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DESIGN AND SYNTHESIS OF ANTI-BREAST CANCER AGENTS

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ABSTRACT

Breast cancer is a cancer of the glandular breast tissue. Worldwide, breast cancer is the fifth most common cause of cancer death (after lung cancer, stomach cancer, liver cancer, and colon cancer). In 2005, breast cancer caused 502,000 deaths (7% of cancer deaths; almost 1% of all deaths) worldwide. Among women worldwide, breast cancer is the most common cause of cancer death. The guidelines were based on studies of SERMs from the MORE, BCPT P-1, and Italian trials. In the MORE trial, the relative risk reduction for raloxifene was 76%. The P-1 preventative study demonstrated that tamoxifen can prevent breast cancer in high-risk individuals. The relative risk reduction was up to 50% of new breast cancers, though the cancers prevented were more likely estrogen-receptor positive (this is analogous to the effect of finasteride on the prevention of prostate cancer, in which only low-grade prostate cancers were prevented).The Italian trial showed benefit from tamoxifen. Selective Estrogen Receptor Modulators (SERMs) are a class of medication that acts on the estrogen receptor. A characteristic that distinguishes these substances from pure receptor agonists and antagonists is that their action is different in various tissues, thereby granting the possibility to selectively inhibit or stimulate estrogen-like action in various tissues. Chalcones bearing non natural substituents have been synthesized during the recent years in order to develop drugs active against cancer. Chalcones are usually

synthesized using the Claisen–Schmidt reaction in basic medium in polar solvent and purified by separation as the reaction led very often to a complex mixture. 2-Pyrazolines can be conveniently synthesized by the treatment of a, ß-unsaturated carbonyl compounds with hydrazine reagents in basic and acidic media. In this method, hydrazones are formed as intermediates, which can be subsequently cyclized to 2-Pyrazolines in the presence of a suitable cyclizing reagent like acetic acid. Pyrazoles act as agonists, which were re-examined using the ER-LBD-DES (agonist) structure. Spiro compounds represent an important class of naturally occurring substances characterized by highly pronounced biological properties.Spirooxindole ring systems are found in a number of alkaloids like horsifiline, spirotryprostatin and (+) elacomine. The derivatives of the Spirooxindole ring systems find wide biological applications as antimicrobial and antitumour agents.

Key Words: - Anti Breast Cancer Activity, SERMs, and Chalcones

INTRODUCTION

Breast cancer is a cancer of the glandular breast tissue. Worldwide, breast cancer is the fifth most common cause of cancer death (after lung cancer, stomach cancer, liver cancer, and colon cancer). [1] In 2005, breast cancer caused 502,000 deaths (7% of cancer deaths; almost 1% of all deaths) worldwide. [1] Among women worldwide, breast cancer is the most common cause of cancer death. [1]

In the United States, breast cancer is the third most common cause of cancer death (after lung cancer and colon cancer). In 2007, breast cancer is expected to cause 40,910 deaths (7% of cancer deaths; almost 2% of all deaths) in the U.S. [2] Among women in the U.S., breast cancer is the most common cancer and the second-most common cause of cancer death (after lung cancer). Women in the U.S. have a 1 in 8 lifetime chance of developing invasive breast cancer and a 1 in 33 chance of breast cancer causing their death. [3] In the U.S., both incidence and death rates for breast cancer have been declining in the last few years.[4] Nevertheless, a U.S. study conducted in 2005 by the Society for Women's Health Research indicated that breast cancer remains the most feared disease [5] even though heart disease is a much more common cause of death among women[6] The number of cases worldwide has significantly increased since the 1970s, a phenomenon partly blamed on modern lifestyles in the Western world.[7,8] Because the breast is composed of identical tissues in males and females, breast cancer also occurs in males, though it is less common. [9,10]

SELECTIVE ESTROGEN REEPTOR MODULATORS (SERMs):

The guidelines were based on studies of SERMs from the MORE, BCPT P-1, and Italian trials. In the MORE trial, the relative risk reduction for raloxifene was 76 %. [11] The P-1 preventative study demonstrated that tamoxifen can prevent breast cancer in high-risk individuals. The relative risk reduction was up to 50% of new breast cancers, though the cancers prevented were more likely estrogen-receptor positive (this is analogous to the effect of finasteride on the prevention of prostate cancer, in which only low-grade prostate cancers were prevented). [12,13] The Italian trial showed benefit from tamoxifen. [14] Additional randomized controlled trials have been published since the guidelines. The IBIS trial found benefit from tamoxifen. [15] In 2006, the NSABP STAR trial demonstrated that raloxifene had equal efficacy in preventing breast cancer compared with tamoxifen, but that there were fewer side effects with raloxifene. [16] The RUTH Trial concluded that "benefits of raloxifene in reducing the risks of invasive breast cancer and vertebral fracture should be weighed against the increased risks of venous thromboembolism and fatal stroke" [17] On September 14, 2007, the US Food and Drug Administration approved raloxifene (Evista) to prevent invasive breast cancer in postmenopausal women. [18]

Selective Estrogen Receptor Modulators (**SERMs**) are a class of medication that acts on the estrogen receptor. A characteristic that distinguishes these substances from pure receptor agonists and antagonists is that their action is different in various tissues, thereby granting the possibility to selectively inhibit or stimulate estrogen-like action in various tissues.

