BF$_3$⋅Et$_2$O Catalysed 4-Aryl-3-phenyl-benzopyrones, Pro-SERMs, and Their Characterization

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1. Introduction

Activity of estrogen receptor can be controlled by a class of compounds which is called selective estrogen receptor modulators (SERMs). The modulators have a distinctive feature in different individual tissues by which they can inhibit or stimulate or selectively suppress or excite estrogen-like behavior in different tissues. The structures of few biologically vital SERMs are shown in Figure 1 in which compound A is a polyhydroxy phenyl benzothiophene which has low physiological response when combined with the receptor estrogen in gnawing uterus [1]. Compound A was initially known as Ly156758/keoxifen and its advancement has been stopped for improved action for treatment of breast cancer [2] due to less bioavailability than the required essential dose [3]. But the concept of SERM was shown by compound A due to sustainable property of bone density [4,5] with restriction in mammary carcinogenesis in rat [6,7]. Studies on compound A reveal the reduction of risk of osteoporosis [8] and breast cancer in women after menopause [9]. Compound B is a nonhydroxy and typical model compound for SERM which was used clinically for the occupational therapy of breast cancer [10,11] with the maintained density in bone of women after menopause [12]. The drawback of the treatment by compound B was the increased possibilities of endometrial cancer [13]. Hence, it is clear that there are various factors which are responsible for estrogenic and antiestrogenic properties of SERM complexes and could be useful in improving targeted therapeutic agents.

Coumarin and its derivatives are important compounds due to their presence in numerous natural products along with their wide ranging applications as drugs, pharmaceuticals, and SERMs. Coumarin based selective estrogen receptor modulator modulators (SERMs) and coumarin-estrogen conjugates have been described as potential anti-breast-cancer agents. Thus, coumarin derivatives acting as SERMs either stimulate or inhibit the estrogen action, thereby generating the possibility of curing estrogen related problems. Coumarins and their derivatives are common in nature [14–18]; among them the 4-substituted coumarins were identified as anticancer and anti-HIV-1 molecules [19,20].

Among the oxygen heterocycles coumarins are one of them which are present in various naturally [21,22] occurring motifs. Due to comprehensive and inexhaustible performance of coumarin in biological activities [23–33] such as anti-HIV [34–37], anticoagulation [38], antibiotic [39–42], anticancer [43,44], anti-inflammatory [45,46], antioxidant [47–49], antitumor [50–52], antiviral [53], antihypertensive, and antimicrobial activity its chemistry grew up widely. Among the nuclear hormone receptor modulators, namely, SERMs, PRMs, and SARMs [54–58], coumarins are also identified with a similar kind of properties. Among the coumarin derivatives more attention is given to 4-substituted coumarins, but there are very few methods known for
Figures 1: Examples of biologically active heterocyclic frameworks.

synthesis. Route 1 (Scheme 1) to coumarins incorporates Pechmann [59, 60], Knoevenagel [61–64], Reformatsky [61–64], Perkin [65], and Wittig [66] condensation reactions. To make these reactions efficacious, several variations in terms of catalyst and reaction conditions have been done. However, the route 1 methodology suffers from laborious multistep procedures, long reaction time, high reaction temperature, nonselectivity, and waste problem. To overcome these, a facile two-step synthesis of 4-aryl-3-phenyl-coumarin-2-one has been reported as shown in Scheme 2, which would be helpful in designing novel SERMs.

2. Results and Discussion

Condensation reactions have been amongst the most useful routes for the synthesis of these compounds, particularly catalyzed by Lewis acids. In Scheme 1, 4-methoxy phenyl acetic acid and phenol were taken as starting material. In the first step, acyl chloride of acid was prepared, where the yield of phenyl acyl chloride obtained was 50%. Further esterification led to some good yield, but the yield was very poorly shed down to 10% with next step reaction, that is, Fries rearrangement. The reaction of ester and AlCl₃ at 145°C led to four products, of which only two (iv-a, iv-b) were important for synthesis purpose. Fries rearrangement with AlCl₃ has no selectivity and gave four products with almost 10% yield, which were separated chromatographically. Then cyclization with phenyl acetyl chloride was carried out with anhydrous K₂CO₃ in dry acetone. There were some shortcomings like low reaction yields and nonselectivity of reaction/more byproduct formation/low atom economic reactions. Hence, the nonselectivity of reactions (via Scheme 1) and low atom economy demanded the search for a simple, short, and high-yielding alternate process to synthesize substituted coumarin based SERMs precursors.

