**Abstract**

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This thesis comprises four chapters. **The** **first** is an introduction which consists of a brief literature survey on the different methods for the synthesis of thieno[2,3-*d*]pyrimidines and pyrido[4',3':4,5]thieno[2,3-*d*] pyrimidines in addition to an account on their cytotoxic activities.

**The** **second** **chapter** clarifies the objectives of the work and schemes designed for the preparation of the new required target compounds.

**The** **third** **chapter** deals with the theoretical discussion of the experimental work for the preparation and spectroscopic confirmation of the target compounds and intermediates according to three schemes.

**Scheme 1** is concerned with the preparation of the root compoundethyl 2-amino-6-methyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carbo-xylate **(I)**. Reaction of **I** with the appropriate isothiocyanates followed by hydrazine hydrate cyclization yielded the key intermediates 3-amino-7-methyl-2-(4-substituted anilino)-5,6,7,8-tetrahydropyrido[4',3':4,5]thieno- [2,3-*d*]pyrimidin-4(3*H*)-ones **(IIIa & b)**.

**Scheme 2** involves the reaction of **IIIa** or **b** with different aromatic aldehydes afforded the arylidene derivatives **IVa-f**. Condensation of **IIIa** or **b** with ethyl acetoacetate yielded the desired butanoate esters **Va** & **b**. Moreover, 3-[(arylcarbamothioyl)amino]-7-methyl-2-(4-substituted anil- ino)-5,6,7,8-tetrahydropyrido[4',3':4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **(VIa-e)** were prepared via the reaction of the amino derivative **IIIa** or **b** with certain selected isothiocyanates. Cyclization of thiourea derivatives **VIa-c** with chloroacetyl chloride produced 1,3-thiazolidin-5-ones **VIIa-c** while cyclization of **VIa** with ethyl bromoacetate afforded 1,3-thiazolidin-4-one isomer **VIII**. The latter was differentiated from **VIIa** by IR & mass fragmentation data.

Furthermore, *N*-[7-methyl-4-oxo-2-(4-substituted anilino)-5,6,7,8-tetrahydropyrido[4',3':4,5]thieno[2,3-*d*]pyrimidin-3(4*H*)-yl]benzamides **(IXa-f)** were obtained through acylation of **IIIa** or **b** with benzoyl chloride, its 2-fluoro and 4-nitro derivatives.

**Scheme 3A** comprises the synthesis of 7-methyl-3-(4-substituted phenyl)-6,7,8,9-tetrahydropyrido[4',3':4,5]thieno[2,3-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-10(3*H*)-ones **(Xa & b)**, 2,7-dimethyl-3-(4-substituted phenyl)-6,7,8,9-tetrahydropyrido[4',3':4,5]thieno[2,3-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-10(3*H*)-ones **(XIa & b)** and 7-methyl-3-(4-substituted phenyl)-6,7,8,9-tetrahydropyrido[4',3':4,5]thieno[2,3-*d*][1,2,4]triazolo[1,5-*a*]pyrimidine-2,10(1*H*,3*H*)-diones **(XIIa & b)** through heating of the amino compound **IIIa** or **b** with triethyl orthoformate, triethyl orthoacetate and *N*,*N'*-carbonyldiimidazole respectively. Reaction of **IIIa** or **b** with carbon disulphide in ethanolic potassium hydroxide yielded the corresponding 2-thioxo derivatives **XIIIa** & **b**. Alkylation of the latter with a variety of alkyl halides gave the target thioethers **XIVa-e**.

In addition, 2-(arylamino)-7-methyl-3-(4-methylphenyl)-6,7,8,9-tetrahydropyrido[4',3':4,5]thieno[2,3-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-10 (3*H*)-ones **(XVa-c)** were synthesized via refluxing the appropriate thiourea derivatives **VIa-c** in ethanolic potassium hydroxide.

**Scheme 3B** involves the reaction of **IIIa** or **b** with oxalyl choride or malonyl chloride which gave the corresponding 8-methyl-4-(4-substituted phenyl)-7,8,9,10-tetrahydro-1*H*-pyrido[4'',3'':4',5']thieno[2',3':4,5]pyrimi-do[1,2-*b*][1,2,4]triazine-2,3,11(4*H*)-triones **(XVIa & b)** and 9-methyl-5-(4-substituted phenyl)-8,9,10,11-tetrahydropyrido[4'',3'':4',5']thieno[2',3': 4,5]pyrimido[1,2-*b*][1,2,4]triazepine-2,4,12(1*H*,3*H*,5*H*)-triones **(XVIIa & b)** respectively.

Other triazepine derivatives were obtained when **IIIa** or **b** was reacted with acetyl acetone or ethyl ethoxymethylidenecyanoacetate to give 2,4,9-trimethyl-5-(4-substituted phenyl)-8,9,10,11-tetrahydropyrido- [4'',3'':4',5']thieno[2',3':4,5]pyrimido[1,2-*b*][1,2,4]triazepin-12(5*H*)-ones **(XVIIIa** **&** **b)** and ethyl 4-amino-9-methyl-12-oxo-5-(4-substituted phenyl)-5,8,9,10,11,12-hexahydropyrido[4'',3'':4',5']thieno[2',3':4,5]pyri-mido[1,2-*b*][1,2,4]triazepine-3-carboxylates **(XIXa & b)** respectively.

The structure elucidation of the new compounds was supported by element analysis, IR, 1HNMR and mass spectrometry. Detailed mass spectral study was done for forty compounds representing all series. The characteristic mass spectral data, possible structures and expected pathways of the main fragments are illustrated in special charts and tables.

Additionally, all compounds were subjected to molecular modeling studies on the active site of 17*β*-HSD1, lead (E2B) (PDB ID: 3HB4) using Molecular Operating Environment (MOE 2008.10) software. Also, the principle and results of cytotoxic activities were briefly discussed. In addition, a correlation between the docking results & cytotoxic activity is also discussed.

**The** **fourth** **chapter** comprises the experimental part of this thesis which contains the detailed procedures used for the synthesis of the target compounds and intermediates. In addition, the physical properties of the synthesized compounds and their element analysis and spectral data are illustrated. Also, it demonstrates the steps involved in the molecular modeling study and the results obtained from the docking study of all compounds.

Finally, thirty of the newly synthesized compounds were subjected to *in* *vitro* cytotoxic activity testing on two human breast cancer cell lines (T-47D & MCF-7) and one cervical cancer cell line (HELA) compared with doxorubicin as a reference anticancer agent. Twenty nine compounds showed cytotoxic activity on T-47D, only three compounds on MCF-7 while ten compounds on HELA.