SERMs are being evaluated and used to treat and prevent such diseases, As breast cancer, osteoporosis, and cardiovascular disease. Currently, three primary SERMs are used clinically, which include tamoxifen, toremifene (triphenylethylenes), and raloxifene (a benzothiophene). Tamoxifen and toremifene have beneficial effects on bone and serum lipids, and are currently used to treat breast cancer. Both have stimulatory effects on the uterus. Raloxifene, indicts cancer, osteoporosis, and cardiovascular disease are undergoing clinical development, including idoxifene, droloxifene, ospemifene, lasofoxifene, arzoxifene, and MDL 103,323. Dated for the treatment and prevention of osteoporosis, also has beneficial effects on bone and serum lipids, but does not stimulate the uterus but all three are associated with venous thromboembolism and hot flashes.

LITERATURE REVIEW

The outline of the project was prepared after the study of Selective estrogen receptor modulator (SERM) which typically consists of a non-steroidal core structure onto which is attached a side chain bearing a basic or polar function. Recently, conformation sensitive peptides have been used to discriminate among different legend induced ER conformations. [19]

From published crystal structures, it is known that the ER-LBD adopts a different conformation when complexed with agonists (E2, DES) versus antagonists (naphthaltamoxifen, raloxifene). A SERM would have different intrinsic activities at different sites but preferably zero intrinsic activity in breast and uterus.

Chalcones (1, 3-diphenyl-2-propen-1-one) and especially chalcones bearing oxygenated function on the aromatic rings are the precursors of all the flavonoids. They are biologically active molecules found in human diet as they are accumulated in many plants and vegetables. Chalcones bearing non natural substituents have been synthesized during the recent years in order to develop drugs active against cancer, malaria, 48 leishmaniase, tuberculosis and cardiovascular diseases or for their properties to modulate the regulation of biochemical pathways like NO or tyrosine kinase. Chalcones are usually synthesized using the Claisen–Schmidt reaction in basic medium in polar solvent and purified by separation as the reaction led very often to a complex mixture. However, few new methodologies for the synthesis of chalcone have been described recently. On the basis of this theoretical information, most efficient methods were employed for the synthesis of the desired pyrazoline moiety designed previously. Chalcones were prepared by condensing an aldehyde with acetophenone in ethanolic NaOH solutions. These chalcones were immediately reacted with suitable hydrazine derivative in the presence of acetic acid to obtain the corresponding 2-pyrazoline molecules. The synthesized heterocycles were characterized on the basis of their chemical properties and spectroscopic data. Due to the interesting activity of variously substituted pyrazolines as biological agents considerable attention has been focused on this class. The pharmaceutical importance of these compounds lies in the fact that they can be effectively utilized as antibacterial, antifungal, antiviral, antiparasitic, antitubercular and insecticidal agents [21]. Some of these compounds have also anti-inflammatory, antidiabetic, anesthetic and analgesic properties. In addition, pyrazolines have played a crucial part in the development of theory in heterocyclic chemistry and also used extensively in organic synthesis. [20]

In 2001, Albert Levae summarized all possible ways for the synthesis of 2-Pyrazolines by the reactions of α, β-unsaturated aldehydes, ketones & esters with diazoalkanes, nitrile imines and hydrazine's. Among all the methods employed in synthesis of pyrazolines, condensation of a variety of substituted chalcones with hydrazine and its derivatives is commonly used. 2-Pyrazolines can be conveniently synthesized by the treatment of a, ß-unsaturated carbonyl compounds with hydrazine reagents in basic and acidic media. In this method, hydrazones are formed as intermediates, which can be subsequently cyclized to 2-Pyrazolines in the presence of a suitable cyclizing reagent like acetic acid [21] as evident from the literature, in recent Years a significant portion of research work in heterocyclic chemistry has been devoted to 2-pyrazolines containing different aryl group's substituents.

Another convenient route to prepare pyrazoles in large quantities is from chalcones via an epoxide formation. The chalcones were subjected to epoxidation by using hydrogen peroxide in alkaline media & then the epoxychalcone was subjected to the Wharton reaction using hydrazine hydrate (1.5–2 mol) as nucleophilic reagent without the addition of acetic acid.
Also, studies by John A. Katzenellenbogen et.al. Showed that [20]

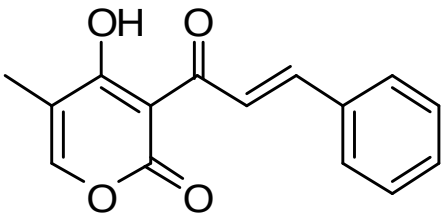
•Pyrazoles act as agonists, which were re-examined using the ER-LBD-DES (agonist) structure. As a result of this modeling work, as well as further structure activity relationship studies, it was believed that these core pyrazoles, which behave as agonists, bind in an orientation in which the C (3) phenol plays a role analogous to the critical A-ring of estradiol.

