ISSN 1068-1620, Russian Journal of Bioorganic Chemistry, 2021, Vol. 47, No. 6, pp. 1312–1323. © Pleiades Publishing, Ltd., 2021.

Synthesis and Anticancer Activity Evaluation of Some Thienopyrimidine Derivatives

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Received January 29, 2021; revised February 12, 2021; accepted February 15, 2021

Abstract—The current study focused on effective and straightforward routes for preparing a new series of thieno[2,3-*d*]pyrimidine derivatives in addition to their acyclo nucleosides analogue. The chemical structures of the synthesized products have been elucidated through diverse spectroscopy analyses such as (IR, NMR, MS, and elemental analyses). Some selected thienopyrimidine derivatives were investigated for their anticancer activity against two human cancer cell lines (HepG-2 and MCF-7). The results revealed that compounds 3-ethyl-2-hydrazineyl-3,5,6,7-tetrahydro-4*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidin-4-oneand3-ethyl-2-(2-glucozylidenehydrazineyl)-3,5,6,7-tetrahydro-4*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidin-4-one showed the most potent anticancer activity.

Keywords: thienopyrimidine derivatives, hydrazone derivatives, acyclo *C*-nucleosides, anticancer activity

DOI: 10.1134/S1068162021060194

INTRODUCTION

The risks of cancer are increasing day by day, which makes us resort to intensifying scientific research efforts in the field of medicinal chemistry to confront this malignant disease. Heterocyclic compounds containing thiophenes and pyrimidines nucleus demonstrate a broad range of pharmacological activities, for example; antifungal, CNS depressant, analgesic, anti-inflammatory, antibacterial and antitumor [1–11]. Among the heterocyclic derivatives, class of compounds having thienopyrimidine core exhibit a vast variety of pharmacological effects such as antitumor and anticancer activities [12–15]. Triazole-ring-containing compounds act as a prominent pharmacophores through their cooperating with the biological receptors in high affinity because of their dipole character and hydrogen bonding.

This motif is a fundamental part of assortment of medications accessible in medical therapy such as antiplatelet, anticonvulsant, antidepressant, antifungal, antimigraine, anticancer, anxiolytic, anticonvulsant and antiviral (ribavirin) [16, 17]. Hydrazones holding an azomethine (–NHN=CH–) group exhibit widespread biological activities like antimicrobial, anticonvulsant, analgesic, anti-inflammatory, and antitumor activities [18]. Furthermore thienopyrimidine nucleosides regarded as antiviral agents [19, 20] and as anti-cancer [21]. Based on the aforementioned and expansion of our concern toward the chemistry of thieno[2,3-*d*]pyrimidine [21–24], we plan to synthesize some novel thienopyrimidine moiety fused with a triazole ring as well as their acyclo *C*-nucleoside derivatives and testing their anti-cancer activity.

RESULTS AND DISCUSSION

The starting material 3-ethyl-2-mercapto-3,5,6,7-tetrahydro-4*H*-cyclopenta [4, 5]thieno[2,3-*d*]pyrimidin-4-one (**I**) was obtained according to literature reported [21] (Scheme 1). Treatment of potassium salt of (**I**) with methyl iodide yielded (**II**). Treatment of compound (**II**) with hydrazine hydrate or piperidine in ethanol under reflux gave products (**IIIa**, **b**) in 50 and 55% yield, respectively. The structure of compounds (**IIIa**, **b**) were assigned by (IR, NMR, MS, and elemental analyses). The IR of compound (**IIIa**) as an example showedsignals at 3349 and 3308 cm^{-1} due to (NH_2) and (NH) groups respectively. Its ^1H NMR displayed the disappearance of the signal at δ 2.67 ppm due to S–CH_3 group and the presence of signals for (NH_2) and (NH) protons at δ 4.50 and 8.49 ppm, respectively.

It was interesting to explore the capability of compound (**IIIa**) towards ring closure reactions using different reagents (Scheme 2).Thus, compound (**IIIa**)

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reacted with sodium nitrite in acetic acid, carbon disulfide, triethyl orthoformate, benzoyl chloride and acetic anhydride to afforded compounds (**IVa**), (**IVb**), (**IVc**), (**IVd**) and (**IVe**), respectively. The composition of compounds (**Iva–e**) were evidenced from their (MS, IR and ^{1}H NMR). The IR spectra of (**Iva–e**) designated the presence of band absorption at 1656 to 1663 cm^{-1} for carbonyl groups and the absence of the absorption bands due to (NH) and (NH_2) groups. The ^{1}H NMR of compounds (**Iva–e**) judged the absence of signals corresponding to (NH_2) and (NH) groups. Further support is picked up from MS spectra. The MS of (**IVa**), (**IVb**), (**IVc**), (**IVd**) and (**IVe**) recorded molecular ion peaks at m/z =261 (M^+, 44%), 292 (M^+, 100%), 260 (M^+, 30%), 336 (M^+, 35%) and 274 (M^+, 7%), respectively.

Arylidene derivatives (**Va**, **b**) were prepared by condensing of (**IIIa**) with certain aldehydes namely *p*-chlorobenzaldehyde and *p*-nitrobenzaldehyde in boiling ethanol with a few drops of acetic acid (Scheme 3). The signals characteristic for (NH_2) protons vanish in their IR and ^{1}H NMR spectrum .^{1}H NMR of compounds (**Va**, **b**) showed signals of the aryl part in the area of δ 7.83 to 8.24 ppm and signals due to N=CH at δ 8.51 and 8.58 ppm, respectively. MS of (**Va**) demonstrated a molecular ion peaks at m/z = 372 (M^+, 100%), which was compatible with the calculated molecular mass $C_{18}H_{17}ClN_4OS$.

Cyclization of (**Va**, **b**)was achieved uponrefluxing with $FeCl_3$ giving thienotriazolopyrimidine derivatives (**VIa**, **b**).The probable $FeCl_3$-promoted cyclization mechanism was reported in our previous work [22]. The IR and ^{1}H NMR of compounds(**VIa**, **b**) displayed the absence of the signal attributed to (NH) proton. ^{1}H NMR of compounds (**VIa**, **b**) displayed the lack of the imine –N=CH detected in the ^{1}H NMR spectra of their precursors (**Va**, **b**). MS spectra of (**VIa**) showed a molecular ion peaks at m/z = 370 (M^+, 30%) agreed with the calculated molecular mass $C_{18}H_{15}ClN_4OS$. Furthermore, sugar hydrazones (**VIIIa**, **b**) were synthesized through the reaction of compound (**IIIa**) with D-glucose (**VIIa**) and D-xylose (**VIIb**) in ethanol solution containing catalytic drops of acetic acid (Scheme 4). The IR spectra of compounds (**VIIIa**, **b**) demonstrated the absorption bands characteristic to the (OH) groups at 3430 and 3428 cm^{-1}, respectively. The ^{1}H NMR spectra exhibited peaks due to the protons of the sugar chain in the range of 3.40–5.86 ppm and signals due to C-1' methine proton as doublet at δ 7.08 and 7.10 ppm, respectively. Treatment of compounds (**VIIIa**, **b**)with acetic anhydride in the presence of pyridine at ambient temperature provided per-*O*-acetylated sugar hydrazones (**IXa**, **b**). The acetylation occur only to the hydroxyl groups of the sugar residue without *N*-acetylation of the hydrazone residue [22, 25–28]. The IR of compounds (**IXa**, **b**) showed signals for ester carbonyls groups at 1747 and 1743 cm^{-1}, respectively and absorption bands due to (NH) group at 3434 and 3436 cm^{-1} with the disappearance of signals for hydroxyl groups. ^{1}H NMR spectrum of compounds (**IXa**, **b**) demonstrated singlet signals for (OAc) groups in the area of δ 2.03 to 2.20 ppm, in addition to the high chemical shift for the H-1' proton as a douplet at δ 7.28 and 7.20 ppm, respectively with coupling constant of 7.6 Hz and signals due to (NH) group at δ 8.51 and 8.53 ppm, respectively. ^{13}C NMR spectrum of compound (**IXa**) displayed chemical shift for N=CH-(C-1') at δ 152.06 ppm which confirmed the acyclic form of sugar moiety attached to the amino group which agreed with the assigned structures.

