SUMMARY

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The present work is concerned with the synthesizing and pharmacological testing of some new compounds using some naturally occurring substances as precursors (γ-pyrone,α-pyrone and Triterpene) .

1.1 . γ -Pyrone part

The representative example used in the present study is visnagin, where it were converted to visnagin-9-sulphonylchloride that reacted with 2ry cyclic alcohol and phenol derivatives to prepare the corresponding visnagin-9-sulphonic esters (**IIa-c**), these derivatives were subjected to the following reaction conditions.

1.1.1. Mannich reaction

The derivatives **(IIa-c)** were subjected to the condition of Mannich reaction it afforded the corresponding o-(Aryl)-4-methoxy-6-[(amino)-methyl]-7-methyl-5-oxo-5H-furo [3,2-g] [1] benzopyron-9-sulphonate **(IIIa-i).**

1.1.2. Reaction with hydroxyl amine hydrochloride

The derivatives **(IIa-c)** were reacted with hydroxyl amine hydrochloride which afforded the corresponding o-(Aryl)-6-hydroxy-4-methoxy-5-[4-methyl isoxazol-3yl]benzofuran-7-sulphonate **(IVa-e).**

1.1.3. Reaction with aromatic amines

The reaction of **(II)** with different aromatic amines gave the corresponding o(Aryl)-6-hydroxy-5-[1-(3-amino-aryl-but-2-ene-1-one)] benzofuran-7-sulphonate **(Va-k).**

1.1.4. Reaction with 2ry cyclic amines

The 1,4 Micheal addition of 2ry cyclic amines on derivatives **II** leading to the formation of 4-methoxy-7-methyl-7(merpholino, pyrolidino or piperidino)-5-oxo-5H-furo [3,2-g][1]benzodihydropyran-9-sulphonate **(VIa-c).**

1.1.5. Reaction with hydrazine hydrate

The reaction of hydrazine hydrate with derivatives II gave the o(Aryl)-6-hydroxy-4-methoxy-5-[5`-methoxy-1H-1-(methyl or phenyl) pyrazolo-3-yl] benzofuran-7-sulphonate. **(VIIa-c).**

The in vitro disease-oriented primary antitumer screening of some of these derivatives (carried out in NCI, in USA). Indicated that some of these compounds stop & inhibit some type of ovarian and breast cancer.

1.2. α-pyrone part

This part deals with the introduction of amino acid into different positions of furocoumarin aiming to add to the chemistry of furocoumarin and to its SAR in the medicinal chemistry.

1.2.1. Reaction of 24a,b with methyl glycenate and/or methyl alanine ester

Methyl glycenate gave 4-methoxy-5-hydroxy-5(N-amino methyl ester)-7H[3,2-g]benzopyran-7-one **VIIIa,c** and 4-methoxy-5-(N-amino methyl ester-7H-[3,2-g]benzopyran-7-one **IXa,c** while methyl alanine ester gave 4,9-di-methoxy-5-hydroxy-5-(N-amino acid methyl ester)-7H[3,2-g]benzopyran-7-one **VIIIb,d.** and 4,9-dimethyl-5-(N-amino methyl ester)-7H-[3,2-g]benzopyran-7-one **IXb,d**

1.2.2. Reaction of the 6-bromo α-pyrone derivatives with amino acids

When the bromo derivatives **Xa,b** were treated with the amino acid ester afforded the corresponding 4-methoxy-5-hydroxy-6(N-amino acid methyl ester)-7H [3,2-g] benzopyran-7-one and 4,9 dimethoxy-5-hydroxy-5-(N-amino acid methyl ester)-7H [3,2-g] benzopyran-7-one **(XIa-d).**

1.2.3. Reactions of derivatives XI with hydrazine hydrate

Treating compounds **XI** with hydrazine hydrate afforded the corresponding 6-hydroxy-4-methoxy-5-[4`(amino acid methyl ester)-1H-pyrazol-5-one-3-yl]benzofuran and 6-hydroxy-4,7-methoxy-5-[4`-(amino acid methyl ester)-1H-pyrazol-5-one-3-yl]benzofuran **(XIIa-d).**

1.2.4. Reaction of the chloroformyl furocoumarin with amino acids

Treatting derivative **XIII** with the corresponding amino acid ester give 4-methoxy-5-(amino acid methyl ester)-6-formyl-7H-furo [3,2-g][1] benzopyran-7-one and 4,9-dimethoxy-5-(amino acid methyl ester)-6-formyl-7H-furo[3,2-g][1] benzopyran-7-one **XIV**.