•The orientation of the SERM raloxifene relative to estradiol also suggests that the benzothiophene ring system of raloxifene mimics the AB ring system of estradiol, so that the basic side chain is directed roughly in the estradiol 11β direction, where it extends outward to displace helix-12 which helped them to prove that the pyrazole ligand could even accommodate a basic side chain. When bound with the ER-LBD in the agonist conformation, there is no position on the pyrazole analogue where such a side chain could be disposed so as to occupy a region of the ligand-binding pocket that is normally occupied by this group in other SERMs.

•an orientation of the side chain in a way that it lies between as that of tamoxifene & raloxifen i.e. more orthogonal in comparison to RAL & less perpendicular w.r.t. TAM due to the presence of rigid structure instead of carbonyl hinge of RAL.

•the rigidity in the designed molecule also helps in avoiding the flipping of the molecule leading to a more efficient compound than the previous SERMs.

2-pyrone structures resembling the chalcones, one such chalcone like structure presented below:



3-cinnamoyl-4-hydroxy-5-methyl-2*H*-pyran-2-one

Is theoretically available by aldol condensation of aromatic aldehydes with the methyl ketone group of dehydro acetic acid. The possibility that such a reaction product could be obtained apparently was first recognized by Hale who attempted the aqueous sodium hydroxide catalyzed condensation of benzaldehyde with dehydroacetic acid.

An alternative procedure for the condensation using a piperidine catalyst in chloroform solution gave a uniformly excellent result. After removal of the water formed in the reaction as the chloroform azeotrope, the products precipitated from the chloroform solution in 46-63% yields.[22]

Spiro compounds represent an important class of naturally occurring substances characterized by highly pronounced biological properties. [23,24] Spirooxindole ring systems are found in a number of alkaloids like horsifiline, spirotryprostatin and (+) elacomine. [25] The derivatives of the Spirooxindole ring systems find wide biological applications as antimicrobial, and antitumuor agents.

Heterocyclic compounds fall into an important class of organic compounds. These compounds are found in various natural products as fundamental nuclei and are well recognized for their wide spectrum of pharmacological and biochemical behavior. The indole derivatives have received the attention of biochemists because of their therapeutic and biochemical activities. [26-28] These derivatives undergo various organic reactions including cycloaddition reaction. [29]

Similarly pyrrolidine-2-carboxylic acid, commonly known as L-proline, possesses significant biological and medicinal properties. [30-32] Therefore any heterocyclic compound containing

these two moieties might be expected to have considerably enhanced biological activities. The azomethine ylide derived from the isatin and the L-proline in reactions with different dipolarophiles, The oxazolidinone compound 4, derived from the condensation of isatin 1 with L-proline 2, contains two chiral centers and therefore a total of four stereoisomer 4a–d are possible. We are able to optimize the geometry of all the four isomers. Since product 4 is formed upon dehydration of intermediate iminium species 3, In the presence of a dipolarophile, the intermediate iminium species 3 undergoes decarboxylation to give the azomethine ylide 5, which subsequently undergoes 1, 3-dipolar cycloaddition reactions to give Spiro polycyclic compounds. Geometry optimization of azomethine ylide 5 indicates that it has a planar structure. The proline ring, instead of having an envelope shape, is planar and lies in the same plane as that of the Isatin moiety.

MATERIALS AND METHODS

Experimental Procedure:

Procedure for Synthesis of compound 3 a:

A mixture of 10mmol (1.68gm), Benzaldehyde 1.06 ml, 25ml chloroform, piperidine (6-8 Drops) as a catalyst, were taken in 100ml round bottom flask. The Reaction mixture was refluxed for 16-18 hrs using Dean stark apparatus.

The Reaction mixture was poured in ice water and kept for 15 minutes. The reaction mixture was extracted with chloroform (20x3) the combined organic layers were washed with water (20x3) until the pH=7. Organic layer was dried over anhydrous sodium sulphate and concentrated. The solid was filtered and recrystallized with Benzene and Hexane.

Procedure for Synthesis of compound 3b:

A mixture of 10mmol (1.68gm) Dehydroacetic acid, 1.50gm N-N dimethylamino benzaldehyde, 25ml Chloroform, piperidine (6-8 Drops) as a catalyst were taken in 100 ml round bottom flask. The Reaction mixture was refluxed for 16-18 hrs using Dean stark apparatus.

The Reaction mixture was poured in ice water and kept for 15 minutes. The reaction mixture was extracted with chloroform (20x3) the combined organic layers were washed with water (20x3) until the pH=7.Organic layer was dried over anhydrous sodium sulphate and concentrated. The solid was filtered and recrystallized with Benzene and Hexane.

Procedure for Synthesis of compound 3c:

A mixture of Dehydro acetic acid 1.68gm, P-Hydroxy Benzaldehyde 1.22 gm, Piperidine .5 ml as a catalyst, chloroform 25ml were taken in 100 ml Round bottom flask. The reaction mixture was refluxed for 16-18 hrs using Dean stark apparatus.

The Reaction mixture was poured in ice water and kept for 15 minutes. Now reaction mixture was extracted with chloroform (20x3) the combined organic layers were washed with water (20x3) until the pH=7 and dried over anhydrous sodium sulphate and concentrated. The solid was filtered and recrystallized with Benzene and Hexane.