To decrease the product loss and number of steps, the synthetic strategy was modified and Scheme 2 route was selected in which 4-substituted phenyl acetic acid and substituted phenol were used as starting material and reaction was catalyzed by BF₃·Et₂O which was found to be a very efficient catalyst. In this report, a facile and high-yielding protocol for diverse SERMs precursors through synthesis of functionalized benzylic ketone and further intermolecular cyclization using substituted phenyl acetyl chloride with dry acetone and potassium carbonate under reflux condition has been described. Further, to our ongoing research on novel synthetic methodologies for SERMs precursors synthesis, we commenced our synthetic strategy with environmentally benign phenol, which on coupling with different phenyl acetyl chlorides including p-anisole acetyl chloride, p-phenyl acetyl chloride, and p-hydroxy phenyl acetyl chloride afforded substituted benzylic ketones in good yields. The substituted benzylic ketones (ix (a–i)) on further treatment with substituted phenyl acetyl chloride in the presence of K₂CO₃ and dry acetone led to the formation of various substituted SERMs precursors (4-benzyl-3-phenyl coumarin) (vi (a–i)), in good yields (Scheme 2). Thus, the synthesis of substituted SERMs precursor (4-benzyl-3-phenyl coumarin) was achieved in two steps. Acetylation was regioselective and occurred at ortho position which was the major reaction product. Thus, in just one step, phenol was esterified and the ester readily rearranged to give 4-methoxy phenyl acetyl
Dry benzene reflux Phenol

\[
\text{SOCl}_2 \quad \text{Phenol} \quad \text{AlCl}_3 \quad \text{Dry benzene reflux}
\]

\[
O \quad R \quad Cl \quad \text{O} \quad \text{O} \quad \text{Cl} \quad \text{O} \quad \text{Cl} \quad \text{O} \quad \text{O}
\]

where: \( R_1 = \text{OCH}_3, R_1' = \text{OH}, R_2 = \text{H}, \text{CH}_3, \text{C}_2\text{H}_5, \text{OCH}_3, R = \text{OCH}_3, \text{OH} \)

Scheme 1: Route 1 for the synthesis of coumarin based SERM's precursors.

\[
\text{COC}_2 \quad \text{BF}_3 \quad \text{Et}_2\text{O} \quad \text{Phenol} \quad \text{K}_2\text{CO}_3 \quad \text{reflux}
\]

\[
R \quad \text{Cl} \quad \text{O} \quad \text{R} \quad \text{O} \quad \text{R} \quad \text{O} \quad \text{O}
\]

where \( R = \text{OCH}_3, \text{OH}, R_2 = \text{H, CH}_3, \text{C}_2\text{H}_5, \text{OCH}_3 \)

Scheme 2: Route 2 for the synthesis of coumarin based SERM's precursors.

group at ortho position of phenol. This stage product was achieved by Scheme 1 after 3 steps with low atom economy and many undesirable products. The intermediate ester (Scheme 2) could not be isolated since BF_3-Et_2O readily rearranged it to ortho substituted phenol. Thus, the two-step process was reduced to one step, the probable mechanism of which has been given in Figure 2.

In our early attempts, to synthesize the coumarin based SERMs precursors, we were not successful in converting the reactants to products without the catalyst (BF_3-Et_2O). The anhydrous AlCl_3, FeCl_3, and SnCl_4 were not able to give the desired intermediate selectively in quantitative yield. This was possibly due to poor Lewis acid character of AlCl_3, FeCl_3, and SnCl_4 compared to BF_3. The reaction was investigated carefully and it was observed that the intermediate (benzylic ketones (ix (a–i))) formed after the coupling of phenol with substituted phenyl acetyl chloride was sufficiently stable and could be isolated. In the second step intermolecular cyclization was carried out with substituted phenyl acetyl chloride and a base (anhydrous K_2CO_3).

The desired product (vi–e) was characterized by ^1H NMR (Figure S6(a) in Supplementary Material available online at http://dx.doi.org/10.1155/2015/527159), which contains additional peaks at \( \delta 6.79 \) and 6.98 due to benzylic proton and at \( \delta 7.2 \) and 7.3 due to phenyllic protons and one signal at \( \delta 7.15 \) was due to proton at para position in the phenyl ring. The rest of the protons were the same as in the precursor, that is, ortho substituted phenol (iv–a).