Heating hydrazones (**VIIIa**, **b**) in acetic anhydride at 100°C provided the respective per-*O*-acetylated derivatives (**Xa**, **b**) as previously reported with similar systems [22] (Scheme 4). The IR spectra of compounds (**Xa**, **b**) indicated signals in the carbonyl frequency area due to ester carbonyl groups at 1748 and 1745 cm^{-1}, respectively and at 1643 and 1648, respectively corresponding to carbonyl amide, beside the absence of absorption band in NH area. ^{1}H NMR of compounds (**Xa**, **b**) indicated the presence of *O*-acetyl-methyl protons groups as singlet in the range of δ 1.93 to 2.20 ppm in addition to one *N*-acetyl-methyl protons at δ 2.29 and 2.27 ppm, respectively. Furthermore the lack of a characteristic peak assignable to the C-1'methine proton existed in the starting material (**VIIIa**, **b**) at δ 7.08 and 7.10 ppm, respectively and the occurrence of the lower chemical shift for H-1' at δ 5.72 and 5.70 ppm, respectively provide a strong evidence that the cyclization has occurred. The structure of the product (**Xa**) was promoted by utilizing ^{13}C-NMR which revealed the resonances for acetyl-methyl carbons at δ 20.21–28.66 ppm, in addition to the chemical shift for C–N–Ac (C-1' in (**VIIIa**) at δ 91.61 ppm confirmed its nature as C–N–Ac not being as C=N. Moreover, ^{13}C NMR showed seven signals at δ 168.80–175.31 ppm corresponding to the carbonyl groups. Reaction of compound (**XI**) [29] with *p*-chlorobenzaldehyde and *p*-nitrobenzaldehyde furnished the corresponding hydrazones (**XIIa**, **b**) (Scheme 5). ^{1}H NMR spectrum of compounds (**XIIa**, **b**) clearly demonstrated signals of the aromatic protons and signals characteristic to –N=CH group (*c.f.* Experimental).

Similarly, heating compound (**XI**) with monosaccharaides like D-glucose (**VIIa**), and D-xylose (**VIIb**) in ethanol with small amount of acetic acid for 8h yielded our products (**XIIIa**, **b**) (Scheme 6). The formed sugars revealed the absorption bands for (OH) groups in IR spectrum. ^{1}H NMR spectrum demonstrated the existence of the alditolyl protons in the range of δ 3.46 to δ 5.45 ppm and signals at δ 7.19 and 7.21 ppm characteristic to C-1'methine proton. ^{13}C NMR spectra of (**XIIIb**) showed absorption conforming to five carbon atoms of sugar δ 61.99 for (C-5'),

70.29 for (C-4'), 72.73 for (C-3'), 73.67 (C-2') and 155.92 for (N=CH, C-1').

Acylation of products (**XIIIa**, **b**) using acetic anhydride and pyridine furnished the *O*-acetyl derivatives (**XIVa**, **b**). The IR spectrum of the latter products demonstrated the lake of the absorption bands due to the hydroxyl groups and showed instead the ester carbonyl groups absorption bands at 1744 and 1741 cm^{-1}, respectively. ^1H NMR spectrum of compounds (**XIVa**, **b**) revealed the signals due to *O*-acetyl-methyl protons as a singlet and the rest of the alditolyl chain protons (*c.f.* Experimental). ^{13}C NMR spectrum of compound (**XIVa**) exhibited signals due to 6 sp^2 carbons atom of thecarbonyl groups at δ 166.27, 168.79, 169.42, 169.69, 169.89 and 170.79 ppm.

Anticancer Activity

The twelve selected products (**II**), (**IIIa**), (**IIIb**), (**VIIIa**), (**VIIIb**), (**IXa**), (**Xa**), (**Xb**), (**XIIIa**), (**XIIIb**), (**XIVa**) and (**XIVb**) were investigated in vitro for their anticancer effect using (MTT) method against two human cancer cell lines, hepatocellular carcinoma (HepG-2), and breast cancer (MCF-7). The percentages of the viable cells and their IC_{50} values were measured and were, subsequently, assessed with those of the control, (Doxorubicin®) as perceived in (Figs. 1, 2 and Table 1). Through the results that we obtained, we found that the selected products have diversified degrees of inhibitory effect against the two human cancer cells. The better cytotoxic effect was given by compounds (**IIIa**) and (**VIIIa**). Compounds (**II**) and (**Xa**) demonstrated a good viability against the two human tumor cell lines, whereas, the rest of the compounds had moderate to weak activities relative to the positive control. Compounds (**IIIa**) and (**VIIIa**) demonstrated IC_{50} value at 7.73 ± 0.5 and 9.46 ± 0.8, respectively for the activity against cell lines (HepG-2) and at 5.17 ± 0.4 and 8.38 ± 0.7, respectively against breast cancer (MCF-7). Compounds (**II**) and (**Xa**) showed percentage viability IC_{50} at 12.74 ± 1.1 and 17.59 ± 1.4, respectively for the activity against cell lines (HepG-2) and at 19.21 ± 1.6 and 14.97 ± 1.1, respectively against breast cancer (MCF-7). Based on these findings, these compounds may be promising for to be substances for the candidate for anticancer. The activity result showed that the replacement of S-methyl group in the compound (**II**) by hydazino group improved the anticancer activity. The attachment of primary amino group ($NHNH_2$) to the C-2 of the pyrimidine ring enhanced the cytotoxicity activity towards all cell lines than attachment of secondary amino group (piperidino). The insertion of glycosyl moieties to the our target compound thieno[2,3-*d*]pyrimidine is important which enhancing the anticancer activity. Acetylations of glycosyl moieties had no sufficient effect on improving anticancer activity. The synthesized compounds showed anti-cancer action potential against HepG-2 and MCF-7 breast cancer cell line. The possible mechanism of biological action of our synthesis compounds may be due to capability of inducing intrinsic and extrinsic apoptosis pathway, which are well regulated by caspase enzyme. Further studies such as release of cytochrome C and

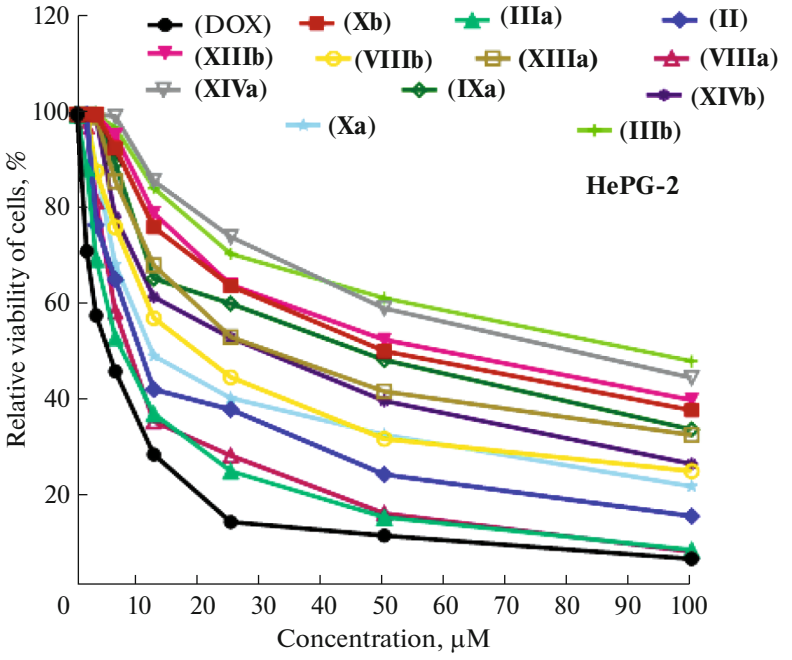


Fig. 1. Average of relative viability of HePG-2 cells (%).