Procedure for synthesis of compound 3d:

A mixture of 1.68gm of Dehydroacetic acid, 1.3ml of cinnamaldehyde, .5ml of piperidine, 20ml of chloroform, were taken in 100ml round bottom flask, The reaction mixture was refluxed for 16-18 hrs using Dean stark apparatus.

The Reaction mixture was poured in ice water and kept for 15 minutes. Now reaction mixture was extracted with chloroform (20x3) the combined organic layers were washed with water (20x3), until the pH=7 and dried over anhydrous sodium sulphate, concentrated. The solid was filtered and recrystallized with Benzene and Hexane.

Procedure for Synthesis of compound 5a:

A mixture of compound (3a) 500mg, hydrazine sulphate (4) 500gm, and pyridine (catalytic amount), were taken in Ethanol (20 ml.). Reaction mixture was refluxed for 10-12 hrs at 60-70°c.

Reaction mixture was poured in ice water, kept for 30 min. Solid separated was filtered off and recrystallized with ethyl acetate and hexane.

Procedure for Synthesis of compound 5b:

A mixture of compound (3b) 500mg, hydrazine sulphate (4) 500mg, pyridine (catalytic amount), were taken in Ethanol (20 ml.) .Reaction mixture was refluxed for 10-12 hrs at 60-70°C.

Reaction mixture was poured in ice water, kept for 30 min. Solid separated was filtered off and recrystallized with ethyl acetate and hexane.

Procedure for Synthesis of compound 5c:

A mixture of compound (3c) 500mg, Hydrazine sulphate (4) 500mg, pyridine (catalytic amount), were taken in Ethanol (20 ml.) .Reaction mixture was refluxed for 10-12 hrs at 60-70°C.

Reaction mixture was poured in ice water, kept for 30 min. Solid separated was filtered off and recrystallized with ethyl acetate and hexane.

Procedure for Synthesis of compound 5d:

A mixture of compound (3d) 500mg, hydrazine sulphate 500mg (4), pyridine (Catalytic amount), were taken in Ethanol (20 ml.) .Reaction mixture was refluxed for 10-12 hrs at 60-70°C.

Reaction mixture was poured in ice water, kept for 30 min. Solid separated was filtered off and recrystallized with ethyl acetate and hexane.

Procedure for Synthesis of compound 6:

A mixture of compound (3a) 500mg, hydroxyl amine hydrochloride 500mg, pyridine (catalytic amount), were taken in Ethanol (20 ml.) .Reaction mixture was refluxed for 10-12 hrs at 60-70°C.

Reaction mixture was poured in ice water, kept for 30 min. Solid separated was filtered off and recrystallized with ethyl acetate and hexane.

Procedure for Synthesis of compound 7:

A mixture of Isatin 10 mmol (1.47gm), Proline 1.3 mmol (1.45gm), and compound (3a) 10 mmol (2.58gm) were taken in 30 ml of Ethanol and stirred at room temperature for 6-8 hrs. The solid was filtered and dry.

Procedure for Synthesis of compound 8:

A mixture of compound (7) 1mmol .456 gm, 1-(2-chloroethyl piperidine) 1.2 mol, K2CO3 10mol was taken in Dry Acetone and the reaction mixture was refluxed for 8-10 hrs at 60-70◦C. The reaction mixture was filter off and extracted with ethyl acetate. Washed with water

2-3 times. Dried over anhydrous Na2So4 .concentrated then solid separated was recrystallized with ethyl acetate and hexane.

SPECTROSCOPIC AND ANALYTICAL DETAILS

3-Cinnamoyl-4-hydroxy-5-methyl-2H-pyran-2-one [3a]

Physical appearance : Yellow color solid
Yield : 64.73%
Melting Point : 135°C
Mass : m/z EIMS (M) 258
IR (KBR) : 3427.6, 1722.1641, 1551.1
1H NMR (CDCl3) : δ=2.1886 (S, 1H), δ=7.3392 (t, 2H, J=2.96S), δ=7.6000 (d, 2HS, J=3.02)

(E)-3(3-(4-dimethylamino) phenyl) acryloyl)-4-hydroxy-5-methyl-2H-pyran-2-one [3b]

Physical appearance: Red color solid
Yield : 56.44 %
Melting Point : 215°C
Mass : m/z EIMS (M) 300.2
IR (KBR) : 3430.4, 1730.4., 1655.3, 1596.9,1242
1H NMR (CDCl3) : δ= 2.2757 (S, 3H), δ=3.0940 (S, 6H), δ=6.7151(d, 1H, J=8.91), δ=7.6419 (d, 1H, J=8.88), δ= 8.0401(d, 1H, J=15.45), δ=8.1611(d, 1H, J=15.42)

4-hydroxy-5[3(4-hydroxy-phenyl)-acryloyls]-3-methyl-pyran-2-one [3c]

Physical appearance: Yellow color solid
Yield : 65 %
Melting Point : 210°C
Mass : m/z EIMS (M+1) 273.3
IR (KBR) : 3271, 1695, 1510.6
1H NMR (DMSO-d_6): δ= 2.24 (s, 3H), δ=6.24 (s, 1H), δ=6.8 (d, 2H, j=8.43), δ=7.6 (D, 2H, J=8.52), δ=7.9(d,1H,J=15.66) , δ=8.04(d,1H,j=15.69)

4-hydroxy-5-methyl-3-[(2E, 4E)-5-phenylpenta-2s, 4-dienoyl)-2H-Pyran-2-one [3d]

Physical appearance: Yellow color solid
Yield : 57 %
Melting Point : 235°C
Mass : m/z EIMS (M+1) 282
IR (KBR) : 3420.5, 1718.9, 1647.5, 1510.9
1H NMR (CDCl3) : δ=2.29 (s, 3H), δ=6.97 (m, 2H), δ=7.13 (d, 1H, j=9), δ= 7.33, (m, 3H), δ= 7.47 (t, 1H, J= 15), δ= 7.77 (d, 2H, J=9)

4-hydroxy-5-methyl-3-(5-phenyl-4, 5-dihydro-1H-pyrazol-3-yl)-2H-Pyran-2-one [5a]

Physical appearance: Yellow color solid
Yield : 66.64 %
Melting Point : 145°C
Mass : m/z EIMS (M+1) 271
IR (KBR) : 3426.2, 1703.1, 1539.2
1H NMR (CDCl3) : δ= 2.26 (s, 3H), δ=7.28 (s, 1H), δ= 7.50 (s, 1H), δ= 8.0134 (d, 2H, J=15.75), δ=8.36, (d, 2H, J=15.81)

3-(5-(4-(dimethylamino) phenyl)-4, 5-dihydro-1H-pyrazol-3yl)-4-Hydroxy-5-methyl-2H-pyran-2-one [5b]

Physical appearance: Red color solid
Yield : 67 %
Melting Point : 130°C
Mass : m/z EIMS (M+1) 315
IR (KBR) : 3400, 1716.1, 1596.3, 1216.5
1H NMR (CDCl3) : δ= 2.26, (s, 3H), δ= 3.08, (s, 6H), δ= 5.90, (s, 1H), δ= 6.70 (d, 2H, j=13.2), δ= 7.26 (s, 1H), δ= 7.63 (d, 2H, J=13.5)

4-hydroxy-3-(5-(4-hydroxyphenyl)-4, 5-dihydro-1H-pyrazol-3-yl)-5-Methyl-2H-pyran-2-one [5c]

Physical appearance: Yellow color solid
Yield : 61 %

Melting Point : 170°C

Mass : m/z EIMS (M+1) 287.1

IR (KBR) : 3421.7, 3019.7, 1694.4

(E)-3-hydroxy-4-methyl-2-(5-styryl-4, 5-dihydro-1H-pyrazol-3-yl) cyclohexa-2, 4-dienone) [5d]

Physical appearance: Yellow color solid

Yield : 58.55 %

Melting Point : 155°C

Mass : m/z EIMS (M+1) 297.1s

IR (KBR) : 3441.8, 1707.0, 1523.4

1H NMR (CDCl3) : δ= 2.29, (s, 3H), δ= 5.96 (s, 1H), δ= 7.42 (m, 5H), δ=7.47 (s, 1H), δ=7.54, (d, 2H, J=6.45), δ=7.84, (t, 1H, J=6.45)

4-hydroxy-3-(5-hydroxyphenyl) 4, 5-dihydroisoxazol-3-yl)-5-methyl-2H-pyran-2-one [6]

Physical appearance: Yellow color solid

Yield : 64 %

Melting Point : 135°C

Mass : m/z EIMS (M+1) 272.1

1H NMR (CDCl3) : δ= 1.90 (d, 2H, J=8.97) δ= 2.20, (s, 3H), δ= 5.91, (s, 1H), δ= 7.33, (m, 5H)

2'-(4-hydroxy-3-methyl-2-oxo-2H-pyran-5-carbonyl)-1'-phenyl-1', 2', 5', 6', 7', 7a'-hexahydrospiro [indoline-3, 3'-pyrrolizin]-2-one [7]

Physical appearance: Off white color solid

Yield : 90 %

Melting Point : 190°C

Mass : m/z EIMS (M+1) 457.1

IR (KBR) : 3437.6, 1723, 1645.7, 1556.5

1H NMR (CD_3OD) : δ= 2.26 (s, 3H), δ= 2.05 (m, 6H), δ=4.95, (d, 1H, J=14.31), δ= 6.84, (d, 2H, J=12.3), δ=7.32, (m, 9H), δ=7.61, (d, 2H, J=10.86), δ=7.98 (s, 1H).

2'-(4-hydroxy-3-methyl-2-oxo-2H-pyran-5-carbonyl)-1'-phenyl-1-(2-(piperidin-1-yl) ethyl)-1', 2', 5', 6,'7', 7a'-hexa hydro Spiro [indoline-3, 3'-pyrrolizin]-2-one (8)

Physical appearance: Off white color solid

Yield : 45%

Melting Point : 175°C

Mass : m/z EIMS (M+1), 567

1H NMR (CD_3OD) : δ=1.56 (m, 6H), δ= 2.05 (m, 6H), δ=2.50 (m, 4H), δ=3.32 (m,3H), δ=4.95, (d, 1H, J=14.31), δ=6.84, (d, 2H, J=12.3), δ=7.32, (m, 9H), δ=7.61, (d, 2H, J=10.86), δ=7.98 (s, 1H),

RESULTS AND DISCUSSION

The entire literature survey reveals that there is an urgent need to develop a strategy for the synthesis of a novel SERM, effective against breast cancer with minimal side effects.

The objective of our study was to synthesize compound 3-Cinnamoyl-4-hydroxy-5-methyl-2H-pyran-2-one [3] & its derivatives by conjugating it with various side chains & then to establish their anti-cancer activities.

The synthesis started with the preparation of 3-Cinnamoyl-4-hydroxy-5-methyl-2H-pyran-2-one [3] derivatives by the variation of corresponding aldehydes with DAA. One of the derivatives i.e., 3-Cinnamoyl-4-hydroxy-5-methyl-2H-pyran-2-one [3] which was further used to make tetra-substituted pyrazoline derivative, was confirmed by corresponding mass, IR & NMR spectra. (Shown in spectral details) While the synthesis of Compound 7, was synthesized by Proline, Isatin, and compound 3a, by using Ethanol as a solvent.

Synthesis of compound 3a, 3b, 3c &3d

Result: Reaction was complete & was confirmed by corresponding mass, IR & NMR spectra. (Shown in spectral details)

Synthesis of pyrazoline derivative using ethanol as a solvent by compound 3a, 3b, 3c, and 3d

Result: Reaction was complete.

Synthesis of pyrazoline derivative using pyridine as a solvent

Result: Yield=good (60%approx)

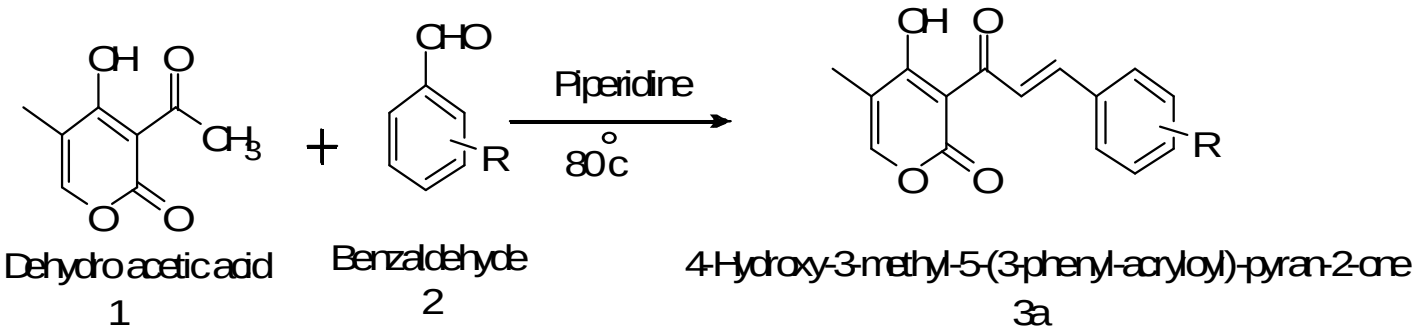
Synthesis of Spiro compound 7

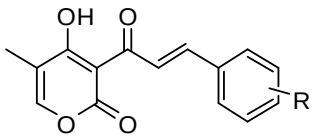
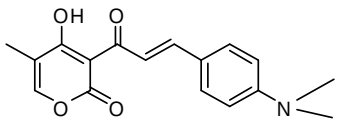
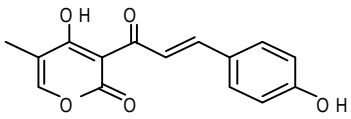
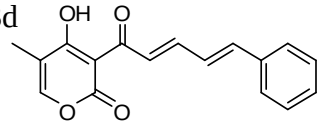
Result: Reaction was complete.

Synthesis of Spiro compound 8

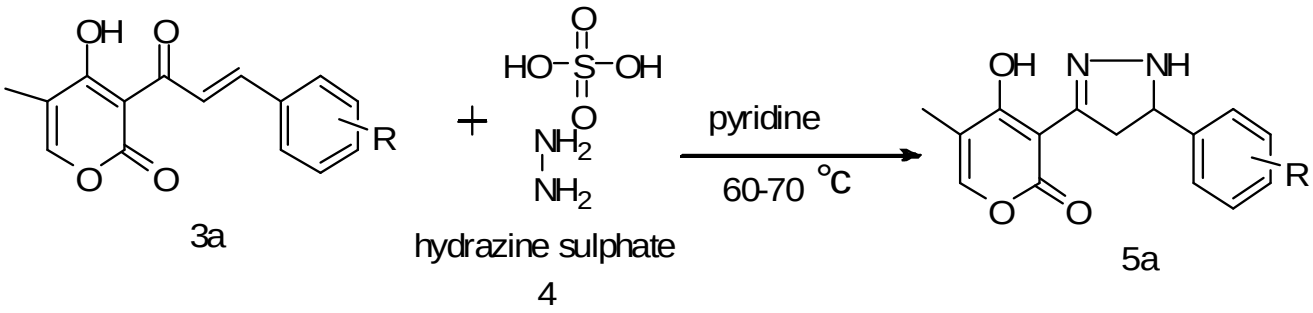
Result: Reaction was complete.