\(^{13}\)C NMR (Figure S6(b)) also confirmed the formation of 4-(4-hydroxy-benzyl)-3-phenyl-chromen-2-one; peaks at 119.60, 126.40, 128.38, 129.53, 134.05, and 161.22 show six different types of carbons which are present in 4-aryl-3-phenyl-benzopyrone in addition to the carbons already present in the starting, that is, 2-(4-hydroxy-phenyl)-1-(2-hydroxy-phenyl)-ethanone. FTIR spectrum also confirmed the formation of lactone ring; that is, the cyclized product shows carbonyl absorption at a higher wavenumber, that is, at 1707 cm\(^{-1}\) (Figure S6(c)), while it was 1633 cm\(^{-1}\) in the 2-(4-hydroxy-phenyl)-1-(2-hydroxy-phenyl)-ethanone (Figure S2(a)). Mass spectroscopy shows (m + 1) peak at 343 while the molecular weight of (vi–e) is 342 (Figure S6(d)).

Finally the single crystal diffraction studies showed the space orientation (Figures 3(a) and 3(b)), bond lengths, and bond angles regarding the crystal structure (Table 1). The
Figure 2: Probable mechanism related to Scheme 2.

structure reflects that the coumarin ring is planar, phenyl ring which is attached at position 3 is slightly out of plane, and substituted benzyl group is perpendicular to the ring coumarin (Figure 3(a)). Compound (vi-e) exhibited “Z” like packing diagram (Figure 3(b)).

This new procedure allows facile introduction of substituents at position 4 of the 4-(4-substituted-benzyl)-3-phenyl-chromen-2-one skeleton and gives the flexibility for the construction of novel precursors.

Various derivatives have been prepared with para substituted benzyl chloride with hydroxyl, methoxy, acetoxy, methyl, and ethyl groups as shown in Table 2. All the derivatives have been prepared smoothly under the same reaction conditions. The reactions are simple, easy to handle, and feasible and have simple workup procedures.

After the establishment of the protocol for the synthesis of substituted SERMs precursors (4-benzyl-3-phenyl coumarins), we shifted our focus towards the role of solvents like CH₂Cl₂, CHCl₃, acetone, and toluene upon yield and the reaction time. The results illustrated that the reaction in toluene did not give the desired precursors, whereas the reaction in CHCl₃ was slow and the yield was low. However, for this cyclization, CH₂Cl₂ was found to be good in terms of yield and handling but took a slightly longer time to afford the products. Eventually, acetone appeared as a solvent of choice for intermolecular cyclization in very good yield. Intermolecular cyclization was greatly influenced by the base used; therefore, to find out the appropriate base, we examined K₂CO₃ and triethylamine in the intermolecular cyclization

| S. number | Atoms     | Bond lengths | Atoms     | Bond angles |
|-----------|-----------|--------------|-----------|-------------|
| 1         | O3-C20    | 1.3772(1)    | C20-O3-C23| 117.76      |
| 2         | O3-C23    | 1.3963(1)    | C8-O1-C7  | 121.71      |
| 3         | O1-C8     | 1.3848(1)    | O3-C20-C21| 115.93      |
| 4         | O1-C7     | 1.3722(1)    | O1-C8-C1  | 115.40      |
| 5         | C5-C6     | 1.3610(1)    | O3-C20-C19| 124.73      |
| 6         | C6-C7     | 1.4647(1)    | O1-C7-C6  | 117.78      |
| 7         | O2-C7     | 1.2114(1)    | C6-C7-O2  | 125.71      |
reaction of (ix-a) with (v) and found that the reaction in the presence of K$_2$CO$_3$ afforded the cyclized product (vi-a) in 74% yield after 7 h, whereas triethylamine gave this product in 57% yield. We believe that potassium carbonate may be more dissociated in aprotic polar solvents and consequently proved to be more reactive.

### 3. Conclusion

In conclusion, a simple, efficient, and novel method has been developed for an easy access to synthesis of the 4-(4-hydroxy-benzyl)-3-phenyl-chromen-2-one via Scheme 2 and this has been supported by $^1$H NMR, FTIR, $^{13}$C NMR, mass spectroscopy, and single crystal X-ray data analysis. Synthetic pathway with just 2 steps proved to be the best with less side reactions and greater yield. Thus, the number of steps has been decreased and the yield was increased. Herein we reported some precursors 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 workup procedure, (c) moderately high yields of the desired products, (d) the selectivity of the product, and finally (e) economic availability of the reagents making the whole process simple and feasible. Efforts to extend the span of the procedure on SERMs are under progress in our laboratory.

### 4. Experimental Section

#### 4.1. General Methods.
All the required chemicals are purchased since they are commercially available and used as received without further purification. Commercially available acetone and benzene 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 recorded in KBr, and wavelengths ($\nu$) have been reported in cm$^{-1}$; $^1$H and $^{13}$C NMR spectra were recorded on NMR spectrometers operating at 300 and 75.5 MHz, respectively. Chemical shifts ($\delta$) 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 electrospray ionization (ESI) mass spectrometer. The melting points were taken in open capillary and uncorrected.