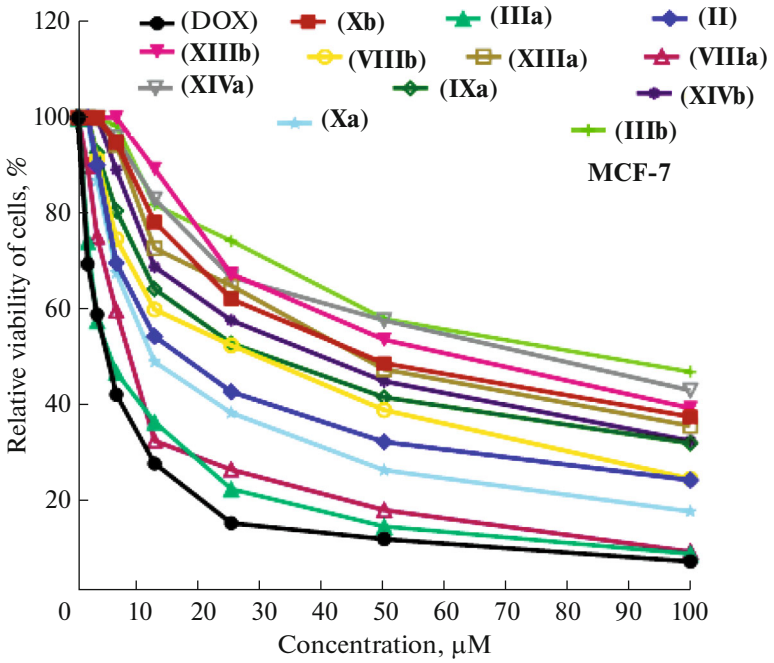


Fig. 2. Average of relative viability of MCF-7 cells (%).

Table 1. In vitro cytotoxic activity of the selected compounds

Comp.	IC_{50} (μM) ± SD	
	HePG-2	MCF-7
Doxorubicin (DOX)	4.50 ± 0.2	4.17 ± 0.2
(II)	12.74 ± 1.1	19.21 ± 1.6
(IIIa)	7.73 ± 0.5	5.17 ± 0.4
(IIIb)	82.27 ± 4.5	75.70 ± 4.2
(VIIIa)	9.46 ± 0.8	8.38 ± 0.7
(VIIIb)	21.59 ± 1.9	25.82 ± 2.0
(IXa)	42.35 ± 2.9	31.74 ± 2.4
(Xa)	17.59 ± 1.4	14.97 ± 1.1
(Xb)	51.53 ± 3.2	48.87 ± 3.3
(XIIIa)	35.18 ± 2.5	46.57 ± 3.1
(XIIIb)	56.49 ± 3.4	58.76 ± 3.7
(XIVa)	74.50 ± 3.9	65.74 ± 3.8
(XIVb)	29.13 ± 2.3	38.39 ± 2.8

reactive oxygen species elevation are warranted to confirm the proposed mechanism.

EXPERIMENTAL

All melting points were carried out using a kofler block apparatus and are uncorrected. The IR spectra were recorded using Perkin-Elmer model 1720 FTIR spectrometer for KBr disc. NMR measurements were made on a brucker high performance digital FT-NMR spectrometer avance III at 400 MHz for ^{1}H and at 100 MHz for ^{13}C. Chemical shifts were reported in δ scale (ppm) relative to TMS as a reference standard. The coupling constants *J* values are given in Hz. The progress of the reactions was controlled by TLC using aluminum silica gel plates 60 F245. Mass spectra were recorded on a Shimadzu QP-2010 plus at 70 eV. Elemental analyses were determined on a PerkinElmer 240. IR, ^{1}H NMR and ^{13}C NMR, were performed at the Faculty of Pharmacy, Cairo University, Egypt. Mass spectra and Elemental analyses were processed at Microanalytical data centre at Faculty of science, Cairo University, Egypt.

3-Ethyl-2-(methylthio)-3,5,6,7-tetrahydro-4*H*-cyclopenta [4, 5]thieno[2,3-*d*]pyrimidin-4-one (II). A warm ethanolic potassium hydroxide [prepared by dissolving (10 mmol) of potassium hydroxide in ethanol (20 mL)] was added to compound **(I)** (2.39 g, 10 mmol) and refluxed for (2 h). After cooling, a solution of methyl iodide (10.50 mmol) in ethanol (10 mL) was added. The reaction mixture was refluxed for (6 h). The reaction content was then triturated with ice cold water (50 mL). The product was collected by filtration and purified from ethanol. Brown; yield 76%; mp 95–197°C; IR(KBr): ν (cm^{-1}) = 1659 (C=O); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 1.06 (t, 3H, *J* = 4.9 Hz, $-CH_2\underline{CH_3}$), 2.40 (m, 2H, CH_2), 2.51 (m, 2H, CH_2), 2.67 (s, 3H, $S-CH_3$), 2.90 (m, 2H, CH_2), 4.35 (q, 2H, *J* = 4.9 Hz, $-\underline{CH_2}CH_3$); ^{13}C NMR (DMSO-d_6): δ_{ppm} = 21.88 ($-CH_2\underline{CH_3}$), 23.54 ($S-CH_3$), 27.72 (CH_2),

28.88 (CH_2), 29.49 (CH_2), 38.10 ($-\underline{CH_2}CH_3$), 117.18, 127.33, 137.43, 139.47 (4C, C=C), 157.09 (C=N), 166.05 (C=O); MS *m/z* (%): 266 (M^+, 100).

General procedure for preparation of 3-ethyl-2-substituted-3,5,6,7-tetrahydro-4*H*-cyclopenta[4,5]thieno-[2,3-*d*]pyrimidin-4-one (IIIa,b). Refluxing of **II** (2.66 g, 10 mmol) with hydrazine hydrate (0.96 g, 30 mmol) or piperidine (2.55 g, 30 mmol) in absolute ethanol (50 mL) for 8 h. The reaction was cooled and the product was picked up by filtration, dried, and purified from ethanol.

3-Ethyl-2-hydrazineyl-3,5,6,7-tetrahydro-4*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidin-4-one (IIIa). Pale brown crystals; yield 50%; mp 210–212°C; IR (KBr): ν (cm^{-1}) = 3349, 3308 (NH_2 + NH), and 1644 (C=O); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 1.13 (t, 3H, *J* = 4.9 Hz, $-CH_2\underline{CH_3}$), 2.32 (m, 2H, CH_2), 2.50 (m, 2H, CH_2), 2.82 (m, 2H, CH_2), 3.97 (q, 2H, *J* = 4.9Hz, $\underline{CH_2}CH_3$), 4.50 (br, NH_2, D_2O exchangeable), 8.49 (br, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ_{ppm} = 19.17 ($-CH_2\underline{CH_3}$), 27.72 (CH_2), 29.10 (CH_2), 34.75 (CH_2), 35.88 ($-\underline{CH_2}CH_3$), 110.87, 129.73, 139.44, 147.14 (4C, C=C), 152.57 C=N), 171.75 (C=O); MS *m/z* (%): 250 (M^+, 100).

3-Ethyl-2-(piperidin-1-yl)-3,5,6,7-tetrahydro-4*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidin-4-one (IIIb). Black crystals; yield 55%; mp 260–262°C; IR (KBr ν (cm^{-1}) = 1649 (C=O); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 1.04 (t, 3H, *J* = 4.9 Hz, $-CH_2\underline{CH_3}$), 2.49 (m, 6H, CH_2), 2.59 (m, 6H, CH_2), 2.96 (m, 4H, CH_2), 4.09 (q, 2H, *J* = 4.9Hz, $-\underline{CH_2}CH_3$).

4-Ethyl-7,8-dihydro-6*H*-cyclopenta[4,5]thieno-[3,2-*e*]tetrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (IVa). A solution of compound **IIIa** (1.25 g, 5 mmol) in 10 mL acetic acid allowed to cold at 5°C then a solution of (0.15 g, 0.01 mmol) sodium nitrite dissolved in cold water 3 mL was added, the reaction mixture was stirred for 24 h at room temperature. The product was picked up by filtration, dried, and purified from ethanol. Brown crystals; yield 50%; mp 180–182°C; IR (KBr): ν (cm^{-1}) = 1660 (C=O); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 1.06 (t, 3H, *J* = 4.9 Hz, $-CH_2\underline{CH_3}$), 2.53 (m, 2H, CH_2), 2.67 (m, 2H, CH_2), 2.99 (m, 2H, CH_2), 4.35 (q, 2H, *J* = 4.9Hz, $-\underline{CH_2}CH_3$); MS *m/z* (%): 261 (M^+, 44).

4-Ethyl-1-mercapto-7,8-dihydro-6*H*-cyclopenta [4,5]thieno[3,2-*e*][1,2,4]triazolo[4,3-*a*]pyrimidin-5(4*H*)-one (IVb). A mixture of compound (**IIIa**) (0.79 g, 3 mmol) and CS_2 (1.5 mL) in 10 mL (3%) alcoholic KOH, was refluxed for 6 h. The deposited precipitate gained on acidification with HCl was collected and purified from ethanol, light brown powder; yield 70%; mp 190–192°C; IR (KBr): ν (cm^{-1}) = 1661 (C=O); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 1.25 (t, 3H, *J* = 4.9 Hz, $-CH_2\underline{CH_3}$)), 2.52 (m, 2H, CH_2), 2.70 (m, 2H, CH_2), 2.91 (m, 2H, CH_2), 4.37 (q, 2H, *J* = 4.9 Hz, $-\underline{CH_2}CH_3$), 11.80 (s, 1H, S-H), MS *m/z* (%) 292 (M^+, 100).

4-Ethyl-7,8-dihydro-6*H*-cyclopenta[4,5]thieno-[3,2-*e*][1,2,4]triazolo[4,3-*a*]pyrimidin-5(4*H*)-one (IVc). A mixture of compound (**IIIa**) (0.79 g, 3 mmol) and 20 mL triethyl orthoformate was boiled under reflux for 6 h. The reaction was cooled; the deposited precipitate, was filtered, dried, and purified from ethanol. Brown powder; yield 55%; mp 222–224°C; IR (KBr): ν (cm^{-1}) = 1659 (C=O); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 1.05 (t, 3H, *J* = 4.9 Hz, $-CH_2\underline{CH_3}$), 2.49 (m, 2H, CH_2), 2.65 (m, 2H, CH_2), 2.96 (m, 2H, CH_2), 4.13 (q, 2H, *J* = 4.9 Hz, $-\underline{CH_2}CH_3$), 9.06 (s, 1H, CH, triazole ring), MS *m/z* (%) 260 (M^+, 30).

4-Ethyl-1-phenyl-7,8-dihydro-6*H*-cyclopenta[4, 5]-thieno[3,2-*e*][1,2,4]triazolo[4,3-*a*]pyrimidin-5(4*H*)-one (IVd). Refluxing of compound (**IIIa**) (0.79 g, 3 mmol) with benzoyl chloride (10 mL) for 8 h, filtered, cooled and poured into ammonia solution. The precipitate formed was filtered, dried and purified from ethanol/dioxane. light brown; yield 50%; mp 150–152°C; IR (KBr): ν (cm^{-1}) = 1663 (C=O); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 1.13 (t, 3H, *J* = 4.9 Hz, $-CH_2\underline{CH_3}$), 2.54 (m, 2H, CH_2), 2.60 (m, 2H, CH_2), 2.94 (m, 2H, CH_2), 4.31 (q, 2H, *J* = 4.9 Hz, $-\underline{CH_2}CH_3$), 7.80 (m, 5H, Ar–CH), MS *m/z* (%) 336 (M^+, 35).

4-Ethyl-1-methyl-7,8-dihydro-6*H*-cyclopenta[4,5]-thieno[3,2-*e*][1,2,4]triazolo[4,3-*a*]pyrimidin-5(4*H*)-one (IVe). Refluxing of compound (**IIIa**) (0.79 g, 3 mmol) with acetic anhydride (10 mL) for 6 h, cooled. The precipitate formed was filtered, dried and purified from ethanol/dioxane. Black crystals; yield 55%; mp 195–197°C; IR (KBr): ν (cm^{-1}) = 1656 (C=O); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 1.14 (t, 3H, *J* = 4.9 Hz, $-CH_2\underline{CH_3}$), 2.20 (s,3H,CH_3), 2.40 (m, 2H, CH_2), 2.67 (m, 2H, CH_2), 3.00 (m, 2H, CH_2), 4.29 (q, 2H, *J* = 4.9 Hz, $-\underline{CH_2}CH_3$), MS *m/z* (%) 274 (M^+, 7).

General procedure for preparation compounds (Va, b) and (XIIa, b). To a solution of compound (**IIIa**) (10 mmol) or (**XI**) (10 mmol) in ethanol (30 mL), *p*-chlorobenzyldehyde (10 mmol) or *p*-nitrobenzyldehyde (10 mmol) with two drops of acetic acid were added. The reaction mixture was heated under reflux for for 8 h. The products thus, formed on cooling was filtered, and purified from ethanol.

2-(2-(4-Chlorobenzylidene)hydrazineyl)-3-ethyl-3,5,6,7-tetrahydro-4*H*-cyclopenta[4,5]thieno[2,3-*d*]-pyrimidin-4-one (Va). Light green crystals; yield 85%; mp 180–182°C; IR (KBr): ν (cm^{-1}) = 1662 (C=O);

^{1}H NMR (DMSO-d_6): δ_{ppm} = 1.21 (t, 3H, J = 4.9 Hz, $-CH_2\underline{CH_3}$)), 2.53 (m, 2H, CH_2), 2.69 (m, 2H, CH_2), 3.00 (m, 2H, CH_2), 4.39 (q, 2H, J = 4.9 Hz, $-\underline{CH_2}CH_3$), 7.86 (d, 2H, J = 8.3 Hz, Ar–H), 8.24 (d, 2H, J = 8.3 Hz, Ar–H), 8.51 (s, 1H, N=CH), 11.12 (br, NH, D_2O exchangeable). MS m/z (%) 372 (M^+, 100).

2-(2-(4-Nitrobenzylidene)hydrazineyl)-3-ethyl-3,5,6,7-tetrahydro-4*H*-cyclopenta[4,5]thieno[2,3-*d*]-pyrimidin-4-one (Vb). Light yellow crystals; yield 87%; mp 195–197°C; IR (KBr): ν (cm^{-1}) = 1664 (C=O); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 1.24 (t, 3H, J = 4.9 Hz, $-CH_2\underline{CH_3}$), 2.49 (m, 2H, CH_2), 2.64 (m, 2H, CH_2), 2.98 (m, 2H, CH_2), 4.36 (q, 2H, J = 4.9Hz, $-\underline{CH_2}CH_3$), 7.83 (d, 2H, J = 8.3 Hz, Ar–H), 8.20 (d, 2H, J = 8.3 Hz Ar–H), 8.58 (s, 1H, N=CH), 11.10 (br, NH, D_2O exchangeable).

General procedure for preparation of 1-(4-substituted)-4-ethyl-7,8-dihydro-6*H*-cyclopenta[4,5]thieno-[3,2-*e*][1,2,4]triazolo[4,3-*a*]pyrimidin-5(4*H*)-one (VIa, b). A solution of (**Va**, **b**) (10 mmol) in ethanol (50 mL) was boiled then a 2 M solution of $FeCl_3$ in ethanol (2 mL) was added dropwise. Refluxing for 20 min then stand 12 h at room temperature. The precipitate was filtered, and purified from ethanol.

1-(4-Chlorophenyl)-4-ethyl-7,8-dihydro-6*H*-cyclopenta[4, 5]thieno[3,2-*e*][1,2,4]triazolo[4,3-*a*]pyrimidin-5(4*H*)-one (VIa). Brown crystals; yield 58%; mp 189–191°C; IR (KBr): ν (cm^{-1}) = 1665 (C=O); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 1.13 (t, 3H, J = 4.9 Hz, $-CH_2\underline{CH_3}$), 2.40 (m, 2H, CH_2), 2.60 (m, 2H, CH_2), 2.97 (m, 2H, CH_2), 4.34 (q, 2H, J = 4.9 Hz, $-\underline{CH_2}CH_3$), 7.80 (d, 2H, J = 8.3 Hz, Ar–H), 8.20 (d, 2H, J = 8.3 Hz Ar–H); MS m/z (%) 370 (M^+, 30).

