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DEVELOPMENT AND CHARACTERIZATION OF COUMARIN BASED PRECURSORS TARGETING SELECTIVE ESTROGEN RECEPTOR MODULATION

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ABSTRACT

We have synthesized the novel 4-(4-hydroxy-benzyl)-3-phenyl-chromen-2-one which serves as a core pharmacophore or scaffold in the synthesis of SERMs due to its planar, heterocyclic structure that mimics estrogen like binding motifs and enhances receptor affinity. The benzopyran-2-one ring of coumarin provides hydrophobic and hydrogen bonding sites essential for derivatization at different positions with a smaller number of steps and good yield. Easy methodology for the synthesis has been worked out. Anhydrous $AlCl_3$, $FeCl_3$ and $SnCl_4$ catalysts were used for the reaction.

KEYWORDS: Coumarin, 4-(4-hydroxy-benzyl)-3-phenyl-chromen-2-one, SERMs, Estrogen

Selective Estrogen Receptor Modulators (SERMs) are a class of compounds that act 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. Few biologically active SERM's are shown in Figure 1 in which Raloxifene is a polyhydroxy phenyl benzothiophene antiestrogen that has low estrogen agonist activity in the rodent uterus (Black *et al.* 1983). Keoxifene was abandoned for treatment for breast cancer because its bioavailability was less than 2% administered dose (Snyder *et al.* 2000). However, the recognition that Raloxifene maintains bone density (Black *et al.* 1994) and inhibits mammary carcinogenesis in the rat (Anzano *et al.* 1996) illustrates the concept of selective estrogen receptor modulation. Raloxifene is used for the prevention of osteoporosis in postmenopausal women (Ettinger *et al.* 1999) and treatment is associated with a reduced incidence of breast cancer (Cummings *et al.* 1999). Tamoxifen is the prototype selective estrogen receptor modulator (SERM) that is used clinically for the treatment and prevention of breast cancer (Clarke *et al.* 1998) with the ability to maintain bone density in postmenopausal women (Love *et al.* 1992). However, Tamoxifen therapy is also associated with estrogen-like effects in the uterus with an increased incidence of endometrial cancer (Assikis *et al.* 1996). Clearly, an understanding of the factors that govern the estrogenic and antiestrogenic properties of SERMs complexes will provide additional opportunities to improve targeted therapeutic agents in the future.