#### 4.1.1. Procedure for Scheme 1

**Compound (ii).** To a solution of 4-methoxy phenyl acetic acid (42.5 g, 0.25 mol) in dry benzene (50 mL) was added thionyl chloride (30 mL, 0.25 mol) dropwise with syringe. After the reaction was complete, the reaction mixture was distilled to remove excess thionyl chloride and the solvent benzene. Brown colored liquid was obtained. Yield:- 50%. $^1$H NMR- (300 MHz, CDCl$_3$): $\delta$ 3.77 (s, 3H, -CH$_3$), 4.20 (s, 2H, -CH$_2$), 6.68 (d, $J$ = 7.8 Hz, 2H, Ar-H), 7.10 (d, $J$ = 7.8 Hz, 2H, Ar-H).
**Compound (iii).** A solution of p-methoxy phenyl acetyl chloride (24 g, 0.13 mol) and phenol (12.2 mL, 0.13 mol) in dry benzene (63 mL) was refluxed for 21 h, until the reaction was complete as monitored by TLC. Then the reaction mixture was washed with 5% aqueous NaOH to remove excess unreacted phenol and then washed with water three times and dried over anhydrous Na$_2$SO$_4$ and concentrated over vacuum. Orange colored liquid compound was obtained. Yield: 70%.

**Compounds (iv (a-d)).** A solution of ester (23.6 g, 0.1 mol) and AlCl$_3$ (13.3 g, 0.1 mol) was refluxed at 150°C till completion of reaction (as monitored by TLC). The reaction mixture was cooled, and then 5% cooled aqueous HCl was added till all the excess AlCl$_3$ neutralized. The reaction mixture was extracted with ethyl acetate and the organic layer was collected, dried over Na$_2$SO$_4$, and concentrated over vacuum. The residue was chromatographed to obtain the pure compound. Yield: 12%.

**General Procedure for Compounds (vi (a-h)).** To a solution of ortho substituted phenol (236 mg, 1 mmol) and K$_2$CO$_3$ (690 mg, 5 mmol) in dry acetonitrile (25 mL) was added phenyl acetyl chloride (308 mg, 2 mmol) dropwise. The reaction mixture was refluxed at 100°C for 7 h. After the reaction was completed (as monitored by TLC), the reaction mixture was cooled, filtered, and concentrated. The residue was chromatographed to obtain the pure compound with 20% ethyl acetate-hexane. Yield: 70%.

**4.1.2. Procedure for Scheme 2**

**Compound (ix-e).** To a solution of 4-methoxy phenyl acetic acid (166 mg, 1 mmol) in dry acetonitrile (10 mL) was added BF$_3$·Et$_2$O (0.4 mL, 3 mmol) at 0°C. After 30 minutes, we added phenol (0.1 mL, 1 mmol) and refluxed it till the reaction was completed as monitored by TLC. Then we filtered the reaction mixture and evaporated the solvent in vacuum. White solid was obtained, recrystallized from ethanol. Yield: 80%, m.p. 65°C.

**Compound (vi-e).** Phenyl acetyl chloride (0.13 mL, 1 mmol) was added to a solution of (ix-e) (242 mg, 1 mmol) in dry acetonitrile and K$_2$CO$_3$ (552 mg, 4 mmol) and pyridine (0.25 mL, 9 mmol) and refluxed for 6 h.

**Procedure for Compound (vi-i).** Acetic anhydride (920 mg, 1 mL) was added to a solution of (vi-a) (328 mg, 1 mmol) and pyridine (0.25 mL, 9 mmol) and refluxed under nitrogen atmosphere for 6 h at 90°C. After the reaction was completed (as monitored by TLC), solvent was removed under vacuum. The residue was washed with saturated Na$_2$HCO$_3$ until excess pyridine was removed and then it was washed with aqueous HCl and finally with saturated brine solution and dried and chromatographed with 20% ethyl acetate-hexane. Yield: 90%, m.p. 160°C.

**Analytical Data for Compounds (vi (a-i))**

**Compound (vi-a).** 1H NMR (300 MHz, CDCl$_3$): $\delta$ 4.03 (s, 2H, -CH$_2$), 6.717 (d, $J = 8.4$ Hz, 2H, -Ar-H), 6.932 (d, $J = 8.1$ Hz, 2H, -Ar-H), 7.170 (t, $J = 7.5$ Hz, 1H, -Ar-H), 7.273 (d, $J = 8.4$ Hz, 2H, -Ar-H), 7.384 (d, $J = 7.5$ Hz, 4H, -Ar-H), 7.459 (m, 2H, -Ar-H); FTIR (KBr, cm$^{-1}$): 3484, 3433, 3059, 2931, 1707, 1604, 1564, 1513, 1446, 1267, 1173, 828, 750. Figure S5 (a, b & c).