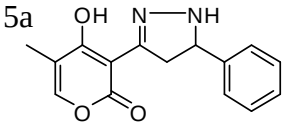
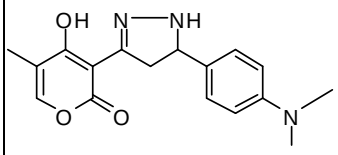
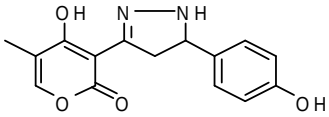
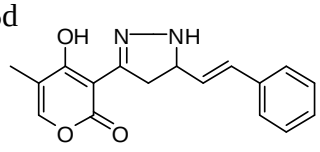
Scheme I :



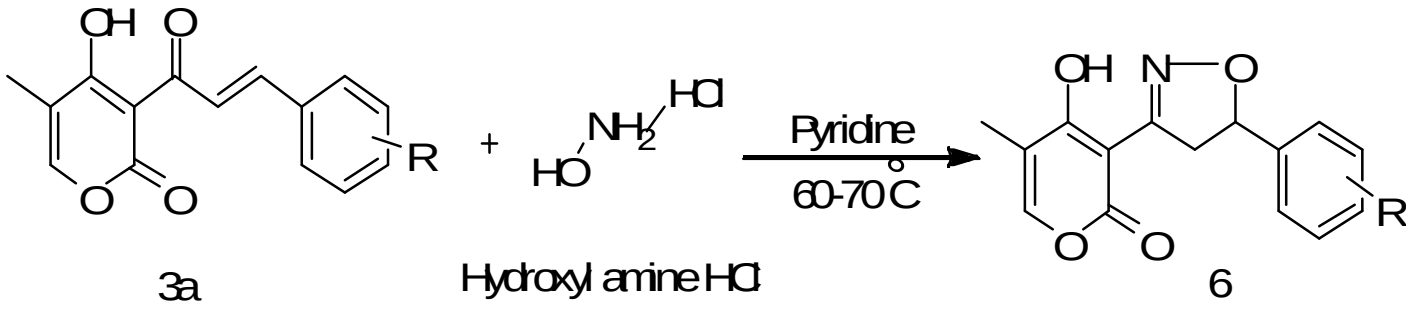
1.	R	Compound	Time	Yield
Dehydro acetic acid	H	3a 	16-18 Hrs	64.73%
Dehydro acetic acid	P-N-N-Dimethylamiono Benzaldehyde	3b 	16-18 Hrs	56.44%
Dehydro acetic acid	P-Hydroxy Benzaldehyde	3c 	16-18 Hrs	65%
Dehydro acetic acid	Cinnamaldehyde	3d 	16-18 Hrs	57%

Scheme 2:

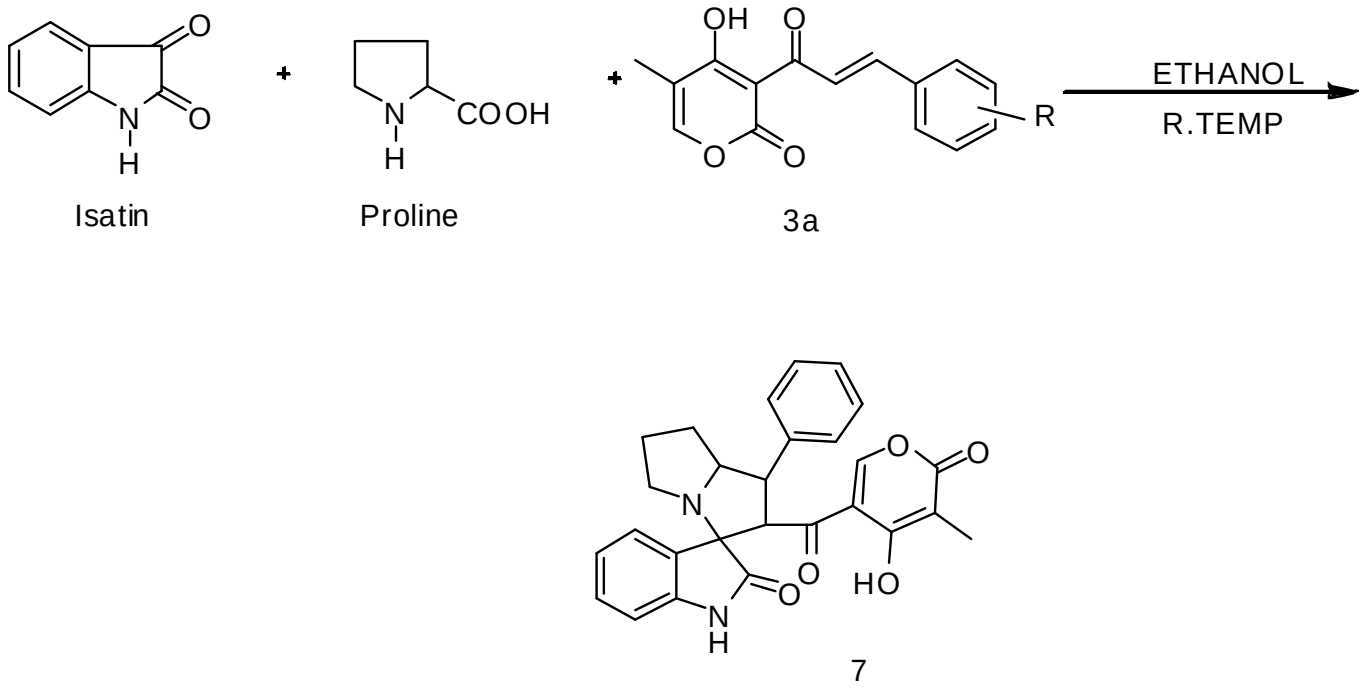


Compound	4	Compound 5	Time	Yield
3a	Hydrazine sulphate	5a 	10-12 hrs	66.64%
3b	Hydrazine sulphate	5b 	10-12 hrs	67%
3c	Hydrazine sulphate	5c 	10-12 hrs	61%
3d	Hydrazine sulphate	5d 	10-12 hrs	58.55%

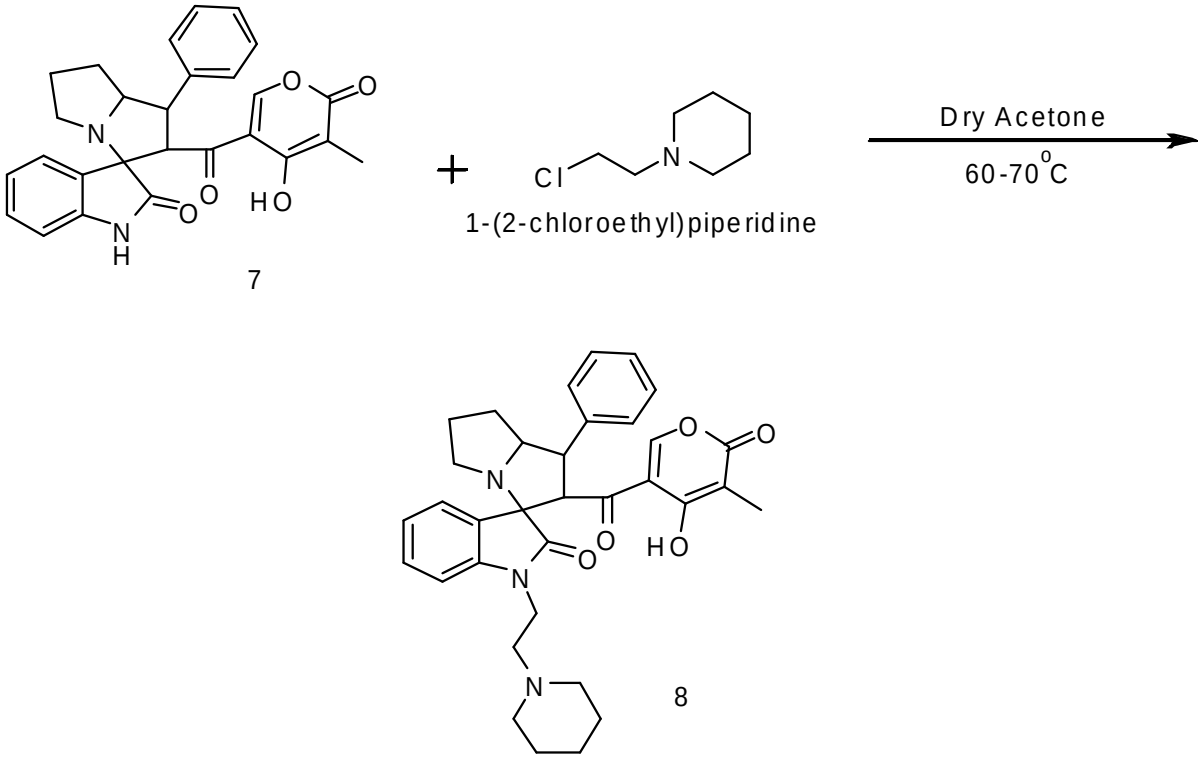
Scheme 3:



Scheme 4:



Scheme 5:



CONCLUSION

Our understanding of the molecular mechanisms of ER action continues to expand. With the advent of our knowledge of co-activators & co-repressors, we are now in a better position to understand now SERMs like TAM & RAL elicit their varied biologic responses in breast, uterus, bone & other body tissues. The recent progress in our understanding of the role of the ubiquitinproteasome protein degradation system on receptor stability & function also promises to provide additional critical insights into defining the mechanisms of SERM biologic action.

A more complete picture of SERM interaction with ERα & ERβ, which integrates these recent findings, should facilitate the search for novel SERMs those possess ideal tissue specific agonist/antagonist properties & can provide simultaneous therapeutic advantages in multiple tissues throughout the body. The Compound, which had synthesized, was submitted

for biological activity (anti-proliferative activity as well as an agonistic & antagonistic activity against ER in MCF-7 cancer line). Results are awaited.

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