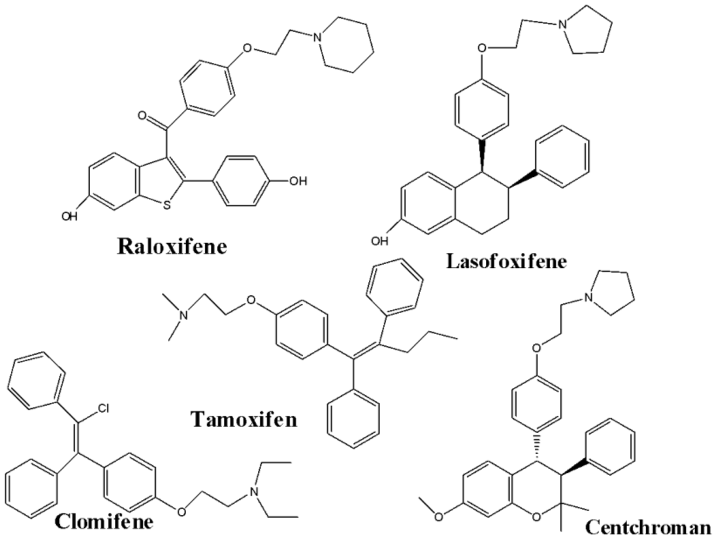

Figure 1: **Some Biologically Active Heterocyclic Compounds**

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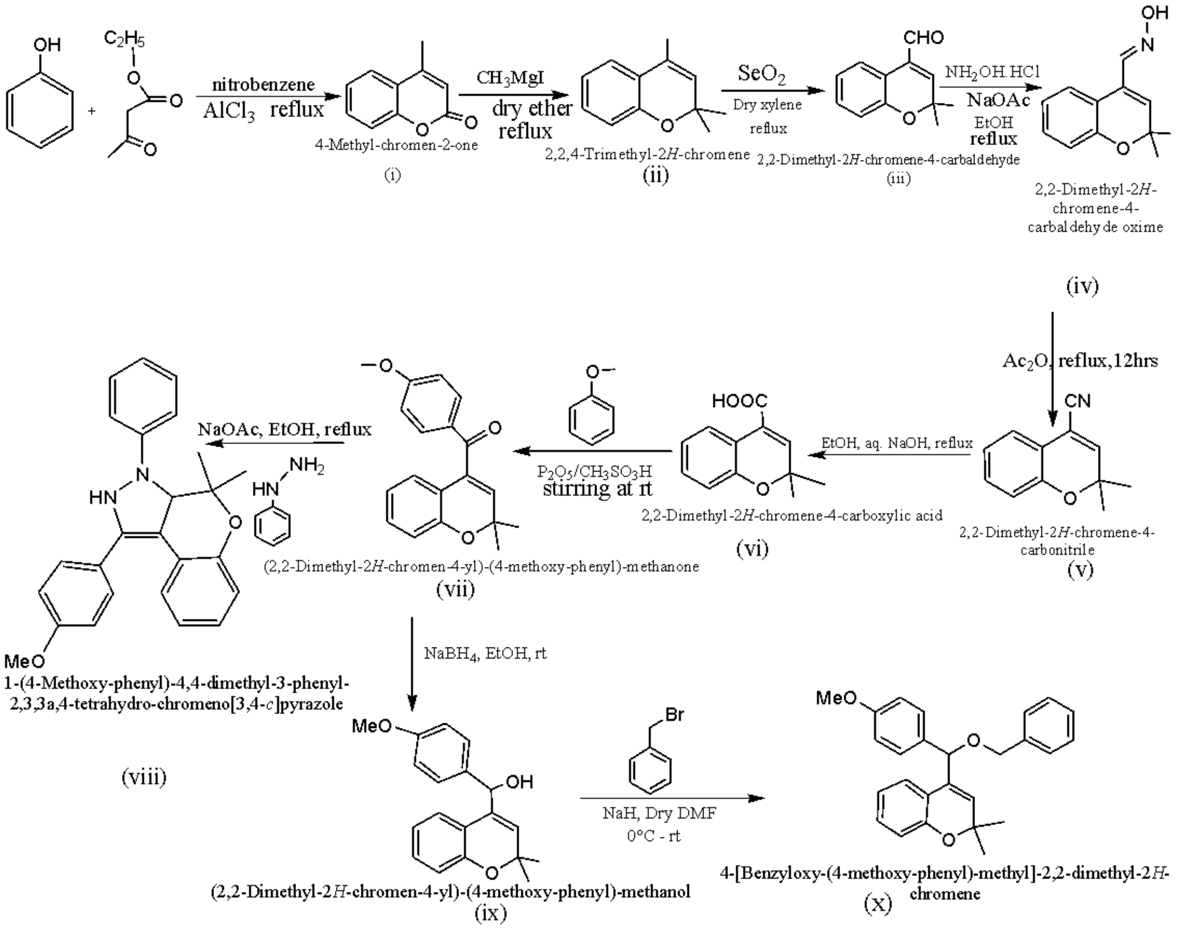
Coumarin and its derivatives are important compounds because of their presence in several natural products along with their applications in drugs, pharmaceuticals and SERMs. Coumarin based selective estrogen receptor modulators (SERMs) have been considered as potential anti breast cancer agents. Thus, coumarin derivatives acting as SERMs either stimulate or inhibit the estrogen action, result in curing estrogen related problems. Coumarin compounds are well known in nature (Freeman 1965), the 4-substituted derivatives of coumarins are especially interesting, exhibiting anticancer and HIV-1-reverse transcriptase inhibitory properties (Naser-Hijazi 1994). Coumarins are present in numerous natural products including edible vegetables and fruits (Hepworth *et al.* 1996). Interest in their chemistry is because they possess a broad range of biological activities (Joule *et al.* 2006) such as anti HIV (Bedoya *et al.* 2005), anticoagulation (Kidane *et al.* 2004), antibiotic (Hamdi *et al.* 2007).

Kostova, I. 2005, anti-inflammatory, antioxidant, antitumor, antiviral, antihypertensive, and antimicrobial activity. In addition, several coumarin derivatives have been identified as nuclear hormone receptor modulators including SERMs, PRMs and SERMs, anticancer (Pechmann 1884). Although the biological benefits of the 4-substituted coumarins are well known, there are very few general methods known to prepare these compounds. Scheme-1 is displayed where coumarins are converted to SERM precursor. To make these reactions efficacious, several variations in terms of catalyst and reaction conditions have been done. The scheme 1 methodology has multi-step procedures with moderate to good yields which would be helpful in designing novel SERMs.



Scheme 1: Route 1 for the synthesis of Coumarin based SERM's precursor

EXPERIMENTAL METHODS

All starting materials were commercially available and used as received without further purification. Commercially available ether, xylene and diethyl formamide were further purified and dried following the known procedure. Thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates. Column chromatography was carried out on silica gel 60 (100-200 mesh). Infrared (FTIR) spectra were measured in KBr, and wavelengths (ν) have been reported in cm^{-1}, ^{1}H and ^{13}C NMR spectra were recorded on NMR spectrometers operating at 300 and 75.5MHz, respectively. Chemical shifts (δ) were given in parts per million (ppm) using the residue solvent peaks as reference relative to TMS. J values have been given in Hz. Mass spectra were recorded using an electro spray ionization (ESI) mass spectrometer.

Synthesis of 4-methyl-chromen-2-one(i)

In a stirred heated solution of nitrobenzene(15ml) and $AlCl_3$(200mg, 1.5mmol) added mixture of phenol (0.09ml, 1mmol) and ethyl acetoacetate (0.10ml, 1mmol) and refluxed at 145 C for 3-4 hrs till the reaction completed as monitored by TLC. Cooled the reaction mixture and added aq. HCl drop wise till all the $AlCl_3$ neutralises. Extracted with ethyl acetate, dried with anhy. Na_2SO_4, steam distilled to recover the product 4-methyl coumarin as a pale yellow crystalline solid. Yield: - 60 %. 1H NMR (300MHz;$CDCl_3$): 2.43 (s,3H,CH_3), 6.27 (s,1H,=CH), 7.30-7.27 (d,J=8.4Hz,1H,Ar-H), 7.33-7.32 (t,J=8.4Hz,1H,Ar-H), 7.55-7.50 (t,J=7.8Hz,1H,Ar-H), 7.62-7.59 (d,J=7.7Hz,1H,Ar-H); 13C NMR (75MHz;$CDCl_3$): 18.6, 115.0, 117.0, 119.9, 124.2, 124.5, 131.7, 152.4, 153.4, 160.7; m/z 161; IR:-3064 (=CH str.), 2921 (-CH_3 str.), 1726 (-C=O str.), 1603, 1529, 1483, 1443 (C=C str.), 1186 (-C-O str.).

Synthesis of 2,2,4-trimethyl-2H-chromene(ii)

In a 50ml two neck round bottomed flask prepared the grignard reagent of methyl iodide (0.12ml, 2mmole) with Mg turnings (48mg, 2mmole) in ether under nitrogen atmosphere. Then added 4- methyl coumarin (160mg, 1mmole) dissolved in ether (4ml) and refluxed the reaction mixture for 6hrs.After the reaction is complete, cooled and added 5% aq. HCl (20ml) dropwise. Then extracted with ethyl acetate, dried the organic layer with Na_2SO_4 and concentrated in vacuum. Chromatographed with hexane. Oily orange liquid obtained, yield: - 65%. 1H NMR(300MHz;$CDCl_3$): 1.42 (s,6H,2CH_3), 2.03 (s,3H,CH_3), 5.44 (s, 1H,=CH), 6.83-6.80 (d,J=7.9Hz,1H,Ar-H), 6.92-6.90 (t,J=7.5Hz,1H,Ar-H), 7.18-7.12 (m,2H, Ar-H); 13C NMR (75MHz;$CDCl_3$): 22.7, 28.0, 75.3, 116.3, 120.4, 123.6, 127.2, 128.5, 131.3, 152.9.

Synthesis of 2,2-dimethyl-2H-chromene-4-carbaldehyde(iii)

In a 50 ml round bottomed flask added 2,2,4-trimethyl coumarin (158mg, 1mmol) and SeO_2 (111mg, 1.5mmol) in dry xylene(10ml) and refluxed for 12 hrs. Completion of reaction was monitored by TLC. Reaction mixture was filtered while hot, evaporated in vacuum. Dark orange liquid obtained, yield: - 70%. 1H NMR(300MHz;$CDCl_3$): 1.42 (s,6H,CH_3), 6.45 (s,1H,=CH), 6.89-6.86 (d,J=8.1Hz,1H,Ar-H), 6.98-6.95 (t,J=7.6Hz,1H,Ar-H), 7.23-7.20 (t,J=7.5Hz,1H,Ar-H), 8.22-8.19 (d,J=7.8Hz,1H,Ar-H), 9.67 (s,1H,Ar-CHO); 13C NMR (75MHz;$CDCl_3$): 26.7, 75.7, 116.8, 117.0, 121.2, 125.7, 130.4, 131.8, 149.8, 152.5, 191.2.

Synthesis of 2,2-dimethyl-2H-chromene-4-carbaldehyde oxime(iv)

In a stirred solution of ambi-16(1.04g, 5mmole) dissolved in ethanol(10ml) added hydroxylamine hydrochloride (0.7g,10mmole) and sodium acetate (0.8g,10mmole). Refluxed the reaction mixture for 1 hr, monitored the reaction by TLC. After the reaction completed, evaporated the solvent, extracted with ethyl acetate-water and chromatographed with 20% ethyl acetate-hexane, dark reddish-brown liquid obtained, yield: - 92%. 1H NMR (300MHz;$CDCl_3$): 1.46 (s,6H,2CH_3), 5.94 (s,1H,=CH), 6.90 (m,2H,Ar-H), 7.20 (t,1H,Ar-H), 7.96 (d,1H,Ar-H), 8.0 (s,1H,-NOH), 13C NMR (75MHz; $CDCl_3$): 27.1, 75.5, 117.0, 119.1, 120.8, 125.9, 129.7, 135.3, 149.2, 152.9, 176.2.

Synthesis of 2,2-dimethyl-2H-chromene-4-carbonitrile(v)

In a 100ml round bottomed flask taken ambi-17 (850mg) and acetic anhydride excess (25ml) and refluxed for 12hrs. After the reaction completed, acetic anhydride was removed on rotavapor and chromatographed with 10% ethyl acetate- hexane, dark orange liquid obtained, yield: - 96%. 1H NMR (300MHz; $CDCl_3$): 1.53 (s,6H,2CH_3), 6.37 (s,1H, =CH), 6.86-6.83 (d,1H, Ar-H), 7.30-6.96 (t,1H, Ar-H), 7.30-7.22 (t,1H, Ar-H), 7.37-7.34 (d,1H, Ar-H).

Synthesis of 2,2-dimethyl-2H-chromene-4-carboxylic acid(vi)

In a stirred solution of ambi-18(448mg,2.5mmole) in ethanol(10ml) added 10% aquous NaOH and refluxed till the reaction completed, as monitored by TLC. After the reaction is complete, cooled and added 50% aq. HCl just to make the medium acidic, the product starts precipitating. The precipitate is filtered, washed with water and dried. Yield:- 87%. 1H NMR (300MHz;$CDCl_3$): 1.48 (s,6H,2CH_3), 6.83 (s,1H,=CH), 6.88-6.83 (d,1H,Ar-H), 6.98-6.91 (t,1H,Ar-H), 7.25-7.15 (t,1H,Ar-H), 8.00-7.95 (d,1H,Ar-H) ; 13C NMR (75MHz;$CDCl_3$): 26.5, 75.3, 117.1, 118.0, 121.1, 124.4, 126.2, 129.9, 142.2, 152.8, 170.9

Synthesis of (vii)

In a 50 ml round bottomed flask added phosphorous pentoxide (200mg) and methane sulphonic acid (2ml) in nitrogen atmosphere and stirred till P_2O_5 dissolves in acid. Then added anisole(0.26ml) and ambi-19(1mmole, 200mg) and stirred at rt till reaction completes as monitored by TLC. Then poured the reaction mixture in crushed ice, the product starts precipitating. Filtered the precipitate, washed with saturated $NaHCO_3$ solution. Recrystallised from ethanol. Yield: - 72%. 1H NMR (300MHz;$CDCl_3$): 1.53 (s,6H,2CH_3), 3.89 (s,3H,OCH_3), 5.88 (s,1H,=CH), 6.96-6.84 (m,4H,Ar-H), 7.28-7.16 (m,2H,Ar-H), 7.94-7.91 (d,2H,Ar-H); 13C NMR (75MHz;$CDCl_3$): 27.3, 55.5, 75.4, 113.7, 117.0, 119.3, 121.0, 125.5, 129.8, 132.3, 133.1, 133.8, 152.6, 163.8, 193.9.

Synthesis of (viii)

In a stirred solution of (a) (0.30mmole, 100mg) in ethanol(5ml) added sodium acetate (0.8mmole, 65mg) and phenyl hydrazine (0.33mmole, 36mg) and refluxed for 6 hrs. After the reaction was complete, ethanol was evaporated and solid was chromatographed with 5% ethyl acetate- hexane, yield: -70%. 1H NMR (300MHz; $CDCl_3$): 1.52 (s,6H,2CH_3), 3.84 (s,3H, OCH_3), 5.77 (s,1H, =CH), 6.83-6.76 (t,1H, Ar-H), 7.20-6.85 (m,4H, Ar-H), 7.35-7.10 (m,5H, Ar-H), 7.6 (s,1H, -NH), 7.80-7.77 (d,2H, Ar-H).

Synthesis of (ix)

In stirred solution of (a)(0.5mmole,147mg) in ethanol(3ml) added $NaBH_4$ (0.7mmole, 25mg) and continued the stirring till the completion of reaction. After the reaction, evaporated the solvent on rotavapor, quenched with water and extracted with ethyl acetate. Yield: - 80%. 1H NMR (300MHz;$CDCl_3$): 1.50 (s,6H,2CH_3), 3.81 (s,3H,-OCH_3), 5.64 (s,1H,=CH), 5.87 (s,1H,=CH), 6.78-6.73 (t,1H,Ar-H), 6.85-6.80 (d,1H,Ar-H), 6.91-6.87 (d,2H,Ar-H), 7.03-7.00 (d,1H,Ar-H), 7.13-7.05 (t,1H,Ar-H), 7.38-7.35 (d,2H,Ar-H); 13C NMR (75MHz;$CDCl_3$): 27.8, 55.2, 72.1, 75.9, 113.7, 116.7, 120.4, 123.9, 127.8, 128.4,128.90, 128.96, 133.2, 133.8, 153.0, 159.3.

Synthesis of (x)

In a 50ml round bottomed flask under nitrogen atmosphere added NaH (1mmole, 36mg) in a stirred solution of (a) (0.33mmole, 100mg) in dry DMF (2.5ml) at 0 C and stirred for 1hr. Then added benzyl bromide (0.33mmole, 0.12ml) dropwise. Stirred the reaction at rt till the reaction completed as monitored by TLC. Then poured the reaction mixture in crushed ice and extracted with ethyl acetate. Organic layer dried with Na_2SO_4 and concentrated in vacuum. Orange –yellow solid obtained which was recrystallised from ethanol. Yield: - 65%. 1H NMR (300MHz;$CDCl_3$): 1.49 (s,6H,2CH_3), 3.80 (s,3H,-OCH_3), 5.62 (s,1H,=CH), 5.86 (s,1H,=CH), 6.78-6.74 (t,1H,Ar-H), 6.84-6.80 (d,1H,Ar-H), 6.90-6.86 (d,2H,Ar-H), 7.04-7.00 (d,1H,Ar-H), 7.14-7.05 (t,1H,Ar-H), 7.38-7.36 (d,2H,Ar-H).

RESULTS AND DISCUSSION

In scheme-1, ethyl aceto acetate and phenol were taken as starting material. In the first step, 4-methyl coumarin-2-one (i) is prepared which was separated chromatographically where the yield was 60%. Further methylation led to the formation of (ii) with good yield and the yield went on upto 70% with the formation of product (iii) in the presence of dry xylene and Selenium dioxide. The reaction of (iii) with hydroxylamine leads to the formation of oxime (iv) with 92% yield. The yield further increases upto 96% with the formation of (v), which was further oxidized to carboxylic acid (vi) in the presence of ethanol and aq. NaOH. Then reaction with methoxy benzene, phosphorous pentoxide and methyl sulphonic acid leads to the formation of product (vii) which on reduction with sodium borohydride gives product(ix). Finally, protection of the hydroxyl group by benzyl bromide leads to the formation of product (x).

To decrease the product loss and number of steps, the synthetic strategy was modified and scheme-1 was selected in which ethyl acetoacetate and phenol were used as starting material and reaction was catalyzed by $AlCl_3$ which was found to be a very effective catalyst. In this paper, a facile and high-yielding strategy for diverse SERMs precursors has been described. Further, to our ongoing research for SERMs precursors synthesis, we commenced our synthetic strategy with environmentally benign phenol, which can couple with different compounds affording substituted coumarins in good yields. The substituted coumarins on further treatment with suitable reagents led to the formation of various substituted SERMs precursor in good yields. Thus, the synthesis of substituted SERMs precursor was achieved in nine steps.

This new methodology allows facile introduction of substituents at position 4 of the coumarin skeleton and gives the flexibility for the construction of novel precursors. Various derivatives can be prepared with para substitution with hydroxyl, methoxy, acetoxy, methyl and ethyl groups. The reactions shown here are simple, simple workup procedures and feasible.

CONCLUSION

In conclusion, a simple and effective method has been developed as an easy way to synthesize 4-aryl-3-

phenyl-benzopyrones via scheme-1 and this has been supported by ^{1}H NMR, FTIR, ^{13}C NMR and mass spectroscopy. Synthetic pathway has been proved to be the best with less side reactions and greater yield. Herein, we have reported a precursor of coumarin based SERMs which could be useful in designing new SERMs. The pure products were obtained by column chromatography. This methodology presents several advantages including (a) mild reaction conditions (b) simple work-up procedure (c) moderately high yields of the desired products (d) economic availability of the reagents makeing the whole process simple and feasible.

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