**Compound (vi-b).** 1H NMR (300 MHz, CDCl$_3$): $\delta$ 2.33 (s, 3H, -CH$_3$), 6.806 (d, $J = 8.4$ Hz, 2H, -Ar-H), 6.886 (d, $J = 7.5$ Hz, 1H, -Ar-H), 6.960 (t, $J = 8.4$ Hz, 1H, -Ar-H), 7.132 (d, $J = 8.4$ Hz, 2H, -Ar-H), 7.466 (t, $J = 7.2$ Hz, 1H, -Ar-H), 7.852 (d, $J = 7.8$ Hz, 1H, -Ar-H); FTIR (KBr, cm$^{-1}$): 3447, 3045, 2909, 1635, 1515, 1483, 1434, 1341, 847, 798, 754 (Figures S3 (a) & S3(b)); m/z 328, Elemental Analysis C, 80.47, H, 4.91, O, 14.62.

**Compounds (vi (a-h)).** To a solution of ortho substituted phenol (236 mg, 1 mmol) and K$_2$CO$_3$ (690 mg, 5 mmol) in dry acetonitrile (25 mL) was added phenyl acetyl chloride (308 mg, 2 mmol) dropwise. The reaction mixture was refluxed at 100°C for 7 h. After the reaction was completed (as monitored by TLC), the reaction mixture was cooled, filtered, and concentrated. The residue was chromatographed to obtain the pure compound with 20% ethyl acetate-hexane. Yield: 70%.
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129.79, 131.19, 134.05, 149.06, 153.13, 158.18, 161.22; FTIR (KBr, cm−1): 3075, 2928, 2857, 1707, 1509, 1445, 1384, 1211, 1121, 836, 798; m/z 342.13. Elemental Analysis C, 80.68, H, 5.30, O, 14.02; Figure 56(a, b, c & d); (vi-f): 1H NMR (300 MHz, CDCl3): δ 2.36 (s, 3H, -CH3), 3.75 (s, 3H, -OCH3), 4.04 (s, 2H, -CH2), 6.79 (d, J = 8.4 Hz, 2H, -Ar-H), 6.98 (d, J = 8.4 Hz, 2H, -Ar-H), 7.10 (s, 2H, -Ar-H), 7.29 (s, 2H, -Ar-H), 7.49 (q, J = 8.64 Hz, 2H, -Ar-H), 7.19 (s, 2H, -Ar-H), 7.29 (s, 4H, -Ar-H), 7.49 (q, J = 8.64 Hz, 2H, -Ar-H), 7.20 (t, J = 8.4 Hz, 2H, -Ar-H), 7.10 (s, 2H, -Ar-H), 7.29 (s, 4H, -Ar-H), 7.49 (q, J = 8.1 Hz, 2H, -Ar-H), 7.10 (s, 2H, -Ar-H), 7.29 (s, 4H, -Ar-H), 7.49 (q, J = 8.1 Hz, 2H, -Ar-H); 13C NMR (75 MHz, CDCl3): δ 21.0, 40.0, 56.4, 114.1, 121.6, 122.0, 125.5, 126.1, 126.8, 128.1, 128.4, 129.3, 130.1, 130.6, 132.2, 137.2, 1451, 1509, 160.3, 162.0; (vi-g): 1H NMR (300 MHz, CDCl3): δ 3.75 (s, 3H, -OCH3), 4.04 (s, 2H, -CH2), 6.67 (d, J = 8.4 Hz, 2H, -Ar-H), 6.88 (d, J = 8.4 Hz, 2H, -Ar-H), 7.15 (s, 2H, -Ar-H), 7.29 (s, 4H, -Ar-H), 7.45 (q, J = 8.1 Hz, 2H, -Ar-H); 13C NMR (75 MHz, CDCl3): δ 40.0, 56.4, 114.0, 115.6, 121.6, 125.7, 126.9, 127.6, 127.8, 128.1, 130.0, 130.4, 144.0, 150.9, 156.7, 159.6, 162.3; m/z 358, C, 77.08, H, 5.06, O, 17.86; (vi-h): 1H NMR (300 MHz, CDCl3): δ 1.30 (s, 3H, -CH3), 3.51 (s, 2H, -CH2), 3.75 (s, 3H, -OCH3), 4.04 (s, 2H, -CH2), 6.67 (d, J = 8.4 Hz, 2H, -Ar-H), 6.88 (d, J = 8.4 Hz, 2H, -Ar-H), 7.15 (s, 2H, -Ar-H), 7.29 (s, 4H, -Ar-H), 7.45 (q, J = 8.1 Hz, 2H, -Ar-H); 13C NMR (75 MHz, CDCl3): δ 18.1, 29.6, 40.1, 56.0, 114.2, 121.4, 125.7, 126.3, 127.8, 128.4, 130.0, 130.2, 132.1, 140.0, 144.0, 151.1, 159.2, 162.0.