1.2.5. Reaction of derivatives XIV with hydrazine hydrate

Treating derivative **XIV** with hydrazine hydrate gave the corresponding 4-methoxy-5(amino acid methyl ester)-7H-furo[3,2-g][1]benzopyran [7,6-b] pyrazoline-7-one and 4,9-dimethoxy-5-(amino acid methyl ester)-7H-furo[3,2-g][1] benzopyran [7,6-b] pyrazoline-7-one **XV**.

The in vitro disease-oriented primary antitumor screening of some of these derivatives (carried out in NCI, USA) indicated that some of these compounds stop & inhibit some type of ovarian and breast cancer.

Also compounds **VIIIa,c, IXb,d, XIa,c, XIId, XIVc** and **XV** exhibit pronounced antiestrogenic activities.

1.3. Triterpenoid part

In this part the author add to both the chemistry and SAR of oleanolic acid new entities.

1.3.1. Aldol condensation of some new model of oleanolic acid derivative:-

From oleanolic acid the author prepared methyl-1`-methyl-3-oxo-18β-olean-12-ene-28.oate **XX** and its acid derivative ewre prepared via treating the 3-oxo-methyl oleanolate **XVII** with DDQ to prepare the

Δ^1-analougue **XVIII** that upon treating with diazomethane gave the ring A pyrazoline fused system **XIX**, that photolyzed to give compound **XX** when on hydrolysis **XXI.** The aldol condensation of XX with different patterns of substituted aromatic aldehydes afforded three categories of the following compounds

Aryilidene derivatives (XXIIa-d)

Methyl-1`-methyl-2[substituted benzylidene]-3-oxo-18β-olean-12-en-28-oate.

α-Ethoxy benzyl derivatives (XXIIIa-d)

Methyl-1`-methyl-2-[(α-ethoxy) substituted benzyl]-3-oxo-18β-olean-12-en-28-oate.

α-Hydroxy benzyl derivatives (XXIVa-d)

Methyl-1`-methyl-2-[(α-hydroxy) substituted benzyl]-3-oxo-18β-olean-12-en-28-oate. Derivatives **XXII** were converted to derivative **XXIII** via treating with Na/Ethanol.

Also derivatives **XXIII** where converted to derivatives XXII via the action of etherated boron trifluoride. In the same line products XXII where obtained chemically from derivatives **XXIV** using the dehydrating character of sulfuric acid.

The Aldol condensation of derivative **XXI** with different patterns of aromatic aldehydes afforded only two products.

Arylidene derivatives.

1`-Methyl-2-[substituted benzylidene]-3-oxo-18β-olean-12-en-28-oic acid **(XXVa-c).**

α-Ethoxy benzyl derivatives

1`-Methyl-2-[(α-ethoxy) substituted benzyl]-3-oxo-18β-olean-12-en-28-oic acid **XXVIa-c**. But no α-hydroxy benzyl derivatives (case 3 for derivative **XX**) these derivatives obtained by another chemical way achieved via hydrolysis of derivatives **XXIV**

Hydrolysis of derivatives **XXII** afforded derivatives **XXV**. Conversion of derivative **XXV** to **XXVI** done by the action of sodium ethoxide, while conversion of those **XXVI** to **XXV** made possible by the action of ethereated boron trifluoride

1.3.2 Reactions of oleanolic acid lactone containing diene system in Ring C.

Allylic bromination of locant 11 of 3-acetyl methyl oleanolate give the 11-bromo analogue **XXIX,** that upon dehydrobromonation with lithium salts in DMF afforded the $\Delta^{10,12}$ diene system **XXX;** the latter upon hydrolysis with alcohlic potassium hydroxide gave the acid **XXXI,** Protection of the 3β-hydroxyl group of the latter acid as acetoxy function made possible by acetic anhydride to give compound **XXXII.** that when treated with ethyl chloroformate in DMSO-TEA and in the presence of sodium azide gave the corresponding lactone **XXXIII**.

Treating the lactone with anilines form the corresponding anilinide with C-21 hydroxyl namely N-(substituted phenyl)-3β-acetoxy-21-hydroxy-18β-olean-10,12-diene-28-carboxamide **XXXIV.**

Treating the lactone with phenoles form the corresponding esters with C-21 hydroxyl that chemically named as (substituted phenyl)-3β-acetoxy-21-hydroxy-18β-olean-10,12-diene-28oate **XXXV**.

The introduction of C-21 hydroxyl group in the field of triterpenes attained .

1.3.3 Formation of heterocyclic fused ring systems to ring A of oleanolic acid

On treating 3-oxo-methyl oleanolate **XVII** with either formaldehyde or acetaldehyde it afforded the corresponding formyledine **XXXVIa** and the corresponding acetylidene **XXXVIb** that use to build different types of hyterocyclic six membered ring systems as follow.

1.3.3.1 Treating derivatives XXXVI with ethyl cyano acetate in ethanol in the presence of sodium ethoxide gave the Ring A-fused pyran system chemically named as methyl-2`-oxo-3`-cyano-18β-olean[3,2-c]pyran-12-en-28oate **XXXVIIa,b**.

1.3.3.2 Treating derivatives XXXVI with either ethyl cyano acetate in the presence of eight folds of ammonium acetate or cyanoacetamide in the presence of ammonium acetate give the corresponding Ring A-fused pyrido system chemically named as methyl-

2`-oxo-3`-cyano-18β-olean[3,2-b]pyrido-12-en-28oate and methyl-2`-oxo-3`-cyano-4`-methyl-18β-olean[3,2-b]pyrido-12-en-28oate **XXXVIIIa-b**.

1.3.3.3 Treating derivatives XXXVI with cyanoacetamide in the presence of sodium ethoxide gave the Ring A-fused pyridine system chemically named as methyl-2`-hydroxy-3`-cyano-18β-olean[3,2-c]pyridine-12-ene-28oate and methyl-2`-hydroxy-3`-cyano-6`-methyl-18β-olean[3,2-c]pyridine-12-ene-28oate **XXXIXa,b.**

1.3.3.4 Treating derivatives XXXVI with thiocyanoacetamide in the presence of sodium ethoxide give also a different manner of Ring A-fused pyridine system chemically named as methyl-2`-mercapto-3`-cyano-18β-olean[3,2-c]pyridine-12-ene-28oate and methyl-2`-mercapto-3`-cyano-6`-methyl-18β-olean[3,2-c]pyridine-12-ene-28oate **XL.**

Another category of Ring A fused pyridine system chemically named as methyl-2`-mercapto-3`-cyano-18β-olean[3,2-b]pyridine-12-en-28oate and methyl-2`-mercapto-3`-cyano-4`-methyl-18β-olean[3,2-b]pyridine-12-en-28oate **XLI** were obtained by treating derivatives **XXXVI** with thiocycnoacetamide in the presence of eight folds of ammonium acetate.

1.3.3.5 Treating derivative XXXVI with malononitrile in the presence of sodium ethoxide give another type of pyridine derivatives fused to ring A of the olean nucleus named as methyl-2`-ethoxy-3`-cyano-18β-olean[3,2-b]pyridine-12-en-28oate and methyl-2`-ethoxy-3`-cyano-6`-methyl-18β-olean[3,2-b]pyridine-12-en-28oate **XLII.**

On the other hand repeating the same reaction between derivatives **XXXVI** and malononitrile replacing sodium ethoxide with ammonium acetate give different fusion sites of the pyridine onto Ring A of the olean this chemically named as methyl-2`-amino-3`-cyano-18β-olean[3,2-b]pyridine-12-en-28oate and methyl-2`-amino-3`-cyano-6`-methyl-18β-olean[3,2-b]pyridine-12-ene-28oate **XLIII.**

1.3.3.6 Robenson Annulation reaction of derivatives **XXXIV** with ethyl acetoacetate in ethanol in the presence of sodium ethoxide afforded the cyclohexnone fused ring system onto Ring A of the olean skeleton chemically known as methyl-6`-ethylcarboxylate-1`-oxo-18β-olean[3,2-c]cyclohex-12,2`-diene-28oate and methyl—6`-ethylcarboxylate-1`-oxo-6`-methyl-18β-olean[3,2-c]cyclohex-12,2`-diene **XLIVa-b.**

While Robenson Annulation with acetyl acetone gave the corresponding methyl-6`-acetyl-1`-oxo-18β-olean[3,2-c]cyclohex-12,2`-diene-28oate and methyl—6`-acetyl-1`-oxo-6`-methyl-18β-olean[3,2-c]cyclohex-12,2`-diene-28oate **XLVa-b.**

1.3.3.7 Treating derivatives XXXVI with guanidine hydrochloride gave the pyrimidine fused system onto Ring A of the olean nucleus chemically named as methyl-2`-amino-18β-olean[3,2-d]pyrimidine -12-ene-28oate and methyl-2`-amino-6`-methyl-18β-olean[3,2-d]pyrimidine-12-ene-28oate **XLVIa-b,** while, replacing guanidine with thiourea gave the corresponding methyl-2`-mercapto-18β-olean[3,2-d]pyrimidine-12-ene-28oate and methyl-2`-mercapto-6`methyl-18β-olean[3,2-d] pyrimi dine -12-ene-28oate **XLVIIa-b** which is a pyrimidine thiol fused to ring A of the olean skeleton.

The anti-inflammatory and anti-ulcerogenic activities of some representative examples of the newly synthesized derivatives in this study were investigated. Where some of these compounds combine both the anti inflammatory and antiulcer activities a property long-sought since most NSAIDs cause ulcerogenicity upon medium term used (3-6-monthes).