resulting in formation of a yellow solid which was filtered and re-crystallized from ethanol. Yield 61%, m.p. 250-252 °C, yellow powder. IR (KBr) υ, cm^{-1}: 3260-3240 (NH). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.60 (s, 3H, OCH_3), 4.64 (s, 6H, $2OCH_3$), 5.23 (d, 1H, *J* = 6.2 Hz, pyrimidine H-4), 5.87 (d, 1H, *J* = 6.2 Hz, pyrimidine H-5), 6.84 (s, 2H, Ar-H), 7.20-7.23 (m, 1H, thiophene-H), 7.34 (d, 1H, *J* = 7.5 Hz, thiophene-H), 7.55 (d, 1H, *J* = 7.5 Hz, thiophene-H), 7.94 (brs, 2H, 2NH), 10.80 (brs, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_c 52.9 (pyrimidine C-4), 55.8 (2 OCH_3), 55.8 (OCH_3), 102.7 (pyrimidine C-5), 121.2, 128.4, 128.8, 131.2, 132.6, 135.2, 137.9, 149.3 (Ar-C, thiophene-C and pyrimidine C-6), 155.1 (*C*=NH). Anal. calcd. for $C_{17}H_{19}N_3O_3S$ (345.42): C, 59.11; H, 5.54; N, 12.17. Found: 58.96; H, 5.68; N, 12.04.

General procedure for preparation of compounds 5b,c

A mixture of compound **3b,c** (10 mmole), chloroacetic acid (15 mmole), anhydrous sodium acetate (2 g), acetic anhydride (8 mL) and glacial acetic acid (16 mL) was heated at reflux temperature for 2-3 hours. The mixture was poured onto water to afford a brownish solid which was filtered and re-crystallized from acetic acid/water mixture (1:1).

5-(3,4-Dimethoxyphenyl)-7-(thiophen-2-yl)-5H-thiazolo[3,2-a]pyrimidin-3(2H)-one (5b)

Yield 67%, m.p. 85-87 °C, reaction time; 3 hours, pale brown needles. IR (KBr) υ, cm^{-1}: 1660 (C=O). ^{1}H NMR for compound **5b** (400 MHz, DMSO-d_6): δ_H 3.64 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.78 (s, 2H, CH_2), 5.33 (d, 1H, *J* = 6.2 Hz, pyrimidine H-4), 5.87 (d, 1H, *J* = 6.2 Hz, pyrimidine H-5), 6.78-6.84 (m, 2H, Ar-H), 7.21 (d, 1H, *J* = 7.5 Hz, Ar-H), 7.32-7.35 (m,

1H, thiophene-H), 7.50 (d, 1H, *J* = 7.8 Hz, thiophene-H), 7.55 (d, 1H, *J* = 7.6 Hz, thiophene-H). Anal. calcd. for $C_{18}H_{16}N_2O_3S_2$ (372.46): C, 58.05; H, 4.33; N, 7.52. Found: C, 57.88; H, 4.19; N, 7.66.

7-(Thiophen-2-yl)-5-(3,4,5-trimethoxyphenyl)-5H-thiazolo[3,2-a]pyrimidin-3(2H)-one (5c)

Yield 91%, m.p. 85-87 °C, reaction time; 2 hours, yellow needles. IR (KBr) υ, cm^{-1}: 1670 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.64 (s, 3H, OCH_3), 3.74 (s, 6H, $2OCH_3$), 3.80 (s, 2H, CH_2), 3.93 (d, 1H, pyrimidine H-4), 6.64 (d, 1H, pyrimidine H-5), 7.05 (s, 2H, Ar-H), 7.12-7.15 (m, 1H, thiophene-H), 7.59-7.64 (m, 2H, thiophene-H). ^{13}C NMR (75 MHz, DMSO-d_6): δ_c 32.8 (CH_2), 52.9 (C-5), 56.01 ($2CH_3O$), 60.02 (CH_3O), 107.98 (C-6), 123.8, 124.02, 125.7, 127.5, 135.5, 138.8, 132.2, 138.8, 144.3, 152.8 (Ar-C, thiophene-C, C-7 and C=N), 179.4 (C=O). MS, *m/z* (%) (402, 3.19%, M^+). Anal. calcd. for $C_{19}H_{18}N_2O_4S_2$ (402.48): C, 56.70; H, 4.51; N, 6.96. Found: C, 56.90; H, 4.62; N, 6.79.

General procedure for preparation of compounds 7b,c

A stirred mixture of thiazolopyrimidine derivative **5b,c** (10 mmole), the aldehyde (3,4-dimethoxybenzaldehyde or 3,4,5-trimethoxybenzaldehyde) (**6a,b**) (10 mmole) in absolute ethanol (20 mL) was heated at reflux temperature for 2-3 hours. Crushed ice-water was then provided affording a precipitate that was filtered and re-crystallized from acetic acid/water (1:1).

2-(3,4-Dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)-7-(thiophen-2-yl)-5H-thiazolo[3,2-a]pyrimidin-3(2H)-one (7b)

Yield 78%, m.p. 130-132 °C, reaction time; 2 hours, black powder. IR (KBr) υ, cm^{-1}: 1660 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.59 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.73 (s, 6H, $2OCH_3$), 5.93 (d, 1H, *J* = 6.2 Hz, pyrimidine H-4), 6.03 (d, *J* = 6.2 Hz, 1H, pyrimidine H-5), 7.07-7.14 (m, 3H, Ar-H), 7.18-7.26 (m, 5H, Ar-H and thiophene H-3,4), 7.55 (s, 1H, C*H*=C), 7.61 (d, 1H, *J* = 7.6 Hz, thiophene H-5). Anal. calcd. for $C_{27}H_{24}N_2O_5S_2$ (520.62): C, 62.29; H, 4.65; N, 5.38. Found: C, 62.03; H, 4.50; N, 5.51.

7-(Thiophen-2-yl)-2-(3,4,5-trimethoxybenzylidene)-5-(3,4,5-trimethoxyphenyl)-5H-thiazolo[3,2-a]pyrimidin-3(2H)-one (7c)

Yield 71%, m.p. 120-122 °C, reaction time; 3 hours, yellow needles. IR (KBr) υ, cm-1: 1657 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.63 (s, 6H, $2CH_3O$), 3.66 (s, 6H, $2CH_3O$), 3.70 (s, 6H, $2CH_3O$), 5.44 (d, *J* = 6.2, 1H, pyrimidine H-4), 6.13 (d, 1H, *J* = 6.2 Hz, pyrimidine H-5), 7.08-7.14 (m, 4H, Ar-H), 7.17-7.21 (m, 2H, thiophene-H), 7.38 (s, 1H, C*H*=C), 7.45 (d, 1H, *J* = 7.5 Hz, thiophene-H). Anal. calcd. for $C_{29}H_{28}N_2O_7S_2$ (580.67): C, 59.99; H, 4.86; N, 4.82. Found: C, 60.28; H, 4.94; N, 4.70.

General method for preparation of compounds 8a-c

A mixture of the substituted epoxides **2a-c** (10 mmole), thiourea (10 mmole) and dry KOH (0.5 g) in ethyl alcohol (10 mL) was refluxed for 45 minutes. The reaction mixture was added portion-wise in a conical flask containing cold hydrochloric acid (20 mL), filtered, dried and re-crystallized from ethanol/water mixture (1:1).

4-Phenyl-6-(thiophen-2-yl)-2-thioxotetrahydropyrimidin-5(6H)-one (8a)

Yield 61%, m.p. 165-167 °C, yellow needles. IR (KBr) υ, cm^{-1}: 3280 (NH), 1710 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.84 (d, 1H, *J* = 7.2 Hz, pyrimidine-H), 3.86 (d, 1H, *J* = 7.2 Hz, pyrimidine-H), 7.25-7.32 (m, 4H, Ar-H), 7.39-7.52 (m, 4H, Ar-H and thiophene H-3,4,5), 9.88 (brs, 1H NH), 10.27 (brs, 1H NH). Anal. calcd. for $C_{14}H_{12}N_2OS_2$ (288.38): C, 58.31; H, 4.19; N, 9.71. Found: C, 58.14; H, 4.05; N, 9.86.

4-(3,4-Dimethoxyphenyl)-6-(thiophen-2-yl)-2-thioxotetrahydropyrimidin-5(6H)-one (8b)

Yield 73%, m.p. 95-97 °C, yellow needles. IR (KBr) υ, cm^{-1}: 3310 (NH), 1706 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.66 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.70 (d, 1H, *J* = 7.2 Hz pyrimidine-H), 3.73 (d, 1H, *J* = 7.2 Hz, pyrimidine-H), 7.15-7.20 (m, 2H, Ar-H), 7.39-7.48 (m, 4H, Ar-H and thiophene H-3,4,5), 9.90 (brs, 1H, NH), 10.25 (brs, 1H, NH). Anal. calcd. for $C_{16}H_{16}N_2O_3S_2$ (348.44): C, 55.15; H, 4.63; N, 8.04. Found: C, 54.98; H, 4.50; N, 8.15.

4-(Thiophen-2-yl)-2-thioxo-6-(3,4,5-trimethoxyphenyl)tetrahydropyrimidin-5(6H)-one (8c)

Yield 63%, m.p. 110-112 °C, yellow needles. IR (KBr) υ, cm^{-1}: 3318 (NH), 1716 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.64 (s, 3H, OCH_3), 3.66 (s, 6H, $2OCH_3$), 3.84 (d, 1H, *J* = 6.8 Hz, pyrimidine-H), 3.87 (d, 1H, *J* = 6.8 Hz, pyrimidine-H), 6.55 (s, 2H, Ar-H), 7.01-7.06 (m, 2H, thiophene H-3,4), 7.49 (d, 1H, *J* = 7.5 Hz, thiophene H-5), 9.85 (brs, 1H, NH), 10.24 (brs, 1H NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_c 54.3 ($2CH_3O$), 57.6 (CH_3O), 60.5 (pyrimidine-C), 60.7 (pyrimidine-C), 107.1, 124.6, 125.3, 126.5, 127.2, 130.2, 131.4, 136.9, 152.8 (Ar-C and thiophene-C), 176.9, 191.2 (C=O and C=S). MS, *m/z* (%) (378, 1.17 %, M^+). Anal. calcd. for $C_{17}H_{18}N_2O_4S_2$ (378.46): C, 53.95; H, 4.79; N, 7.40. Found: C, 53.73; H, 4.61; N, 7.58.

General method for preparation of compounds 9a-c

To the thiopyrimidine derivatives **8a-c** (10 mmole) was added chloroacetic acid (10 mmole) and the mixture was heated under reflux (TLC control; ethyl acetate/pet. ether: 1/3) till perfecting of reaction. The mixture was poured into ice-water, filtered, and then re-crystallization from acetic acid/water afforded the thiazolopyrimidines **9a-c**, respectively.

5-Phenyl-7-(thiophen-2-yl)-2H-thiazolo[3,2-a]pyrimidine-3,6(5H,7H)-dione (9a)

Yield 85%, m.p. 105-107 °C, reaction time; 3 hours, yellow needles. IR (KBr) υ, cm^{-1}: 1708 (C=O), 1680 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.64 (s, 2H, CH_2), 3.80 (s, 1H,

pyrimidine-H), 3.85 (s, 1H, pyrimidine-H), 7.18 (d, 2H, *J* = 7.8 Hz, Ar-H), 7.25 (m, 2H, Ar-H), 7.56-7.65 (m, 4H, Ar-H and thiohene H-3,4,5). MS, *m/z* (%) (327, 2.2%, M^+-1). Anal. calcd. for $C_{16}H_{12}N_2O_2S_2$ (328.40): C, 58.52; H, 3.68; N, 8.53. Found: C, 58.69; H, 3.77; N, 8.39.

5-(3,4-Dimethoxyphenyl)-7-(thiophen-2-yl)-2H-thiazolo[3,2-a]pyrimidine-3,6(5H,7H)-dione (9b)

Yield 76%, m.p. 110-112 °C, reaction time; 4 hours, black powder. IR (KBr) υ, cm^{-1}: 1705 (C=O), 1680 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.33, 3.36 (2s, 6H, 2 OCH_3), 3.72 (s, 2H, CH_2), 3.86 (s, 1H, pyrimidine-H), 3.90 (s, 1H, pyrimidine-H), 6.91-6.97 (m, 2H, Ar-H), 7.06 (d, 1H, *J* = 7.8 Hz, Ar-H), 7.10-7.15 (m, 2H, thiophene H-3,4), 7.29 (d, 1H, *J* = 7.4 Hz, thiophene H-5). MS, *m/z* (%) (388, 2.9%, M^+). Anal. calcd. for $C_{18}H_{16}N_2O_4S_2$ (388.46): C, 55.66; H, 4.15; N, 7.21. Found: C, 55.39; H, 4.05; N, 7.35.

7-(Thiophen-2-yl)-5-(3,4,5-trimethoxyphenyl)-2H-thiazolo[3,2-a]pyrimidine-3,6(5H,7H)-dione (9c)

Yield 79%, m.p. 117-118 °C, reaction time; 5 hours, brownish powder. IR (KBr) υ, cm^{-1}: 1718 (C=O), 1647 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.58 (s, 6H, 2 OCH_3), 3.64 (s, 3H, OCH_3), 3.78 (s, 2H, CH_2), 3.81 (s, 1H, pyrimidine-H), 3.85 (s, 1H, pyrimidine-H), 6.86 (s, 2H, Ar-H), 7.07-7.12 (m, 2H, thiophene H-3,4), 7.19 (d, 1H, *J* = 7.5 Hz, thiophene H-5). MS, *m/z* (%) (418, 1.3%, M^+). Anal. calcd. for $C_{19}H_{18}N_2O_5S_2$ (418.48): C, 54.53; H, 4.34; N, 6.69. Found: C, 54.30; H, 4.25; N, 6.82.

General methods for preparation of compounds 10b,c

A mixture of the thiopyrimidine **8b,c** (10 mmole), 2-chloroacetic acid (10 mmole) and acetic anhydride (10 mL) in acetic acid (20 mL) was stirred for 15 minutes, then the corresponding aromatic aldehyde (10 mmole) and dry CH_3COONa (2 g) were provided separately. The reaction components were refluxed for 4 h at which TLC showed completion of the reaction. The flask content was then added portion-wise to crushed ice and the precipitated solid was collected washed with water then re-crystallized from acetic acid/water, to afford compound **10b,c**, respectively**.**

2-(3,4-Dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)-7-(thiophen-2-yl)-2H-thiazolo[3,2-a]pyrimidine-3,6(5H,7H)-dione (10b)

Yield 83%, m.p. 120-122 °C, brownish powder. IR (KBr) υ, cm^{-1}: 1712 (C=O), 1674 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.69, 3.71, 3.74, 3.77 (4s, 12H, 4 OCH_3), 3.83 (s, 1H, pyrimidine-H), 3.86 (s, 1H, pyrimidine-H), 6.72-6.77 (m, 2H, Ar-H), 6.79 (s, 1H, C*H*=C), 6.83-7.12 (m, 6H, Ar-H and thiophene H-3,4), 7.85 (d, 1H, *J* = 7.5 Hz, thiophene H-5). Anal. calcd. for $C_{27}H_{24}N_2O_6S_2$ (536.62): C, 60.43; H, 4.51; N, 5.22. Found: C, 60.29; H, 4.35; N, 5.32.

7-(Thiophen-2-yl)-2-(3,4,5-trimethoxybenzylidene)-5-(3,4,5-trimethoxyphenyl)-2H-thiazolo[3,2-a]pyrimidine-3,6(5H,7H)-dione (10c)

Yield 83%, m.p. 115-117 °C, yellow needles. IR (KBr) υ, cm^{-1}: 1718 (C=O), 1647 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.53 (s, 6H, 2 OCH_3), 3.57 (s, 6H, 2 OCH_3), 3.60 (s, 6H, 2O CH_3), 3.76 (s, 1H, pyrimidine-H), 3.80 (s, 1H, pyrimidine-H), 6.39 (s, 2H, Ar-H), 7.32-7.38 (m, 4H, Ar-H, C*H*=C and thiophene-H), 7.51 (d, *J* = 7.4 Hz, 1H, thiophene-H), 7.72 (d, 1H, *J* = 7.6 Hz, thiophene-H). Anal. calcd. for $C_{29}H_{28}N_2O_8S_2$ (596.67): C, 58.38; H, 4.73; N, 4.70. Found: C, 58.61; H, 4.81; N, 4.48.

General procedure for the preparation of compounds 11a-c

To a suspension of compounds **2a-c** (10 mmole) and thiosemicarbazide (10 mmole) in ethanol (20 mL) was added portion wise potassium hydroxide (1.5 g) then the mixture was heated under efflux till completion of the reaction (TLC) (ethyl acetate/pet. ether: 1/3). Cold diluted HCl (15 mL) was then added drop wise in an ice bath. The appeared precipitated solid m was filtered and re-crystallized from proper solvent.

1-Amino-6-phenyl-4-(thiophen-2-yl)-2-thioxotetrahydropyrimidin-5(6H)-one (11a)

Yield 73%, m.p. 140-142 °C, reaction time; 1 hour, solvent of crystallization: ethanol/water (2:1), yellow powder. IR (KBr) υ, cm^{-1}: 3420-3363 (NH and NH_2), 1727 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.62 (s, 1H, pyrimidine-H), 3.67 (s, 1H, pyrimidine-H), 5.89 (brs, 2H, NH_2), 6.62-6.68 (m, 2H, Ar-H), 7.26 (d, 1H, *J* = 7.5 Hz, Ar-H), 7.71-7.79 (m, 5H, Ar-H and thiohene H-3,4,5), 9.80 (brs, 1H, NH). Anal. calcd. for $C_{14}H_{13}N_3OS_2$ (303.40): C, 55.42; H, 4.32; N, 13.85. Found: 55.58; H, 4.47; N, 13.66.

1-Amino-6-(3,4-dimethoxyphenyl)-4-(thiophen-2-yl)-2-thioxotetrahydropyrimidin-5(6H)-one (11b)

Yield 85%, m.p.118-120 °C, reaction time; 30 minutes, solvent of crystallization: ethanol/water (1:1), yellow powder. IR (KBr) υ, cm^{-1}: 3430-3325 (NH and NH_2), 1727 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.33, 3.36 (2s, 6H, 2 OCH_3), 3.60 (s, 1H, pyrimidine-H), 3.64 (s, 1H, pyrimidine-H), 5.90 (brs, 2H, NH_2), 6.68 (s, 1H, Ar-H), 6.74-6.79 (m, 2H, Ar-H), 6.99-7.08 (m, 1H, thiohene-H), 7.35 (d, 1H, *J* = 7.2 Hz, thiohene-H), 7.39 (d, 1H, *J* = 7.5 Hz, thiohene-H), 10.02 (brs, 1H, NH). MS, *m/z* (%) (363.1, 4.5%, M^+). Anal. calcd. for $C_{16}H_{17}N_3O_3S_2$ (363.45): C, 52.88; H, 4.71; N, 11.56. Found: C, 52.69; H, 4.55; N, 11.71.

1-Amino-4-(thiophen-2-yl)-2-thioxo-6-(3,4,5-trimethoxyphenyl)tetrahydro-pyrimidin-5(6H)-one (11c)

Yield 72%, m.p. 130-132 °C, reaction time; 25 minutes, solvent of crystallization: ethanol/water (1:1), yellow powder. IR (KBr) υ, cm^{-1}: 3420-3310 (NH and NH_2), 1704 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.77 (s, 6H, 2 OCH_3), 3.81 (s, 3H,

OCH_3), 4.50 (s, 1H, pyrimidine-H), 4.54 (s, 1H, pyrimidine-H), 5.88 (brs, 2H, NH_2), 6.60 (s, 2H, Ar-H), 6.95-7.01 (m, 2H, thiohene H-3,4), 7.39 (d, 1H, *J* = 7.8 Hz, thiohene H-5), 10.05 (brs, 1H, NH). MS, *m/z* (%) (393, 1.27 %, M^+). Anal. calcd. for $C_{17}H_{19}N_3O_4S_2$ (393.48): C, 51.89; H, 4.87; N, 10.68. Found: C, 51.70; H, 4.92; N, 10.79.

General procedure for the preparation of compounds 12a,c

A mixture of the epoxide derivatives **2a,c** (10 mmole), urea (10 mmole) and anhydrous KOH pellets (0.5 g) in absolute ethyl alcohol (10 mL) was heated at reflux temperature for 45 minutes. The reaction mixture poured on cold hydrochloric acid (15 mL), filtered, dried and crystallized from ethanol/water (1:1).

4-Phenyl-6-(thiophen-2-yl)tetrahydropyrimidine-2,5-dione (12a)

Yield 78%, m.p. 150-152 °C, yellow needles. IR (KBr) υ, cm^{-1}: 3320 (NH), 1700 (C=O), 1658 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.85 (d, 1H, *J* = 6.8 Hz, pyrimidine-H), 3.89 (d, 1H, *J* = 6.8 Hz, pyrimidine-H), 7.22-7.28 (m, 4H, Ar-H), 7.79-7.90 (m, 4H, Ar-H and thiophene H-3,4,5), 9.50 (brs, 1H, NH), 10.12 (brs, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_c 70.5 (pyrimidine C), 71.9 (pyrimidine C), 112.1, 127.5, 128.2, 132.1, 135.8, 137.9, 140.5, 152.4 (Ar-C and thiphene-C), 161.1, 179.9 (2C=O). Anal. calcd. for $C_{14}H_{12}N_2O_2S$ (272.32): C, 61.75; H, 4.44; N, 10.29. Found: C, 61.94; H, 4.59; N, 10.18.

4-(Thiophen-2-yl)-6-(3,4,5-trimethoxyphenyl) tetrahydropyrimidine0 2,5-dione (12c)

Yield 78%, m.p. 95-97 °C, yellow needles. IR (KBr) υ, cm^{-1}: 3267 (NH), 1708 (C=O), 1653 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.31 (s, 6H, 2 OCH_3), 3.35 (s, 3H, OCH_3), 3.91 (d, 1H, *J* = 6.8 Hz, pyrimidine-H), 3.94 (d, 1H, *J* = 6.8 Hz, pyrimidine-H), 7.22 (s, 2H, Ar-H), 7.50-7.55 (m, 2H, thiohene H-3,4), 7.78 (d, 1H, *J* = 7.2 Hz, thiohene H-5), 8.72 (brs, 2H, 2NH). MS, *m/z* (%) (362.2, 3.10%, M^+). Anal. calcd. for $C_{17}H_{18}N_2O_5S$ (362.40): C, 56.34; H, 5.01; N, 7.73. Found: C, 56.19; H, 5.16; N, 7.88.

***2-Imino-4-phenyl-6-(thiophen-2-yl)-tetrahydropyrimidin-5(2H)one* (13a)**

A mixture of compound **2a** (10 mmole), guanidine hydrochloride (10 mmole), potassium hydroxide (1.0 g) in ethanol (25 m) was heated at reflux temperature for 3 hours. The solvent was evaporated till dryness and then washed with cold methanol. Yield 50%, m.p. 270-272 °C, white powder. IR (KBr) υ, cm^{-1}: 3379 (NH), 1712 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.70 (s, 1H, pyrimidine-H), 3.73 (s, 1H, pyrimidine-H), 7.22 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.26-7.31 (m, 2H, Ar-H), 7.57-7.63 (m, 4H, Ar-H and thiophene H-3,4,5), 9.72-9.76 (brs, 2H, 2NH), 10.84 (brs, 1H, NH). Anal. calcd. for $C_{14}H_{13}N_3OS$ (271.34): C, 61.97; H, 4.83; N, 15.49. Found: C, 62.12; H, 4.91; N, 15.29.

General method for preparation of compounds 14b,c

A mixture of compound **2b,c** (10 mmole), carbon disulfide (10 mmole), potassium hydroxide (1 g) in ethanol (20 mL) was refluxed for 3 hours. The mixture was put onto crushed ice-water, filtered and crystallized.

(4-(3,4-Dimethoxyphenyl)-2-thioxo-1,3-oxathiolan-5-yl)(thiophen-2-yl)methanone (14b)

Yield 78%, m.p. 180-182 °C, solvent of crystallization: ethanol/water (1:1), white powder. IR (KBr) υ, cm^{-1}: 1702 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.89, 3.92 (2s, 6H, 2 O CH_3), 4.21 (d, 1H, *J* = 6.8 Hz, oxathiolan-H), 4.57 (d, 1H, *J* = 6.8 Hz, oxathiolan-H), 7.19 (d, 1H, *J* = 8.2 Hz, Ar-H), 7.27-7.32 (m, 2H, Ar-H), 7.66-7.71 (m, 2H, thiophene H-3,4), 7.77 (d, 1H, *J* = 7.4 Hz, thiophene H-5). Anal. calcd. for $C_{16}H_{14}O_4S_3$ (366.46): C, 52.44; H, 3.85. Found: C, 52.58; H, 3.70.

Thiophen-2-yl(2-thioxo-4-(3,4,5-trimethoxyphenyl)-1,3-oxathiolan-5-yl)methanone (14c)

Yield 82%, m.p. 160-162 °C, solvent of crystallization: ethanol, yellow crystals. IR (KBr) υ, cm^{-1}: 1710 (NH), 1713 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.88 (s, 6H, 2 OCH_3), 3.90 (s, 3H, OCH_3), 4.34 (d, 1H, *J* = 6.6 Hz, oxathiolan-H), 4.85 (d, 1H, *J* = 6.6 Hz, oxathiolan-H), 7.19 (s, 2H, Ar-H), 7.26-7.31 (m, 2H, thiophene H-3,4), 7.77 (d, 1H, *J* = 6.8 Hz, thiophene H-5). ^{13}C NMR (75 MHz, DMSO-d_6): δ_c 56.1 (2 OCH_3), 59.2 (OCH_3), 60.9 (oxathiolan-C), 105.7 (oxathiolan-C), 120.9, 123.4, 125.3, 128.2, 131.7, 133.8, 140.5, 145.5 (Ar-C and thiophene-C), 173.5 (C=O), 181.9 (C=S). MS, *m/z* (%) (396.50, 1.10%, M^+). Anal. calcd. for $C_{17}H_{16}O_5S_3$ (396.49): C, 51.50; H, 4.07. Found: C, 51.38; H, 3.95.

General method for preparation of compounds 15a,b

A solution of the acetylated bromoglucose or acetylated bromoxylose (5 mmole) in acetone (15 mL) was inserted progressively to a stirred mixture of compound **8a** (5 mmole) and KOH (5 mmole) in water (2 mL). Stirring was continued at r.t. for a time at which reaction was judged complete by TLC (chloroform/methanol; 99.7/0.3 v/v). Evaporation of the solvent resulted in a residue that was washed with water (10 mL). The organic layer was extracted with chloroform, dried and evaporated under reduced pressure. Petroleum ether (b.p. 40-60 °C) (45 mL) was then provided to the remnant with stirring. The resulted solid was filtered and re-crystallized.

4-Phenyl-6-(thiophen-2-yl)-2-(2,3,4-tri-O-acetyl-D-glucopyranosylthio)tetrahydro-pyrimidin-5(6H)-one (15a)

Yield 83%, m.p.142-144 °C, reaction time; 3 hours, solvent of crystallization: ethanol/water (3:1), pale yellow crystals. IR (KBr) υ, cm^{-1}: 3420 (NH), 1703 (C=O), 1742 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.92, 1.96, 1.98, 2.01 (4s, 12H, 4CH_3CO), 3.62 (m, 1H, H-5'), 3.78 (s, 1H, pyrimidine-H), 3.88 (dd, 1H, *J* = 3.6 Hz, *J* = 11.2 Hz, H-6'), 4.20 (dd, 1H, *J* = 3.2, *J* = 11.2 Hz, H-6''), 4.38 (s, 1H, pyrimidine-H), 4.57 (t, 1H, *J* = 9.4 Hz, H-4'), 4.95

(t, 1H, *J* = 9.8 Hz, H-2'), 5.23 (d, 1H, *J* = 9.8 Hz, H-1'), 5.39 (t, 1H, *J* = 9.4 Hz, H-3'), 6.76-6.84 (m, 4H, Ar-H), 7.12-7.25 (m, 4H, Ar-H and thiophene H-3,4,5), 7.93 (brs, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_c 19.8, 20.1, 20.4 (4*C*H_3CO), 61.2 (C-6'), 64.1 (C-4'), 65.2 (pyrimidine-C), 66.3 (pyrimidine-C), 68.2 (C-3'), 71.1 (C-2'), 71.8 (C-5'), 89.6 (C-1'), 110.5, 119.2, 120.6, 122.4, 125.8, 129.3, 130.3, 134.9, 155.4 (Ar-C, thiophene-C and pyrimidine C), 170.1, 170.8, 173.1, 179.5 (5C=O). Anal. calcd. for $C_{28}H_{30}N_2O_{10}S_2$ (618.67): C, 54.36; H, 4.89; N, 4.53. Found: C, 54.20; H, 4.72; N, 4.69.

4-Phenyl-6-(thiophen-2-yl)-2-(2,3,4-tri-O-acetyl-D-xylopyranosylthio)tetrahydro-pyrimidin-5(6H)-one (15b)

Yield 78%, m.p. 149-151 °C, reaction time; 4 hours, solvent of crystallization: ethanol/water (3:1), pale yellow powder. IR (KBr) υ, cm^{-1}: 3367 (NH), 1718 (C=O), 1750 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.92, 1.96, 2.01 (3s, 9H, 3CH_3CO), 3.82 (s, 1H, pyrimidine-H), 3.86 (dd, 1H, *J* = 2.8 Hz, *J* = 11.0 Hz, H-5'), 4.16-4.18 (m, 1H, H-5''), 4.37 (s, 1H, pyrimidine-H), 4.59 (t, 1H, *J* = 9.2 Hz, H-4'), 4.94 (t, 1H, *J* = 9.8 Hz, H-2'), 5.24 (d, 1H, *J* = 9.8 Hz, H-1'), 5.38 (t, 1H, *J* = 9.2 Hz, H-3'), 6.89-7.02 (m, 4H, Ar-H), 7.14-7.27 (m, 4H, Ar-H and thiophene H-3,4,5), 7.98 (brs, 1H, NH). Anal. calcd. for $C_{25}H_{26}N_2O_8S_2$ (546.61): C, 54.93; H, 4.79; N, 5.13. Found: C, 54.71; H, 4.86; N, 4.98.

General method for preparation of compounds 16a,b

The acetylated thioglycosides **15a,b** (5 mmol) was dissolved in dry saturated methanolic ammonia solution (20 mL) and stirred at 0 °C for 1 h, then stirring was persisted at r.t. for 5 h. Removal of the solvent under vacuum at 40 °C gave a solid residue, which was recrystallized from ethanol to give the corresponding free glycoside **16a,b**.

4-Phenyl-6-(thiophen-2-yl)-2-(D-glucopyranosylthio)tetrahydropyrimidin-5(6H)-one (16a)

Yield 81%, m.p. 188-190 °C, brown powder. IR (KBr) υ, cm^{-1}: 3520-3475 (OH), 3420 (NH), 1725 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.39 (m, 2H, H-6',6''), 3.77-3.82 (m, 1H, H-5'), 3.98-4.11 (m, 2H, H-4',3'), 4.20 (s, 1H, pyrimidine-H), 4.35 (s, 1H, pyrimidine-H), 4.72-4.75 (m, 2H, H-2' and OH), 5.22-5.28 (m, 2H, 2OH), 5.40-5.43 (m, 1H, OH), 5.72 (d, 1H, *J* = 9.6 Hz, H-1'), 7.39-7.52 (m, 4H, Ar-H), 7.92-8.02 (m, 4H, Ar-H and thiophene H-3,4,5), 9.02 (brs, 1H, NH). Anal. calcd. for $C_{20}H_{22}N_2O_6S_2$ (450.52): C, 53.32; H, 4.92; N, 6.22. Found: C, 53.49; H, 5.01; N, 6.05.

4-Phenyl-6-(thiophen-2-yl)-2-(D-xylopyranosylthio)tetrahydropyrimidin-5(6H)-one (16b)

Yield 72%, m.p.193-195 °C, brown powder. IR (KBr) υ, cm^{-1}: 3510-3488 (OH), 3363 (NH), 1722 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.40-3.45 (m, 2H, H-5,5''), 3.89-3.92 (m, 1H, H-4'), 4.12-4.15 (m, 1H, H-3'), 4.22 (s, 1H, pyrimidine-H), 4.38 (s, 1H, pyrimidine-H), 4.75-4.51 (m, 2H, H-2' and OH), 5.24-5.27 (m, 1H, OH), 5.40-5.44 (m, 1H, OH), 5.74 (d, 1H, *J* = 9.8 Hz, H-1'), 7.47-7.58 (m, 4H, Ar-H), 7.75-7.86 (m, 4H, Ar-H and thiophene H-3,4,5), 9.15 (brs, 1H, NH). Anal. calcd. for $C_{19}H_{20}N_2O_5S_2$ (420.50): C, 54.27; H, 4.79; N, 6.66. Found: C, 54.03; H, 4.87; N, 6.49.

CYTOTOXIC ACTIVITY

Material

The cell lines namely; Human liver carcinoma (HepG-2), PC-3 (human prostate adenocarcinoma) and HCT116 (human colorectal carcinoma) cell culture were brought from the American Type Culture Collection (Rockville, MD, USA).

Cell culture

The cells were preserved in the medium of Roswell Park Memorial Institute (RPMI-1640) that was replenished with 10% heat-inactivated FBS (fetal bovine serum), 100 U/mL penicillin and 100 U/mL streptomycin. The cells were grown at 37 °C in 5% CO_2 and 95% moisture.

MTT Cytotoxicity Assay

The cytotoxic activity against the three cell lines was investigated by means of 3-[4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) assay, which is founded on the incision of the tetrazolium salt by mitochondrial dehydrogenases in viable cells (Awad *et al*., 2014; Soliman *et al*., 2014).

The cells were distributed in a 96-well sterile microplate (5×10^4 cells/well), and incubated with each of synthesized compound or Doxorubicin® (positive control), prepared in a set of various concentrations in diemthyl sulfoxide, at 37 °C for 48 hours in a serum-free medium prior to the assay. The media were cautiously isolated after incubation, and then MTT (2.5 mg/mL, 40 µL) was provided to each well and then incubated for further four hours. The crystals of purple formazan dye were solubilized by providing dimethyl sulfoxide (200 µL). At 590 nm (SpectraMax® Paradigm®Multi-Mode microplate reader), the absorbance was determined. The average percentage of viable cells with respect to to the untreated control cells expresses the relative cell viability.

Statistical Analysis

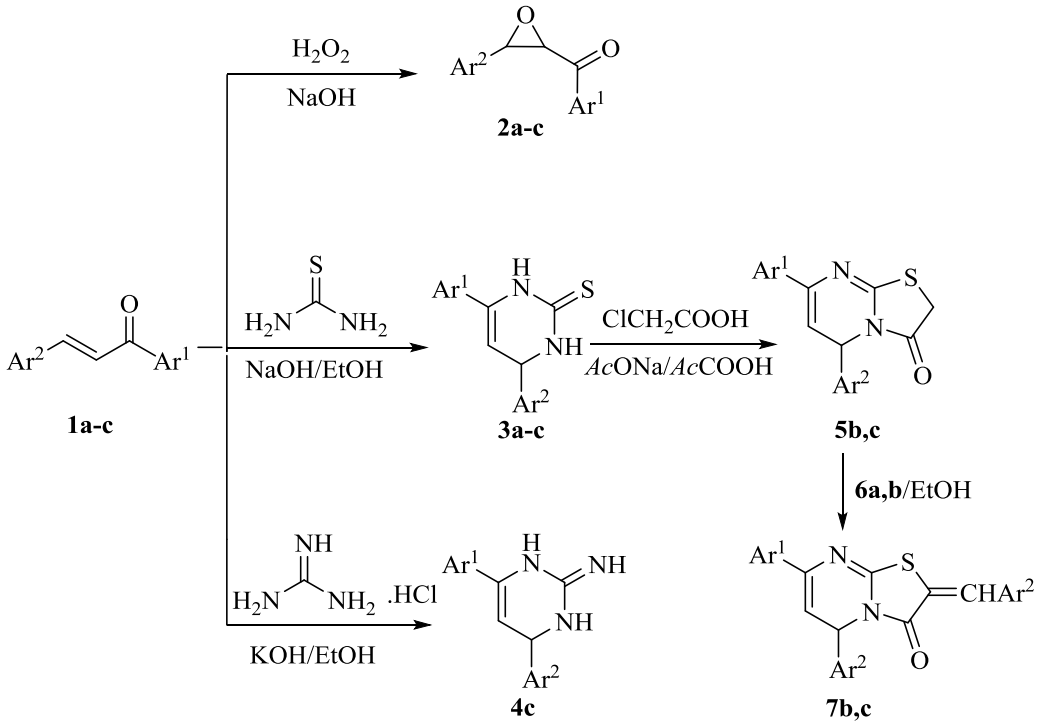
All experimental investigations were performed in triplicate with repeating at three different days. All the OBTAINED values were expressed as mean ± SD. IC_{50}s have been determined by PROBIT analysis by means of SPSS software (version 20, SPSS Inc., Chicago, IL, USA).

RESULTS AND DISCUSSION

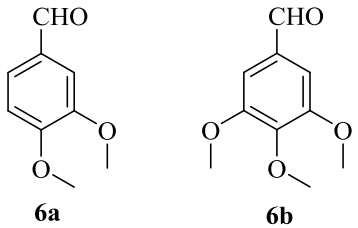
Chemistry

α,β-Unsaturated ketones **1a-c** were prepared by reaction of aromatic aldehyde (namely benzaldehyde, 3,4-dimethoxybenzaldehyde, and 3,4,5-trimethoxybenzaldehyde) with 2-acetylthiophene. The corresponding epoxide derivatives **2a-c** were prepared by reaction of α,β-unsaturated ketones **1a-c** with

hydrogen peroxide in basic medium. Compounds **1a-c** and **2a-c** were used as starting key compounds for the preparation of a variety of substituted pyrimidine derivatives. Reaction of compounds **1a-c** with thiourea in sodium hydroxide afforded the corresponding thiopyrimidine derivatives **3a-c**. The signals assigned to the aryl, pyrimidine ring and NH protons in their ^{1}H NMR spectra confirmed the assigned structure. Thiopyrimidine derivatives **3b,c** were allowed to react with chloroacetic acid and resulted in the formation of thiazolo[3,2-*a*]pyrimidine derivatives **5b,c**. The products revealed absorption band for carbonyl group in the infra-red spectrum and the corresponding ^{1}H NMR data revealed singlet peaks for -SCH_2. Compounds **5b,c** were reacted with 3,4-dimethoxybenzaldehyde and 3,4,5-trimethoxybenzaldehyde (**6a,b**) and afforded the thiazolo[3,2-a]pyrimidin-3(2*H*)-one **7b**, and **7c**, respectively. The ^{1}H NMR spectrum of compounds **7b,c** revealed disappearance of singlet peak of the -SCH_2 and other assignments greed with their structures. Reaction of compounds **1a-c** with guanidine hydrochloride in potassium hydroxide afforded the dihydropyrimidin-2(1*H*)-imine derivative **4c** (scheme 1). The resulting iminopyrimidine derivative **4c** showed the assigned absorption bands for NH functions in the IR spectrum in addition to the doublet signals attributed to the hydrogens (H-4 and H-5) in its ^{1}H NMR spectrum.



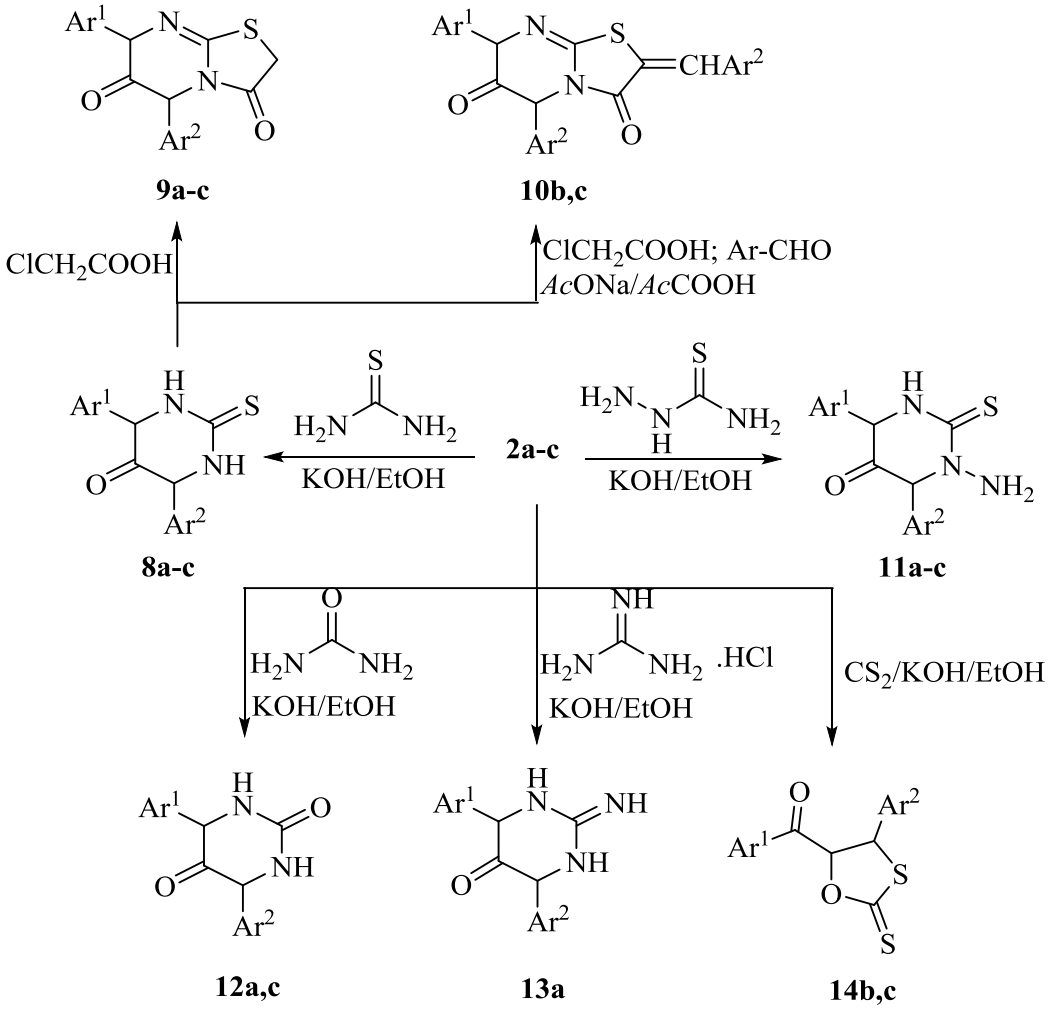
a; Ar^1 = thiophen-2-yl, Ar^2 = -C_6H_5
b; Ar^1 = thiophen-2-yl, Ar^2 = 3,4-$(OCH_3)_2C_6H_3$
c; Ar^1 = thiophen-2-yl, Ar^2 = 3,4,5-$(OCH_3)_3C_6H_2$



6a **6b**

Scheme 1: synthesis of pyrimidine and thiazolopyrimidine derivatives.

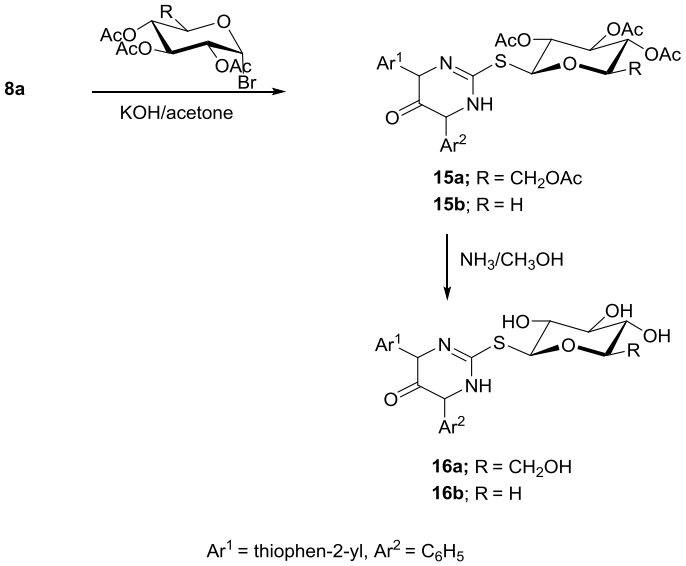
Epoxide derivatives **2a-c** were reacted with thiourea to furnish the thioxopyrimidinone derivatives **8a-c**, respectively. The IR spectra for compounds **8a-c** showed absorption bands for the NH and the ^{1}H NMR spectra showed signals for pyrimidine H-4 and H-6. The presence of such signals each as doublet in ^{1}H NMR data revealed that the pyrimidine moiety in such derivatives is alicyclic, with a twist boat conformation (Flefel *et al*., 2007). Pyrimidine derivative **8a-c** were reacted with chloroacetic acid and formed compounds **9a-c** (Scheme 2). The IR spectra of the latter compounds showed absorption band for carbonyl groups. The signals corresponding singlet signal of the CH_2 appeared in the ^{1}H NMR spectra in addition to aryl and pyrimidine protons. The thioxopyrimidine derivatives **8b,c** were allowed to react with chloroacetic acid and 3,4-dimethoxybenzaldehyde or 3,4,5-trimethoxybenzaldehyde and furnished the arylidine substituted thiazolo[3,2-*a*]pyrimidine derivatives **10b,c** respectively. The oxirane derivatives **2a-c** were reacted with thiosemicarbazide to produce compounds **11a-c**. Also, compounds **2a,c** were reacted with urea in presence of potassium hydroxide to form compounds **12a,c**. Epoxide derivative **2a** was reacted with guanidine hydrochloride in potassium hydroxide to afford the tetrahydropyrimidin-2(1*H*)-imine compound **13a**. Reaction of the unsaturated ketones **2b,c** with carbon disulfide in potassium hydroxide to afforded 1,3-oxathiolane derivatives **14b,c**. The ^{1}H NMR of **14b,c** showed the doublet signals of the oxathiolane ring in addition to aromatic signals.



a, Ar^1= thiophen-2-yl, Ar^2 = -C_6H_5
b, Ar^1= thiophen-2-yl, Ar^2 = 3,4-$(OCH_3)_2C_6H_3$
c, Ar^1 = thiophen-2-yl, Ar^2 = 3,4,5-$(OCH_3)_3C_6H_2$

Scheme 2: Synthesis of amino-and iminopyrimidine and thiazolopyrimidine derivatives.

When compound **8a** was reacted with the acetylated glycopyranosyl bromide for glucose and xylose moieties, in basic medium, the corresponding acetylaed thioglycosides **15a,b** were afforded in good yields. The infra-red spectra of the glycosides **15a,b** indicated the bands in the range 1742-1750 cm^{-1} for the acetyl carbonyl groups. The ^{1}H NMR spectra showed peaks assigned for the protons of the sugar moiety and carbonyl methyl protons. The sugar moiety attachment at the sulfur center rather than the nitrogen atom was also confirmed by the disappearance of a signal corresponding to the C=S in the ^{13}C NMR spectrum of **15a**. Deacetylation of the acetylated thioglycosides **15a,b** in methanol saturated with ammonia produced the free hydroxy thioglycosides **16a,b** (Scheme 3). The IR spectra of the deacetylated products **16a,b** showed absorption bands for the hydroxyl groups and also revealed the absence of the acetyl carbonyl bands. ^{1}H NMR spectra of compounds **16a,b** showed signals corresponding to the hydroxyl protons.



Scheme 3: synthesis of pyrimidine thiolglycosides.

Cytotoxic activity

The cytotoxic activity of prepared compounds was investigated for their activity with respect to HepG-2, PC-3 and HCT-116 cell lines and such activity behavior has been estimated using MTT assay (Awad *et al*., 2014; Soliman *et al*., 2014).

The percentage of the intact cells was determined and compared to the control (table 1 and Fig. 2). The cytotoxicity of compounds under test towards the previously mentioned carcinoma cells were compared with that of Doxorubicin®.

The afforded results indicated that the tested compounds exhibited dose-dependent behavior against the three cancer cell lines. From Table 1 we can deduce that, at 100 µg/mL, two compounds (**11b** and **12a**) showed good cytotoxic activities against HCT-116 carcinoma cells. Compounds **3a**, **5c**, **7c**, **8a** and **11a** showed moderate activities and the remaining compounds displayed weak activities with respect to HCT-116 cells. In addition, in case of PC-3 cancer cells, the synthesized compounds; **7c** and **12a** showed high cytotoxic activity when compared with the reference drug. Furthermore, compound **8a** showed also good cytotoxic activity against such cell line. Three compounds showed moderate activities (**3a**, **11a** and **11b**) and the rest of the compounds showed weak or no cytotoxic activities against this type of cell lines. Furthermore, all the compounds showed weak or no cytotoxic activities against HepG-2 liver cancer.

Table 1: Cytotoxic activity of compounds against cancer cell lines at 100 ppm.

Compound	HCT-116	PC-3	HepG-2
3a	73.42	61.81	24.88
5c	74.60	54.67	39.59
7c	78.36	75.07	32.80
8a	76.55	71.83	17.59
9a	55.18	12.69	1.20
11a	77.63	59.97	18.40
11b	81.99	68.79	20.44
12a	85.84	75.93	18.36
Doxorubicin	92.45	72.21	88.14

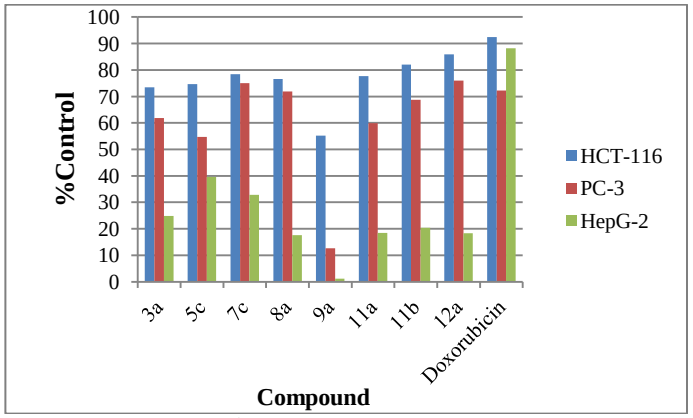


Fig. 2: Cytotoxic activity of compounds against cancer cell lines at 100 ppm.

Table 2: IC_{50} values for synthesized compounds against cancer cell lines.

Compound	HCT-116	PC-3	HepG-2
	IC_{50} (µg/mL)		
3a	68.1 ± 3.6	80.8 ± 3.1	200.8 ± 4.8
5c	67.0 ± 2.9	91.4 ± 3.2	126.2 ± 4.3
7c	63.8 ± 3.2	66.5 ± 3.6	152.4 ± 3.2
8a	65.3 ± 3.1	69.6 ± 2.1	284.1 ± 6.5
9a	90.6 ± 2.6	393.9 ± 4.5	> 1000
11a	64.4 ± 3.1	83.3 ± 2.5	271.7 ± 5.9
11b	60.9 ± 1.8	72.6 ± 3.2	244.5 ± 4.7
12a	58.2 ± 5.1	65.8 ± 2.8	272.2 ± 5.9
Doxorubicin	73.50 ± 2.9	75.24 ± 4.1	67.9 ± 3.2

By correlation of the afforded cytotoxic activity results with structural features of tested compounds it may be deduced that substitution of the thiopyrimidine nucleus at ring nitrogen (N^3) with amino group resulted in an enhanced effects in case of incorporation of phenyl moiety as an aryl function at *C*-6 in the pyrimidine ring. Furthermore, substituted pyrimidine derivatives, with dimethoxyphenyl at *C*-6, revealed more activity against HCT-116 and PC-3 cell lines than their analogues incorporating trimethoxyphenyl moiety. The free 1,3-unsubstituted pyrimidinedione derivatives showed relatively higher activity against HCT-116 and PC-3 cell lines than the corresponding 2-

thioxo analogues. Obviously, the substituted diarylthiazolopyrimidine nucleus free of oxo-substitution at *C*-6 was clearly found to be more active than the corresponding 6-oxo analogue as the activity was lost in compound **10** in which *C*-6 was functionalized with oxo- group. Furthermore, substitution at the methylene carbon in the thiazolopyrimidine system with arylidine function, in absence of oxo- group at *C*-6, led to more active derivatives than their precursors with free CH_2 group, especially in presence of trimethoxyphenyl moiety.

CONCLUSION

New substituted oxo- and thioxopyrimidine, thiazolopyrimidine and pyrimidine thioglycoside derivatives were synthesized and structurally characterized. The prepared compounds showed cytotoxic activity against HCT-116 and PC-3 cell lines revealing moderate to good activities. A number of compounds revealed good effectiveness especially on PC-3 cell line and could be believed as valuable templates for further investigations to get more potent agents.

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