Note. Crystallographic information is given in the supporting file with details of refinement and other structural parameters.

**Conflict of Interests**

The authors declare that there is no conflict of interests regarding the publication of this paper.

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**References**

[1] L. J. Black, C. D. Jones, and J. F. Falcone, “Antagonism of estrogen action with a new benzothiophene derived antiestrogen,” *Life Sciences*, vol. 32, no. 9, pp. 1031–1036, 1983.

[2] A. U. Buzdar, C. Marcus, F. Holmes, V. Hug, and G. Hortobagyi, “Phase II evaluation of LY156758 in metastatic breast cancer,” *Oncology*, vol. 45, no. 5, pp. 344–345, 1988.

[3] K. R. Snyder, N. Sparano, and J. M. Malinowski, “Raloxifene hydrochloride,” *American Journal of Health-System Pharmacy*, vol. 57, no. 18, pp. 1669–1678, 2000.

[4] V. C. Jordan, E. Phelps, and J. U. Lindgren, “Effects of antiestrogens on bone in castrated and intact female rats,” *Breast Cancer Research and Treatment*, vol. 10, no. 1, pp. 31–35, 1987.

[5] L. J. Black, M. Sato, E. R. Rowley et al., “Raloxifene (LY139481 HCl) prevents bone loss and reduces serum cholesterol without causing uterine hypertrophy in ovariectomized rats,” *The Journal of Clinical Investigation*, vol. 93, no. 1, pp. 63–69, 1994.

[6] M. M. Gottardis and V. C. Jordan, “Antitumor actions of keoxifene and tamoxifen in the N-nitrosomethylurea-induced rat mammary carcinoma model,” *Cancer Research*, vol. 47, no. 15, pp. 4020–4024, 1987.

[7] M. A. Anzano, C. W. Peer, J. M. Smith et al., “Chemoprevention of mammary carcinogenesis in the rat: combined use of raloxifene and 9-cis-retinoic acid,” *Journal of the National Cancer Institute*, vol. 88, no. 2, pp. 123–125, 1996.

[8] B. Ettinger, D. M. Black, B. H. Mitlak et al., “Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial,” *The Journal of the American Medical Association*, vol. 282, no. 7, pp. 637–645, 1999.

[9] S. R. Cummings, S. Eckert, K. A. Krueger et al., “The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial,” *The Journal of the American Medical Association*, vol. 281, no. 23, pp. 2189–2197, 1999.

[10] M. Clarke, R. Collins, C. Davies, J. Godwin, R. Gray, and R. Peto, “The EBCTCG secretariat, clinical trial service, unit, radcliffe infirmary, Oxford, OX2 6HE, UK,” *The Lancet*, vol. 351, pp. 1451–1467, 1998.

[11] B. Fisher, J. P. Costantino, D. L. Wickerham et al., “Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study,” *Journal of the National Cancer Institute*, vol. 90, no. 18, pp. 1371–1388, 1998.

[12] R. R. Love, R. B. Mazess, H. S. Barden et al., “Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer,” *The New England Journal of Medicine*, vol. 326, no. 13, pp. 852–856, 1992.

[13] V. J. Assikis, P. Neven, V. C. Jordan, and I. Vergote, “A realistic clinical perspective of tamoxifen and endometrial carcinogenesis,” *European Journal of Cancer A*, vol. 32, no. 9, pp. 1464–1476, 1996.

[14] E. J. Lederer, “Chemistry and biochemistry of some mammalian secretions and excretions,” *The Journal of Chemical Society*, pp. 2115–2125, 1949.

[15] G. G. Freeman, “Isolation of alternariol and alternariol monomethyl ether from *Alternaria dauci* (kühn) groves and skolko,” *Phytochemistry*, vol. 5, no. 4, pp. 719–725, 1966.

[16] W. T. L. Sidwell, H. Fritz, and C. Tamm, “Autumnariniol, zwei neue Dibenzo-

autumnalis Graeb er Bindungen in den magnetischen Protonenresonanz—Spek-

tum aus der Phase II evaluation of LY156758 in metastatic breast cancer; *Oncology*, vol. 45, no. 5, pp. 344–345, 1988.
[19] B. Naser-Hijazi, B. Stolze, and K. S. Zanker, *Second Proceedings of the International Society of the Coumarin Investigators*, Springer, Berlin, Germany, 1994.

[20] R. D. H. Murray, J. Méndez, and S. A. Brown, *The Natural Coumarin: Occurrence, Chemistry and Biochemistry*, John Wiley, Chichester, UK, 1982.

[21] J. D. Hepworth, C. D. Gabbutt, and B. N. Heron, *Comprehensive Heterocyclic Chemistry II*, vol. 5, Pergamon Press, Oxford, UK, 1996.

[22] F. M. Deans, *Naturally Occurring Oxygen Ring Compounds*, Butterworths, London, UK, 1963.

[23] J. A. Joule and K. Mills, Eds., *Heterocyclic Chemistry*, Blackwell Science, Oxford, UK, 4th edition, 2006.

[24] R. D. H. Murray, "Naturally occurring plant coumarins," *Comprehensive Schirrte der Chemie Organischer Naturstoffe*, vol. 35, pp. 199–249, 1978.

[25] G. R. Green, J. M. Evans, and A. K. Yong, in *Comprehensive Heterocyclic Chemistry*, A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds., vol. 5, p. 469, Pergamon Press, Oxford, UK, 1984.

[26] H.-X. Xu and S. F. Lee, "Activity of plant flavonoids against antibiotic-resistant bacteria," *Phytotherapy Research*, vol. 15, no. 1, pp. 39–43, 2001.

[27] J. M. Hamilton-Miller, "Antimicrobial properties of tea (*Camellia sinensis* L.)," *Antimicrobial Agents and Chemotherapy*, vol. 39, no. 11, pp. 2375–2377, 1995.

[28] K. C. Fylaktakidou, D. J. Hadjipavlou-Litina, K. E. Litinas, and J. M. Hamilton-Miller, "Antimicrobial activity of novel coumarin derivatives with anti-inflammatory/antioxidant activities," *Current Pharmaceutical Design*, vol. 10, no. 30, pp. 3813–3833, 2004.

[29] J. R. Hwu, R. Singhia, S. C. Hong et al., "Synthesis of new benzimidazole-coumarin conjugates as anti-hepatitis C virus agents," *Antiviral Research*, vol. 77, no. 2, pp. 157–162, 2008.

[30] S. Sardari, Y. Mori, K. Horita, R. G. Micetich, S. Nishibe, and M. Daneshタル, "Synthesis and antifungal activity of coumarins and angular furanocoumarins," *Bioorganic & Medicinal Chemistry*, vol. 7, no. 9, pp. 1933–1940, 1999.

[31] D. Egan, P. James, D. Cooke, and R. O’Kennedy, "Studies on the cytostatic and cytotoxic effects and mode of action of 8-nitro-7-hydroxycoumarin," *Cancer Letters*, vol. 118, no. 2, pp. 201–211, 1997.

[32] P. Valenti, A. Rampa, M. Recanatini et al., "Synthesis, cytotoxicity and SAR of simple geiparvarin analogues," *Anti-Cancer Drug Design*, vol. 12, no. 6, pp. 443–451, 1997.

[33] C. Spino, M. Dodier, and S. Sotheeswaran, "Anti-HIV coumarins from calophyllum seed oil," *Bioorganic and Medicinal Chemistry Letters*, vol. 8, no. 24, pp. 3475–3478, 1998.

[34] L. M. Bedoya, M. Beltran, R. Sancho et al., "4-Phenylcoumarins as HIV transcription inhibitors," *Bioorganic & Medicinal Chemistry Letters*, vol. 15, no. 20, pp. 4447–4450, 2005.

[35] K.-H. Lee, "Current developments in the discovery and design of new drug candidates from plant natural product leads," *Journal of Natural Products*, vol. 67, no. 2, pp. 273–283, 2004.

[36] D. Yu, M. Suzuki, L. Xie, S. L. Morris-Natschke, and K.-H. Lee, "Recent progress in the development of coumarin derivatives as potent anti-HIV agents," *Medicinal Research Reviews*, vol. 23, no. 3, pp. 322–345, 2003.

[37] S. Kirkicharian, D. T. Thuy, S. Sicsic, R. Bakhchinian, R. Kurkjian, and T. Tonnaire, "Structure–activity relationships of some 3-substituted-4-hydroxycoumarins as HIV-1 protease inhibitors," *Farmaco*, vol. 57, no. 9, pp. 703–708, 2002.

[38] A. G. Kidane, H. Salacinski, A. Tiwari, K. R. Bruckdorfer, and A. M. Seifalian, "Anticoagulant and antiplatelet agents: their clinical and device application(s) together with usages to engineer surfaces," *Biomacromolecules*, vol. 5, no. 3, pp. 799–813, 2004.

[39] K. M. Khan, Z. S. Saify, M. Z. Khan et al., "Synthesis of coumarin derivatives with cytotoxic, antibacterial and antifungal activity," *Journal of Enzyme Inhibition and Medicinal Chemistry*, vol. 19, no. 4, pp. 373–379, 2004.

[40] G. Appendino, E. Mercalli, N. Fuzzati et al., "Antimycobacterial coumarins from the Sardinian giant fennel (*Ferula communis*)," *Journal of Natural Products*, vol. 67, no. 12, pp. 2108–2110, 2004.

[41] N. Hamdi, M. Saoud, and A. Romero, "4-Hydroxy coumarine: a versatile reagent for the synthesis of heterocyclic and vanillin ether coumarins with biological activities," in *Bioactive Heterocycles V*, vol. 11 of *Topics in Heterocyclic Chemistry*, pp. 283–301, Springer, Berlin, Germany, 2007.

[42] F. Chimenti, B. Bizzarri, A. Bolasco et al., "Synthesis and in vitro selective anti-Helicobacter pylori activity of N-substituted-2-oxo-2H-1-benzopyran-3-carboxamides," *European Journal of Medicinal Chemistry*, vol. 41, no. 2, pp. 208–212, 2006.

[43] C. Ito, M. Itogawa, Y. Mishina et al., "Chemical constituents of *Calophyllum brasiliense*. 2. Structure of three new coumarins and cancer chemopreventive activity of 4-substituted coumarins," *Journal of Natural Products*, vol. 66, no. 3, pp. 368–371, 2003.

[44] I. Kostova, "Synthetic and natural coumarins as cytotoxic agents," *Current Medicinal Chemistry—Anti-Cancer Agents*, vol. 5, no. 1, pp. 29–46, 2005.

[45] G. Melagraki, A. Afantitis, O. Iglessiis-Markopoulou et al., "Synthesis and evaluation of the antioxidant and anti-inflammatory activity of novel coumarin-3-aminoamides and their alphalipoic acid adducts," *European Journal of Medicinal Chemistry*, vol. 44, no. 7, pp. 3020–3026, 2009.

[46] C. A. Kontogiorgis and D. J. Hadjipavlou-Litina, "Synthesis and antiinflammatory activity of coumarin derivatives," *Journal of Medicinal Chemistry*, vol. 48, no. 20, pp. 6400–6408, 2005.

[47] S. Stancheska, V. Hadjimitova, T. Traykov, T. Boyanov, and I. Manolov, "Investigation of the antioxidant properties of some new 4-hydroxycoumarin derivatives," *European Journal of Medicinal Chemistry*, vol. 44, no. 7, pp. 3077–3082, 2009.

[48] C. A. Kontogiorgis and D. J. Hadjipavlou-Litina, "Synthesis and biological evaluation of novel coumarin derivatives with a 7-azomethine linkage," *Bioorganic and Medicinal Chemistry Letters*, vol. 14, no. 3, pp. 611–614, 2004.

[49] C. Xiao, Z.-G. Song, and Z.-Q. Liu, "Synthesis of methyl-substituted xanthotoxol to clarify prooxidant effect of methyl on radical-induced oxidation of DNA," *European Journal of Medicinal Chemistry*, vol. 45, no. 6, pp. 2559–2566, 2010.

[50] O. M. Abdel Hafez, K. M. Amin, N. A. Abdel-Latif, T. K. Mohamed, E. Y. Ahmed, and T. Maher, "Synthesis and anti-herpes activity of some new xanthotoxin derivatives," *European Journal of Medicinal Chemistry*, vol. 44, no. 7, pp. 2967–2974, 2009.

[51] V. Neutrikul, P. Leewanich, P. Tuchinda et al., "Cytotoxic coumarins from *Mammea harmandii*," *Planta Medica*, vol. 69, no. 11, pp. 1048–1051, 2003.

[52] I. Kempen, D. Papapostolou, N. Thierry et al., "3-Bromophenyl 6-acetoxy methyl-2-oxo-2H-1-benzopyran-3-carboxylate inhibits cancer cell invasion in vitro and tumour growth in vivo," *British Journal of Cancer*, vol. 88, no. 7, pp. 1111–1118, 2003.
[53] P. O’Kennedy and R. D. Thornes, Eds., *Coumarins: Biology, Applications and Mode of Action*, John Wiley & Sons, Chichester, UK, 1997.

[54] L. