Synthesis and Anticancer Activity of New Substituted Pyrimidines, Their Bicyclic and Thioglycoside Derivatives

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Abstract. New aryl substituted pyrimidine, oxazole, oxathiolane and thiazolopyrimidine derivatives were synthesized. The glycoside and bicyclic condensed derivatives of the pyrimidine ring system were prepared. The anticancer activity of the prepared compounds against MCF-7 human breast cell line was studied and a number of compounds showed good activity.

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1. Introduction

Pyrimidines are important class of heterocycles and their structural skeleton is a key constituent of nucleic bases and alkaloids in addition to numerous pharmacophores with variety of potent biological activities. These pharmacological properties include anticancer,[1-3] antiviral,[4-6] antibacterial,[7] antifungal,[8,9] antiprotozoal,[10,11] anti-inflammatory[12] and central nervous activities.[13] Moreover, novel 4-(4-substituted phenyl)-6-(4-nitro-henyl)-pyrimidine derivatives were reported to possess antiviral, anti-tubercular and antibacterial activity.[14] Pyrimidinedione derivatives have been studied interestingly and found to have antibacterial and anticancer activities.[15,16] Small heterocyclic rings are rich sources for diversity which, in addition to often exhibiting biological activity, may serve as rigid scaffolds for further display of functionalities. 1,3-Oxathiolane represents such class of heterocycles which have attracted much attention as they have been reported to possess biological activities as including antiviral,[17] antiulcer[18] agonists and antagonists on muscarinic receptors.[19]

On the other hand, the synthesis of substitiuted oxazole and thiazole derivatives play an important role in the search of biologically active derivatives with antibacterial,[20] antifungal,[21] anti- inflammatory activities.[22] Several researches have studied the synthesis of several oxazole and thiazole derivatives with potent antibacterial activity. Further various derivatives of azetidinone[23] and thiazolidinone[24] have also been reported to possess antibacterial activity

Considerable interest has been gained to the synthesis of glycosylthio heterocycles[25] including modifications of both the glycon and aglycon parts as biological inhibitors.[26,27] Importantly, presence of several hydroxyl groups in a molecule is expected to enhance their affinity toward protein and nucleic acid due to the presence of potential hydrogen bond (H-bond) donors and acceptors.[28,29] Recently, we became interested in the synthesis of thioglycosides and acyclic nucleoside analogs incorporating five and six membered ring bases, in addition to their anticancer, antiviral and antimicrobial activity properties.[30-34] Consequently, we have considered the synthesis of new substituted pyrimidines and their bicyclic derivatives with anticancer activity evaluation. In addition, the attachment of new the pyrimidine derivative to sugar moiety to produce its derived thioglycoside was reported.

2. Experimental

Material and Methods

All melting points are uncorrected and measured using Electro-ThermalIA 9100 apparatus (Shimadzu, Japan). Infrared spectra were recorded as potassium bromide pellets on a Perkin-Elmer 1650 spectrophotometer, National Research Centre, Cairo, Egypt. ^{1}H NMR spectra were determined on a Jeol-Ex-500 NMR spectrometer and chemical shifts were expressed as part per million; (δ values, ppm) against TMS as internal reference, National Research Centre, Cairo, Egypt. Mass spectra were recorded on EI + Q1 MSLMR UPLR, National Research Centre, Cairo, Egypt. Microanalyses were operated using Mario Elmentar apparatus, Organic Microanalysis Unit, National Research Centre, Cairo, Egypt and the results were within ±0.4 from the theoretical values. Reactions were monitored using thin layer chromatography (TLC), performed on 0.255 mm silica gel plates, with visualization under UV. light (254 nm).

(4-Bromophenyl)[3-(4-bromophenyl)oxiran-2-yl]methanone (2)

Hydrogen peroxide (5 ml, 30%) was added to a solution of compound **1** (0.01 mole) in acetone (50 ml) - methanol (15 ml) mixture containing sodium hydroxide (1g) with stirring. Stirring was continued for 10 h, cold water was added and solid that precipitated was filtered off, washed with water and crystallized from ethanol to give compound **2**. Yield, 80%. mp, 132-134°C. IR (KBr) cm^{-1}: ν 1684 (C=O). ^{1}H NMR (DMSO-d_6, δ ppm): 4.13 (d, *J* = 1.4 Hz, 1H, β-epoxy-H), 4.78 (d, *J* = 2 Hz, 1H, α-epoxy-H), 7.35-7.92 (m, 8H, Ar-H). MS, *m/z* (%): 379.9 (M^+, 6.2%), 381.9 (M+2, 12.4%), 383.9 (M+4, 5.2%).

Synthesis of compounds 3a,b and 4

To a solution of compound **2** (0.01 mole) in ethanol (100 ml) was added potassium hydroxide (2 g), and urea, thiourea or thiosemicarbazide (0.01 mole). The reaction mixture was refluxed for 4 h and the solvent was diminished under reduced pressure and acidified cold water was added. The precipitated solid was filtered, washed with water and recrystallized from benzene to give compounds **3a,b** or **4**, respectively.

4,6-Bis(4-bromophenyl)tetrahydropyrimidine-2,5-dione (3a)

Benzene; yield 77%; m.p. 170-172ºC. IR spectrum (KBr, ν, cm^{-1}): 3227 (NH), 1724 (C=O); ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 3.87 (d, *J* = 11.8 Hz, 2H, pyrimidine-H4,6), 7.12-7.60 (m, 8H, Ar-H), 10.58 (bs, 2H, 2NH).

4,6-Bis(4-bromoophenyl)-2-thioxo-tetrahydropyrimidin-5-one (3b)

Benzene; yield 66%; m.p. 244-246ºC. IR spectrum (KBr, ν, cm^{-1}): 3283 (NH), 1734 (C=O), 1250 (C=S); ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 3.46-3.49 (d, *J* = 11.4 Hz, 2H, pyrimidine-H4,6), 7.16-7.69 (m, 8H, Ar-H), 10.77 (bs, 2H, 2NH). MS, *m/z* (%): (437.9, M^+, 50%), 439.9 (M+2, 86%), 441.9, (M+4, 47%).

1-Amino-4,6-bis(4-bromoophenyl)-2-thioxo-tetrahydropyrimidin-5 (6*H*)-one (4)

Benzene, yield 69%; m.p. 90-92ºC. IR spectrum (KBr, ν, cm^{-1}): 3270 (NH_2), 3175 (NH), 1670 (C=O), 1234 (C=S); ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 3.33 (s, 1H, pyrimidine-H), 3.99 (s, 1H, pyrimidine-H), 5.88 (bs, 1H, NH_2), 7.03-7.64 (m, 8H, Ar-H), 8.52 (bs, 1H, NH). MS, *m/z* (%): 452.9 (M^+, 33%), 454.9, (M^++2, 65%), 456.9, (M+4, 31%).

1,3-Bis(4-bromophenyl)-3-(diethylamino)prop-2-en-1-one (5)

A mixture of the epoxide derivative **2** (0.01 mole) and dimethylamine (0.01 mol) in 50 ml ethanol was heated under reflux for 24 h. The solvent was evaporated and the formed residue was washed with cold ethanol to afford compounds **5** as yellow foam. Yield 58%. IR spectrum (KBr, ν, cm^{-1}): 1676 (C=O); ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 2.86 (s, 6H, $2CH_3$), 7.36-7.81 (m, 5H, Ar-H), 7.90-8.12 (m, 4H, Ar-H and vinyl-H).

5-(4-Bromobenzoyl)-4-(4-bromophenyl)-3-phenyloxazolidin-2-one (6)

To a solution of the epoxide derivative **2** (0.01 mole) in benzene (20 ml) was added phenyl isothiocyanate (0.01 mole) and a catalytic amount of triethyl amine and the resulting mixture was heated at reflux temperature for 14h. The solvent was concentrated, and the residue which formed was washed with dioxane to afford the oxazolidine derivative **6** as yellow foam. Yield 74%; IR spectrum (KBr, ν, cm^{-1}): 1708 (C=O), 1275 (C=S); ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 6.89-6.91 (m, 2H, oxazole-2H), 7.11-7.52 (m, 8H, Ar-H), 7.60-7.11 (m, 5H, Ar-H); MS, *m/z* (%): 514.9 (M^+, 8%), 516.9 (M+2, 15%), 518.9 (M+4, 6%).

5-(4-Bromobenzoyl)-4-(4-bromophenyl)-1,3-oxathiolane-2-thione (7)

Carbon disulphide (10 ml) was added to a solution of the epoxide **2** and sodium hydroxide (0.01 mole) in ethanol (40 ml)]. The mixture was heated at reflux for 12h, then ice-cold water was added and neutralized by hydrochloric acid. The solid that precipitated was filtered off and recrystallized from benzene to give compound **7**. Yield 55%; m.p.168-171°C. IR spectrum (KBr, ν, cm^{-1}): 1681 (C=O), 1276 (C=S); ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 3.47 (d, *J* = 3.6 Hz, 1H, β-CH), 5.94 (d, *J* = 3.6 Hz, 1H, α-CH), 7.41-7.87 (m, 8H, Ar-H).

Synthesis of 5,7-Bis(4-bromophenyl)-*2H*-thiazolo[3,2-*a*]pyrimidine-3,6-dione (8):

Chloroacetic acid (0.01 mole) and anhydrous sodium acetate (1 g) were added to a solution of the thiopyrimidine derivative **3b** (0.01 mole) in acetic acid (25 ml)-acetic anhydride (12 ml) and the resulting mixture was heated at 100 ºC for 4 h. The reaction mixture was added portion wise to ice-cold water to form a precipitate which was filtered off and recrystallized from AcOH to afford the thiazolopyrimidine **8**. Yield 59%; m.p. 124-126ºC. IR spectrum (KBr, ν, cm−1): 1744-1725 (C=O); ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 3.36 (s, 1H, pyrimidine-H), 3.48 (s, 1H, pyrimidine-H), 3.96 (s, 2H, thiazole CH_2), 6.95–7.36 (m, 8H, Ar-H).

2-Benzylidine-5,7-bis(4-bromophenyl)-*5H,7H*-thiazolo [3,2-*a*]pyrimidine-3,6-dione (9):

To a solution of the thiopyrimidine **3b** (0.01 mole) in acetic acid (25 ml)-acetic anhydride (12 ml), chloroacetic acid, benzaldehyde (0.01 mole) and anhydrous sodium acetate (1 g) were added and the mixture was heated under reflux for 6h. Cold water was added to the reaction mixture and the precipitated solid was filtered off washed with cold water and recrystallized from AcOH to give afford compound **9**. Yield 49%; m.p. 115-118°C. IR spectrum (KBr, ν,

cm^{-1}): 1698 (C=O); ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 3.74 (s, 1H, pyrimidine-H), 3.94 (s, 1H, pyrimidine-H), 6.93-7.92 (m, 13H, Ar-H), 7.95 (s, 1H, vinyl-H).

4,6-Bis(4-bromophenyl)-1-(piperidin-1-ylmethyl)-2-thioxo-tetrahydropyrimidin-5(*6H*)-one (10):

To a solution of the thiopyrimidine **3b** (0.01 mole) in absolute ethanol (25 ml) was added formaldehyde (1.5 ml, 40%) and the mixture was heated under reflux for 1 hour and then cooled. Piperidine (0.01 mole) was added drop wise and the reaction mixture was stirred at rt for 5 h. The solid that precipitated was collected by filtration, dried and recrystallized from ethanol to afford **10**. Yield 77%; m.p. 189-190ºC. IR spectrum (KBr, ν, cm^{-1}): 3262 (NH), 1721 (C=O), 1294 (C=S); ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 1.29-2.19 (m, 6H, piperidine-H), 3.44 (s, 1H, pyrimidine-H), 3.54 (m, 5H, 4H piperidine and pyrimidine H), 3.42 (s, 2H, NCH_2), 7.20-7.70 (m, 8H, Ar-H), 11.13 (s, 1H, NH).

Ethyl 2-(4,6–bis[4-bromoophenyl]-5-oxo-4,5-dihydropyrimidin-2-yloxy)acetate (11):

To a solution of **3a** (0.01 mole), in acetone (25 ml) were added ethyl bromoacetate (0.01 mole) and potassium carbonate (0.03 mole). The mixture was heated at reflux temperature for 18h then left over night. Water was added and the product was extracted with diethyl ether. The organic layer was washed several times with water and then dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded compound **11**. Yield 70%, m.p. 158-160ºC. IR (KBr, ν, cm^{-1}): 1778, 1723 (2 C=O). ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 1.15 (t, *J* = 6.9 Hz, 3H, CH_3CH_2O), 4.11 (q, *J* = 5.4 Hz, 2H, CH_3CH_2O), 4.30 (s, 2H, CH_2), 4.76 (s, 1H, pyrimidine-H), 7.09-7.66 (m, 8H, Ar-H).

4,6-Bis(4-bromophenyl)-2-(2,3,4-tri-*O*-acetyl-D-xylopyranosylthio)pyrimidin-5(4*H*)-one (12)

To a suspension of the substituted pyrimidinethione **3b** (0.01 mol) in aqueous KOH [0.01 mol in distilled water (5 mL)] was added *O*-acetyl-D-xylopyranosyl bromide (0.01 mol) dissolved in acetone (25 mL). The reaction mixture was stirred at rt for 12h. The solvent was evaporated under reduced pressure at 35 ºC and the residue was washed with water. The formed precipitate was filtered, dried and crystallized from ethanol-water 3:1. Yield 76%; m.p. 136–137°C; IR (KBr, ν, cm^{-1}): 1705, 1753 (2 C=O). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.90, 2.02, 2.06 (3s, 9H, 3 CH_3), 4.01-4.11 (m, 2H, H-5′,5″), 4.62-4.77 (m, 2H, pyrimidine-H and H-4′), 5.17-5.24 (m, 1H, H-3′), 5.36 (t, *J* = 6.6 Hz, 1H, H-2′), 5.78 (d, *J* = 9.8 Hz, 1H, H-1′), 6.72-7.88 (m, 6H, Ar-H), 8.16 (d, *J* = 7.8 Hz, 2H, Ar-H).

4,6-Bis(4-bromophenyl)-2-(D-xylopyranosylthio)pyrimidin-5(4*H*)-one (13)

A solution of the thioglycoside derivative **12** (0.01 mol) in methanolic ammonia (20 ml, was stirred 5h at room temperature. The solvent was concentrated under reduced pressure and the precipitated solid was filtered, washed with cold ethanol and dried to afford compound **13**. Yield 72%; m.p. 164-166ºC. IR spectrum (KBr, ν, cm−1): 3475-3420 (OH), 1718 (C=O).

3. Results and Discussion

It has been shown α,β-epoxy ketones were formed by the reaction of hydrogen peroxide with α,β -unsaturated carbonyl compounds. When 1,3-bis(4-bromophenyl) propenone **1** was allowed to react with hydrogen peroxide, substituted bis(4-bromophenyl)-2,3-epoxypropanone (**2**) was obtained in 80% yield. The structure of the epoxy ketone **2** was supported by the spectral and analytical data. Its ^{1}H NMR spectrum revealed the two doublet signals at 4.13 and 4.78 for the epoxy protons. Its mass spectrum showed the molecular ion peak M^+ at 379.9 m/z (%) which agrees with the assigned structure.

Compound **2** was used as starting key for the synthesis of many substituted pyrimidine derivatives. Thus, heating compound **2** with urea thiourea or thiosemicarbazide in alcoholic potassium hydroxide solution, produced the corresponding substituted pyrimidine derivatives **3a,b** and **4**, respectively. The IR spectra of the pyrimidine derivatives **3** and **4** showed absorption bands in the carbonyl frequency region and the NH bands at 1670-1734 and 3175-3283 cm^{-1}, respectively. Their ^{1}H NMR spectra showed the signals corresponding to H-1 and H-4 protons in addition to the two NH signals in the pyrimidine ring and the aromatic proton signals. The presence of these signals in compounds **3** and **4** ^{1}H NMR spectra showed that the pyrimidine nucleus in such compounds is alicyclic, with a twist boat shape.[35]

Reaction of the epoxy ketone **2** with dimethylamine in ethanol and produced the (dimethylamino)prop-2-en-1-one derivative **5** in 58% yield. The ^{1}H NMR spectrum showed the singlet signal for the two methyl groups at 2.86 ppm. On the other hand, the reaction of the epoxide derivative **2** with phenyl isothiocyanate in presence of triethyl amine led to the formation of the oxazole thione derivative **6** in 74% yield. Its H NMR spectrum showed the two oxazole signals at 6.89-6.91 ppm in addition to the signals corresponding to the aromatic protons. When compound **2** was allowed to react with carbon disulphide in ethanol in presence of potassium hydroxide it afforded the 1,3-oxathiolane-2-thione derivative **7** not the dithiolane-2-one derivative. Its ^{1}H NMR spectrum showed signals corresponding to the two oxathiolane signals, each as doublet, which agreed with the assigned structure (scheme 1).

The substituted pyrimidines **3a,b** were used as a

key compounds for the preparation of bicyclic ring systems in addition to *N*-, *O*- and *S*-substituted dihydropyrimidine derivatives. Reaction of **3b** with chloroacetic acid gave the thiazolopyrimidine **8** in 57% yield. Furthermore, when such reaction was carried out in presence of benzaldehyde, the benzylidine derivative **9** was obtained. The ^{1}H NMR spectrum of **8** revealed the singlet signal for the CH_2 at 3.94 ppm while the corresponding spectrum of compound **9** showed the benzylidine proton as singlet signal at 7.95 ppm in addition to the signals of the additional phenyl group. Mannich reaction of **3b** using formaldehyde in presence of piperidine gave the *N*-substituted derivative **10**. Its ^{1}H NMR spectrum revealed the presence of the *N*-CH_2 at 3.42 ppm in addition to the methylene protons signals.

Reactions of substituted pyrimidine derivative **3a** with ethyl bromoacetate resulted in the formation of the *O*-substituted ester derivative **11**. The IR spectrum showed the absence of characteristic absorption band of the amide carbonyl band and its ^{1}H NMR spectrum showed the characteristic signals of the ethyl group as triplet and quartet. Reaction of **3b** with 2,3,4-tri-*O*-acetyl-D-xylopyranoside bromide afforded the thioxylosyl derivative **12** in 76% yield. Its IR spectrum showed the carbonyl absorption bands at 1705 and 1753 cm^{-1}. The chemical shift value in addition to the coupling constant of the anomeric proton (9.8) indicates the â-thio-linkage of the xylosyl moiety. The signal of the anomeric proton of β-*N*-glycosides adjacent to C=S group was reported[36–38] to present at higher chemical shift (6.9–7.2 ppm) due to the anisotropic deshielding effect of the C=S. Formation of the previous dihydro derivatives was also indicated by the absence of NH signal in IR and ^{1}H NMR spectra which is in agreement with previously reported work[39]. Deacetylation of the *O*-acetyl thioglycoside **12** afforded the free thioglycoside derivative **13** for which the IR spectrum showed the hydroxyl absorption bands at 3475-3420 in addition to the disappearance of the carbonyl ester band which is in agreement with the assigned structure (Scheme 3).

Anticancer activity

The activity of the synthesized compounds against MCF-7 human breast cell line was studied. The results represented in IC_{50} values are shown in table 1. Adrinamycin® (doxorubicin) (Mr = 579.9) which is a positive control was used as cytotoxic agent giving 100% inhibition and dimethyl sulfoxide (DMSO) for dissolution of tested compounds. Cell viability was measured by neutral red uptake assay[40]. The neutral red uptake assay provides a quantitative estimation of the number of viable cells in a culture. It is based on the ability of viable cells to incorporate and bind the supravital dye neutral red in the lysosomes. The cells were incubated with various concentration of the test compounds (6.25, 12.5, 25 and 50µg/ml) for 48 h at a cell density of 104 cells/well of 96 well plate. Neutral red working solution (0.4 µg/ml) (Sigma, Aldrich, ST. Louis, MO, USA) was incubated overnight at 37 ˚C the same as treated cells.

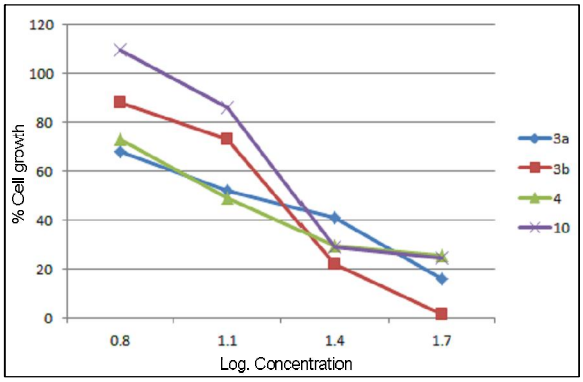
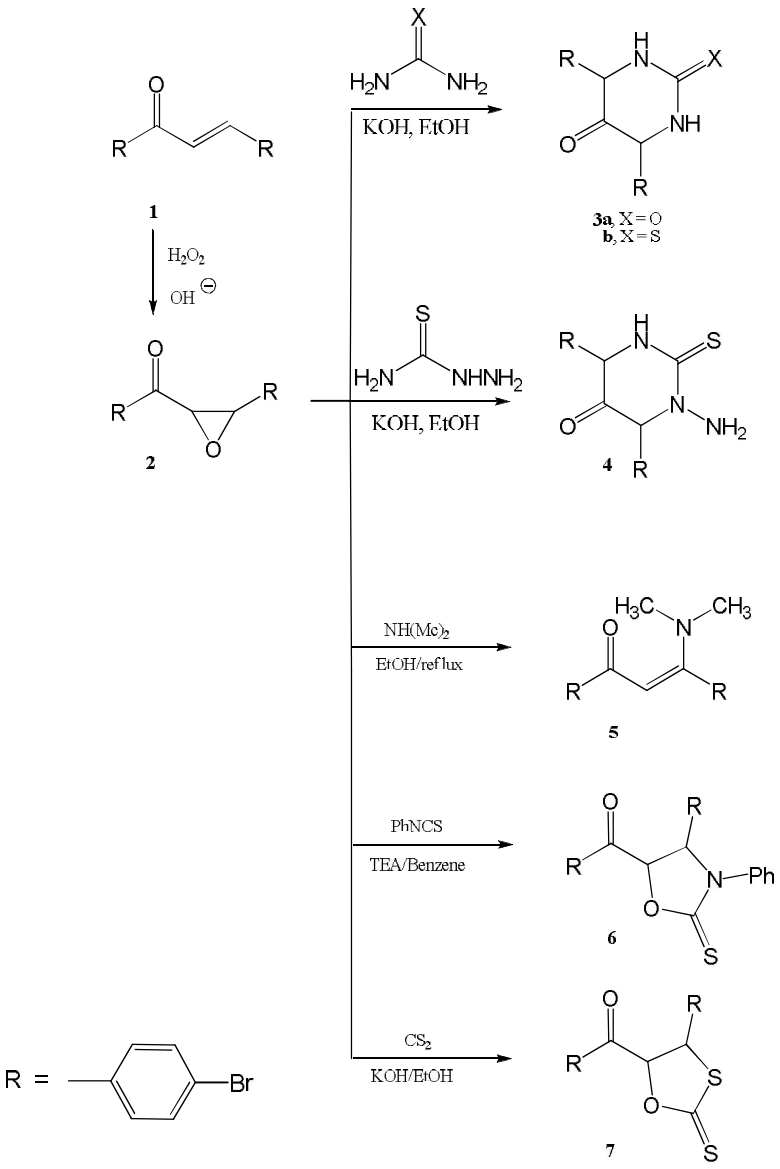


Figure 1: Effect of treatment with various concentrations of compounds **4a,b, 5** and **20** on MCF-7 cell line cytotoxicity (IC_{50})

Studying the anticancer activity of the new compounds against MCF-7 cell line, revealed that compounds presented in table 3 have varied degrees of activity. Compounds **3a**, **3b**, **4** and **10** were the most active with IC_{50} values ranging from 8.51-31.91 µg/ml.

Table 1. *In vitro* cytotoxicity activity of the synthesized compounds in human MCF-7 cell lines.

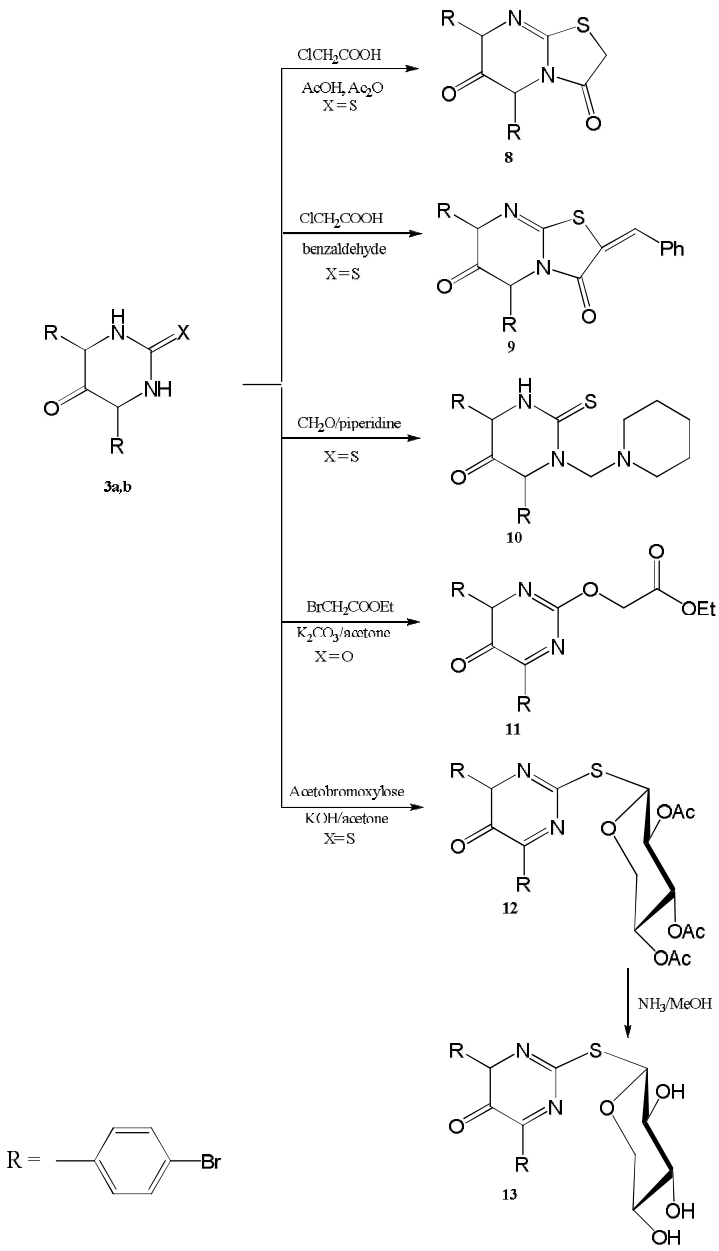
IC_{50}	C6.25	C12.5	C25	C50	**Compound**
13.583	68.281	51.8518	41.12061	16.239	**3a**
16.967	88.22412	73.1244	21.8423	1.7094	**3b**
12.664	73.1244	49.28775	29.344	25.5460	**4**
–	89.458	66.4767	61.158	64.4824	**8**
–	99.814	99.4444	96.111	67.912	**9**
18.836	109.876	86.324	28.933	24.501	**10**
–	97.625	78.632	78.917	95.631	**11**
–	101.259	92.633	85.115	92.704	**12**
2.90±0.27	-	-	-	-	Doxorubicin



Scheme 1: Synthesis of pyrimidine, oxazole and oxathiolane derivatives

Compound **4** exhibited higher potency against MCF-7 cell line with IC_{50} = 12.664 µg/ml which is relatively the closer to that of doxorubicin (IC_{50}: 2.90±0.27µg/ml) among this series. Moreover, the results showed that compounds **3a** and **3b** revealed their potency with IC_{50} values 13.58 and 16.97 µg/ml, respectively (Table 1 and Figure 1). Compounds **10** showed moderate activity with relatively higher IC_{50} values the previously mentioned compounds.

From the above obtained results (Table 1), we can conclude that the aryl substituted pyrimidine nucleus with oxo- or thioxo- attachments at position-2 are with enhanced activity. It is obvious that the activity was reduced in the other derivatives incorporating nitrogen atom in the five membered heterocycles or acyclic structures. On the other hand, substitution at the *N*-3 of the pyrimidine nucleus with amino- or piperidinyl moieties resulted in higher activity than the free or condensed pyrimidines with five member rings. Additionally, the activity of the free amino substituted pyridine at *N*-3 was higher than that of the derivative incorporating the cyclic amine substituent. In the present work, the most active compounds were the substituted pyrimidine derivatives revealing the effect of substituent skeleton. The difference in activity between the compounds may be attributed to the indicated attachments to the pyrimidine ring systems in the molecule.



Scheme 2: Synthesis of thiazolo- and substituted pyrimidines

The synthesized substituted pyrimidine derivatives incorporating free -*NH* or -*NH*$_2$ are centers for a linkage to other molecules. They may constitute scaffolds for diversification that can be used widely in synthetic and medicinal chemistry due to their beneficial physicochemical properties for drug discovery and may serve as building blocks to be integrated into larger structures.

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