1-(4-Nitrophenyl)-4-ethyl-7,8-dihydro-6*H*-cyclopenta[4,5]thieno[3,2-*e*][1,2,4]triazolo[4,3-*a*]pyrimidin-5(4*H*)-one (VIb). Brown crystals; yield 60%; mp 185–187°C; IR (KBr): ν (cm^{-1}) = 1662 (C=O); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 1.19 (t, 3H, J = 4.9 Hz, $-CH_2\underline{CH_3}$), 2.40 (m, 2H, CH_2), 2.65 (m, 2H, CH_2), 2.99 (m, 2H, CH_2), 4.33 (q, 2H, J = 4.9 Hz, $-\underline{CH_2}CH_3$), 7.78 (d, 2H, J = 8.3 Hz, Ar–H), 8.23 (d, 2H, J = 8.3 Hz, Ar–H).

General procedure for the synthesis of compounds (VIIIa, b) and (XIIIa, b). Refluxing compounds (**IIIa**) or (**XI**) (10 mmol) and respective monosaccharides (10 mmol) in ethanol (30 ml) containing two drops of acetic acid for 8 h. The products that separated out on cooling was filtered, driedand purified from ethanol.

3-Ethyl-2-(2-glucozylidenehydrazineyl)-3,5,6,7-tetrahydro-4*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidin-4-one (VIIIa). Pale brown crystals; yield 60%; mp 150–152°C. IR (KBr): ν (cm^{-1}) = 3430 (OH), 3219 (NH), 1661 (C=O). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 1.11 (t, 3H, J = 4.9 Hz, $-CH_2\underline{CH_3}$), 2.31 (m, 2H, CH_2), 2.75 (m, 2H, CH_2), 3.04 (m, 2H, CH_2), 3.40 (m, H-6', H-6'', alditolyl 2H), 3.54 (m, H-5', alditolyl 1H), 3.97 (q, 2H, J = 4.9 Hz, $-\underline{CH_2}CH_3$), 4.35 (m, H-4', alditolyl 1H), 4.46 (m, H-3' alditolyl 1H), 4.63 (m, 1H, OH), 4.76 (m, H-2', alditolyl 1H), 4.83 (m, 1H, OH), 4.91 (m, 1H, OH), 5.33 (m, 1H, OH), 5.86 (m, 1H,OH), 7.08 (d, 1H, J = 7.2 Hz, N=CH), 8.34 (br, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ_{ppm} = 27.30 ($-CH_2\underline{CH_3}$), 27.58 (CH_2), 29.34 (CH_2), 29.57 (CH_2), 36.15 ($-\underline{CH_2}CH_3$), 61.34 (C-6'), 70.96 (C-5'), 72.09 (C-4'), 72.54 (C-3'), 73.68 (C-2'), 111.09, 130.12, 139.22, 147.35 (4C, C=C), 152.79 (N=CH, C-1'), 157.92 (C=N), 170.56 (C=O).

3-Ethyl-2-(2-zylosylidenehydrazineyl)-3,5,6,7-tetrahydro-4*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidin-4-one (VIIIb). Pale beige crystals; yield 65%; mp 145–147°C IR (KBr): ν (cm^{-1}) = 3428 (OH), 3225 (NH), 1666 (C=O). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 1.15 (t,3H, J = 4.9 Hz, $-CH_2\underline{CH_3}$), 2.39 (m, 2H, CH_2), 2.79 (m, 2H, CH_2), 2.99 (m, 2H, CH_2), 3.80 (m, H-5', H-5'', alditolyl 2H), 4.02 (q, 2H, J = 4.9 Hz, $-\underline{CH_2}CH_3$), 4.42 (m, H-3', H-4', alditolyl 2H), 4.59 (m, 1H, OH), 4.70 (m, H-2', alditolyl 1H), 4.97 (m, 1H, OH), 5.38 (m, 1H, OH), 5.78 (m, 1H,OH), 7.10 (d, 1H, J = 7.2 Hz, N=CH), 8.30 (br, NH, D_2O exchangeable).

General procedure for the synthesis of compounds (IXa, b) and (XIVa, b). Stirring compounds (**VIIIa**, **b**) or (**XIIIa**, **b**) (10 mmol) in dry pyridine (15 mL) and (15 mL) acetic anhydride for 24 h then poured onto crushed ice and the separated product was filtered off, washed with water, dried, and purified from ethanol.

3-Ethyl-2-(2-1',2',3',4',5'-*O*-pentacetylglucosylidenehydrazineyl)-3,5,6,7-tetrahydro-4*H*-cyclopenta [4, 5]thieno[2,3-*d*]pyrimidin-4-one (IXa). Grey solid; yield 70%; mp 135–137°C; IR (KBr): IR (KBr): ν (cm^{-1}) = 3434 (NH), 1747 (ester carbonyls), 1663 (C=O); ^{1}H NMR ($CDCl_3$): δ_{ppm} = 1.43 (t, 3H, J = 4.9 Hz, $-CH_2\underline{CH_3}$), 2.03, 2.06, 2.10, 2.16, 2.20 (5s, 15H, $5COCH_3$), 2.50 (m, 2H, CH_2), 2.61 (m, 2H, CH_2), 2.99 (m, 2H, CH_2), 3.86 (d, J = 3.2Hz, H-6', alditolyl 1H), 4.12 (q, 2H, J = 4.9 Hz, $-\underline{CH_2}CH_3$), 4.30 (m, 1H, H-6'', alditolyl 1H), 5.12 (m, H-5', alditolyl 1H), 5.25 (m, H-4', alditolyl 1H), 5.49 (t, J = 7.4 Hz H-3' alditolyl 1H), 5.74 (d, J = 7.6Hz, H-2', alditolyl 1H), 7.28 (d, J = 7.6 Hz, N=CH), 8.51 (br, NH, D_2O exchangeable); ^{13}C NMR ($CDCl_3$): δ_{ppm} = 19.29 ($-CH_2\underline{CH_3}$), 20.97, 25.93, 28.21, 28.29, 28.88 (5C, $5CH_3$), 29.32 (CH_2), 29.35 (CH_2), 29.75 (CH_2), 30.30 ($-\underline{CH_2}CH_3$), 61.55 (C-6'), 67.65 (C-5'), 70.29 (C-4'), 72.76 (C-3'), 77.06 (C-2'), 111.99, 118.89,

141.41, 144.84 (4C, C=C), 152.06 (N=CH, C-1'), 155.37 (C=N), 169.70, 169.89, 170.35, 170.74, 171.24, 175.54 (6C, C=O).

3-Ethyl-2-(2-1',2',3',4'-*O*-tetracetylzylosylidenehydrazineyl)-3,5,6,7-tetrahydro-4*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidin-4-one (IXb). Pale brown solid; yield 65%; mp 139–141°C. IR (KBr): ν (cm^{-1}) = 3436 (NH), 1743 (ester carbonyls), 1660 (C=O). ^{1}H NMR ($CDCl_3$): δ_{ppm} = 1.29 (t, 3H, *J* = 4.9 Hz, $-CH_2\underline{CH_3}$), 2.03, 2.10, 2.13, 2.17 (4s, 12H, $4COCH_3$), 2.40 (m, 2H, CH_2), 2.54 (m, 2H, CH_2), 2.99 (m, 2H, CH_2), 4.25 (m, H-5', H-5", alditolyl 2H), 4.29 (q, 2H, *J* = 4.9 Hz, $-\underline{CH_2}CH_3$), 5.20 (m, H-4', alditolyl 1H), 5.60 (m, H-3', alditolyl 1H), 5.69 (d, *J* = 7.6 Hz, H-2', alditolyl 1H), 7.20 (d, 1H, *J* = 7.6 Hz, N=CH), 8.53 (br, NH, D_2O exchangeable).

General procedure for the synthesis of acetylated (Xa, b). Heating of compounds (**VIIIa, b**) (1 mmol) with acetic anhydride (5 mL) for 1 h at 100°C, cooled, filtered and purified from ethanol.

1-(2-Acetyl-4-ethyl-5-oxo-1,2,4,5,7,8-hexahydro-6*H*-cyclopenta[4,5]thieno[3,2-*e*] [1,2,4]triazolo[4,3-*a*]pyrimidin-1-yl)pentane-1,2,3,4,5-pentayl pentaacetate (Xa). Silver solid; yield 70%; mp 146–148°C. IR (KBr): ν (cm^{-1}) = 1748 (ester carbonyls), 1664 (C=O), 1643 (amide group). ^{1}H NMR ($CDCl_3$): δ_{ppm} = 1.33 (t, 3H, *J* = 4.9 Hz, $-CH_2\underline{CH_3}$), 2.00, 2.03, 2.05, 2.10, 2.20, 2.29 (6s, 18H, $6COCH_3$), 2.44 (m, 2H, CH_2), 2.51 (m, 2H, CH_2), 3.04 (m, 2H, CH_2), 3.84 (m, H-5', H-5", alditolyl 2H), 4.14 (q, 2H, *J* = 4.9 Hz, $mCH_2\underline{CH_3}$), 4.33 (m, H-4', alditolyl 1H), 5.15 (m, H-3', alditolyl H), 5.27 (d, *J* = 7.4 Hz, H-2', alditolyl 1H), 5.46 (t, 1H, *J* = 7.4 Hz, H-1'), 5.72 (d, *J* = 7.6 Hz, 1H triazole ring); ^{13}C ($CDCl_3$): δ_{ppm} = 20.08 ($-CH_2\underline{CH_3}$), 20.21, 20.56, 20.97, 25.93, 27.96, 28.66 (6C, $6CH_3$), 29.10 (CH_2), 29.23 (CH_2), 29.78 (CH_2), 40.19 ($-\underline{CH_2}CH_3$), 61.10 (C-5'), 67.43 (C-4'), 69.17 (C-3'), 69.83 (C-2'), 70.29 (C-1'), 91.61 (C-NAc), 112.21, 119.89, 140.58, 141.51 (4C, 4C=C), 158.18 (N=C), 168.80, 168.85, 168.88, 169.42, 170.13, 170.79, 175.31 (7C, 7C=O).

1-(2-Acetyl-4-ethyl-5-oxo-1,2,4,5,7,8-hexahydro-6*H*-cyclopenta[4,5]thieno[3,2-*e*][1,2,4]triazolo[4,3-*a*]pyrimidin-1-yl)butane-1,2,3,4-tetrayl tetraacetate (Xb). Brown solid; yield, 60%; mp 140–142°C. IR (KBr): ν (cm^{-1}) = 1745 (ester carbonyls), 1665 (C=O), 1648 (amide group). ^{1}H NMR ($CDCl_3$): δ_{ppm} = 1.30 (t, 3H, *J* = 4.9 Hz, $-CH_2\underline{CH_3}$), 1.93, 1.96, 2.00, 2.10, 2.27 (5s, 15H, $5COCH_3$), 2.45 (m, 2H, CH_2), 2.66 (m, 2H, CH_2), 2.99 (m, 2H, CH_2), 3.80 (m, H-4', H-4" alditolyl 2H), 4.18 (q, 2H, *J* = 4.9 Hz, $-\underline{CH_2}CH_3$), 5.19 (m, H-3', alditolyl 1H), 5.30 (d, *J* = 7.4 Hz, H-2', alditolyl 1H), 5.48 (t, 1H, *J* = 7.4 Hz, H-1', alditolyl 1H), 5.70 (d, *J* = 7.6Hz, 1H triazole ring).

3-((4-Chlorobenzylidene)amino)-2-methyl-3,5,6,7-tetrahydro-4*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidin-4-one (XIIa). Brown solid; yield 65%; mp 205–207°C; IR (KBr): ν (cm^{-1}) = 1675 (C=O); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 1.94 (s, 3H, CH_3), 2.43 (m, 2H, CH_2), 2.63 (m, 2H, CH_2), 2.99 (m, 2H, CH_2), 7.80 (d, 2H, *J* = 8.1 Hz, Ar–H), 8.25 (d, 2H, *J* = 8.1 Hz, Ar–H); 8.57 (s, 1H, N=CH).

2-Methyl-3-((4-nitrobenzylidene)amino)-3,5,6,7-tetrahydro-4*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidin-4-one (XIIb). Brown solid; yield 70%; mp 210–212°C; IR (KBr): ν (cm^{-1}) = 1673 (C=O); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 1.90 (s, 3H, CH_3), 2.40 (m, 2H, CH_2), 2.64 (m, 2H, CH_2), 3.00 (m, 2H, CH_2), 7.95 (d, 2H, *J* = 8.1 Hz, Ar–H), 8.27 (d, 2H, *J* = 8.1 Hz Ar–H); 8.63 (s, 1H, N=CH).

3-(Glucozylidenamino)-2-methyl-3,5,6,7-tetrahydro-4*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidin-4-one (XIIIa). Beige crystals; yield 67%; mp 140–142°C. IR (KBr): ν (cm^{-1}) = 3335 (OH), 3239 (NH), 1671 (C=O). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 1.90 (s, 3H, CH_3), 2.45 (m, 2H, CH_2), 2.61 (m, 2H, CH_2), 2.90 (m, 2H, CH_2), 3.87 (m, H-6', H-6", alditolyl 2H), 4.06 (m, H-5', alditolyl 1H), 4.24 (m, H-3', H-4' alditolyl 2H), 4.70 (m, 1H, OH), 4.72 (m, H-2' alditolyl 1H), 4.83 (m, 1H, OH), 4.97 (m, 1H, OH), 5.05 (m, 1H, OH), 5.35 (m, 1H, OH), 7.19 (d, 1H, *J* = 7.6 Hz, N=CH).

2-Methyl-3-(zylosylidenamino)-3,5,6,7-tetrahydro-4*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidin-4-one (XIIIb). Pale brown crystals; yield 65%; mp 155–157°C. IR (KBr): ν (cm^{-1}) = 3339 (OH), 3237 (NH), 1673 (C=O). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 1.91 (s, 3H, CH_3), 2.38 (m, 2H, CH_2), 2.54 (m, 2H, CH_2), 2.89 (m, 2H, CH_2), 3.46 (m, H-5', alditolyl 1H), 3.64 (d, *J* = 5.1 Hz, H-5", alditolyl 1H), 4.14 (d, *J* = 5.2 Hz, H-4', alditolyl 1H), 4.47 (d, *J* = 6.7 Hz, H-3', alditolyl 1H), 4.85 (m, H-2', alditolyl 1H),4.98 (m, 1H, OH), 5.10 (m, 1H, OH), 5.20 (m, 1H, OH), 5.45 (m, 1H,OH), 7.21 (d, *J* = 7.6 Hz, N=CH), ^{13}C NMR (DMSO-d_6): δ_{ppm} = 21.88(CH_3), 27.53 (CH_2), 29.10 (CH_2), 29.55 (CH_2), 61.99 (C-5'), 70.29 (C-4'), 72.73 (C-3'), 73.67 (C-2'), 117.16, 118.32, 137.45, 139.74 (4C, C=C), 155.92 (N=CH, C-1'), 157.09 (N=C), 166.29 (C=O).

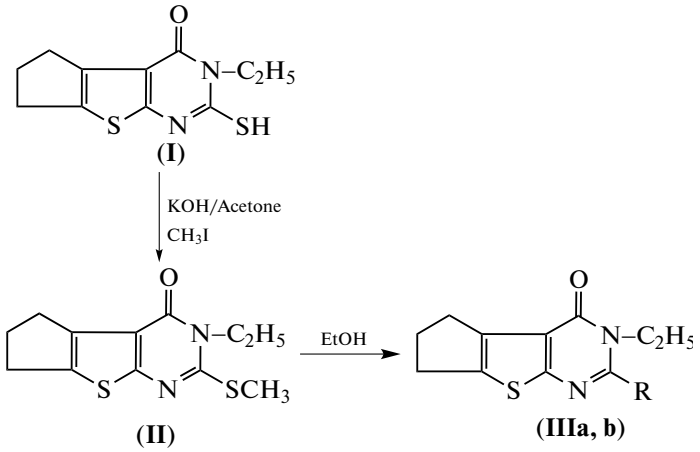
2-Methyl-3-(1',2',3',4',5'-*O*-pentacetylglucosylidenamino-3,5,6,7-tetrahydro-4*H*-cyclopenta[4,5]thieno-[2,3-*d*]-pyrimidin-4-one (XIVa). Light brown solid; yield 74%; mp 130–132°C; IR (KBr): ν (cm^{-1}) = 1744 (ester carbonyls), 1692 (C=O). ^{1}H NMR ($CDCl_3$): δ_{ppm} = 1.27 (s, 3H, CH_3), 2.03, 2.06, 2.11, 2.13, 2.20

(5s, 15H, $5COCH_3$), 2.41 (m, 2H, CH_2), 2.48 (t, 2H, J = 1.9 Hz, CH_2), 3.00 (t, 2H, J = 1.9 Hz CH_2), 4.13 (m, H-6', H-6", alditolyl 2H), 4.27 (d, J = 3.9 Hz, H-5', alditolyl 1H), 5.13 (m, H-4', alditolyl 1H), 5.49 (t, J = 7.3 Hz, H-3', alditolyl 1H), 5.72 (d, J = 7.3 Hz, H-2', alditolyl 1H), 7.28 (d, J = 7.3 Hz, N=CH); ^{13}C NMR ($CDCl_3$): δ_{ppm} = 20.06, 20.31, 20.58, 20.97, 21.19, 24.82 (6C, $6CH_3$), 27.96 (CH_2), 28.73 (CH_2), 29.62 (CH_2), 61.54 (C-6'), 67.85 (C-5'), 69.17 (C-4'), 70.06 (C-3'), 72.55 (C-2'), 118.10, 118.55, 140.38, 140.83 (4C, C=C), 153.24 (N=CH, C-1'), 155.48 (N=C), 166.27, 168.79, 169.42, 169.69, 169.89, 170.79 (6C, C=O).

2-Methyl-3-(1',2',3',4'-*O*-tetracetylzylosylidenamino-3,5,6,7-tetrahydro-4*H*-cyclopenta[4,5]thieno-[2,3-*d*]pyrimidin-4-one (XIVb). Brown solid; yield 73%; mp 125–127°C; IR (KBr): ν (cm^{-1}) = 1741 (ester carbonyls), 1697 (C=O). ^1H NMR ($CDCl_3$): δ_{ppm} = 1.17 (s, 3H, CH_3), 1.98, 2.00, 2.10, 2.12, (4s, 12H, $4COCH_3$), 2.47 (m, 2H, CH_2), 2.55 (m, 2H, CH_2), 2.98 (m, 2H, CH_2), 4.25 (m, H-5', H-5", alditolyl 2H), 5.28 (m, 1H, H-4', alditolyl 1H), 5.42 (t, J = 7.3 Hz, H-3', alditolyl 1H), 5.77 (d, J = 7.3 Hz, H-2', alditolyl 1H), 7.21 (d, 1H, J = 7.3 Hz, N=CH).

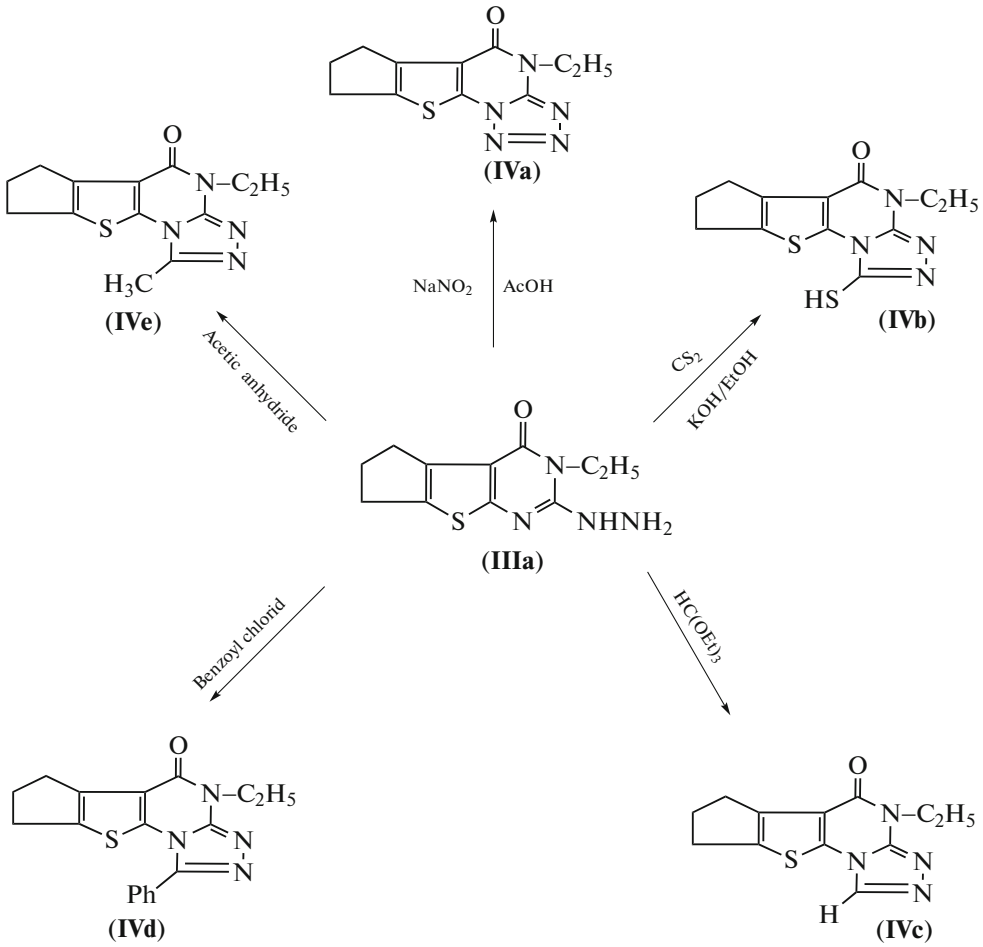
Biological Evaluation

Supply of cell lines carcinoma cells by Holding company for biological products and vaccines (VACSERA), Cairo, Egypt. For the comparison (doxorubicin) employed as a standard, RPMI-1640 medium, "3-(4,5-dimethylthiazol-2-yl)2,5-diphenyltetrazoliumbromide" (MTT) and "Dimethyl sulfoxide" (DMSO) (sigma co., St. Louis, USA). Fetal Bovine serum (GIBCO, UK).Two human cancer cell lines (HepG-2, and MCF-7) were used to define the inhibitory effects of compounds on cell growth using the (MTT) assay. This colorimetric assay is depended on thecleavage of the tetrazolium saltand thenthe conversiona yellow tetrazolium bromide to a purple formazan derivative by mitochondrial succinate dehydrogenase in viable cells. The cell lines were seeded in a 96-well plate at a density of 1.0×10^4 cells/well at 37°C for 48 h under 5% CO_2 incubator. After incubation the cells were treated with different concentration of compounds or Doxorubicin (positive control) in a serum free medium prior to the (MTT) assay and incubated for 24 h. Cells were suspended in RPMI-1640 medium with 10% fetal bovine serum. Antibiotics of 100 units/mL penicillin and 100 μg/mL streptomycin were added at 37°C in a 5% CO_2 incubator. After 24 h 20 μL of (MTT) solution at 5 mg/mL was added and incubated for 4 h. The purple formazan were solubilized by the addition of 100 μL of (DMSO). The absorbance was recorded at 570 nm using a plate reader (EXL 800, USA). The relative cell viability in percentage was calculated as: (Absorbance of treated samples/ Absorbance of untreated sample) X 100 [30, 31].

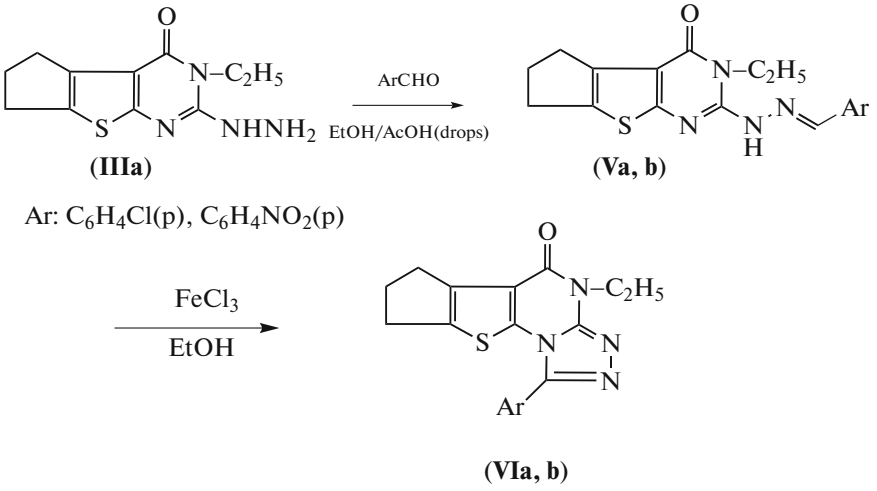


R = **a**; $NHNH_2$, **b**; piperidino

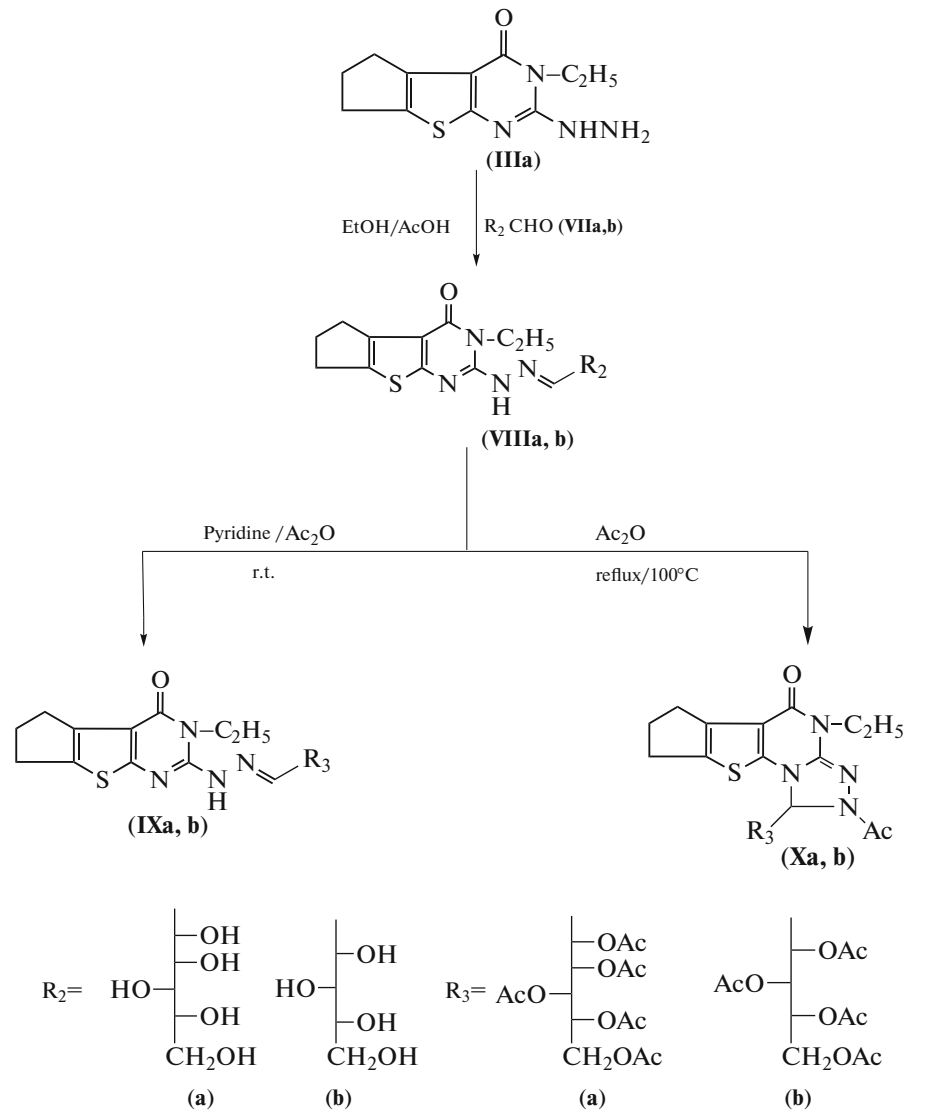
Scheme 1. Synthetic scheme of thienopyrimidine derivatives.



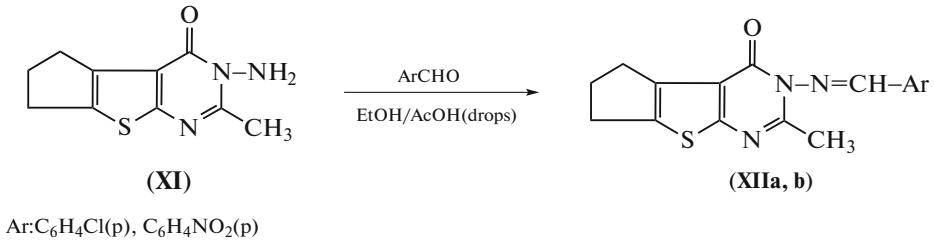
Scheme 2. Synthetic scheme of the ring closure reactions of thienopyrimidine derivatives (**IVa**–**e**).



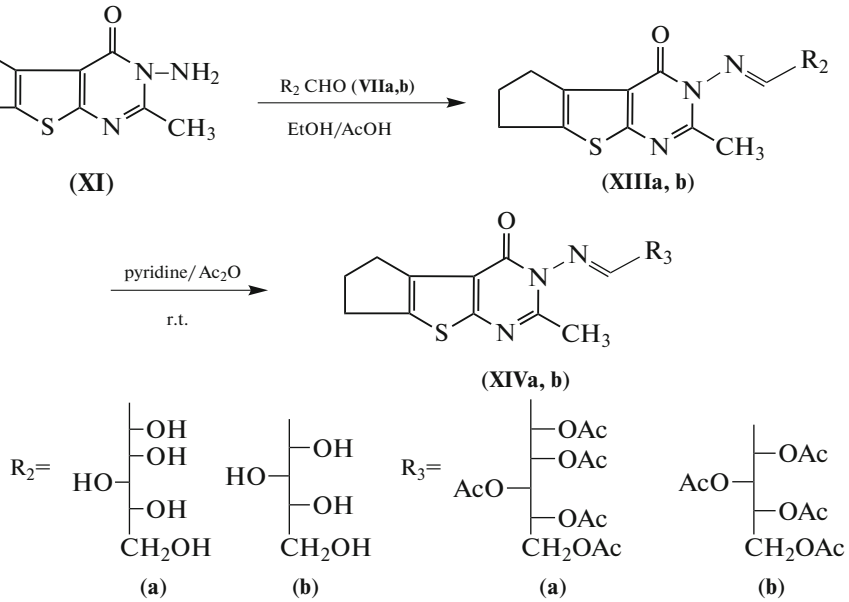
Scheme 3. Thienotriazolopyrimidine derivatives (**VIa**, **b**) synthesis.



Scheme 4. Synthetic scheme of per-*O*-acetylatedderivatives.



Scheme 5. Hydrazones of thienopyrimidine synthesis (**XIIa**, **b**).



(XI) (XIIIa, b) (XIVa, b) (a) (b) (a) (b)

Scheme 6. *O*-Acetyl thienopyrimidine derivatives synthesis.

CONCLUSIONS

In brief, the newly compounds in this article have prepared and characterized. Twelve selected products tested against the two human cancer cell lines (HepG-2 and MCF-7). The compounds (**IIIa**) and (**VIIIa**) demonstrated the highest anticancer activity and compounds (**II**) and (**Xa**) showed a good viability against the two tested human cancer cell lines, whereas, the rest of the products had moderate to weak activities relative to the positive control.

COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any studies involving human participants performed by any of the authors and does not contain any studies involving animals performed by any of the authors.

Conflict of Interests

The authors declare no conflict of interests, financial or otherwise.

SUPPLEMENTARY INFORMATION

The online version contains supplementary material available at https://doi.org/10.1134/S1068162021060194.

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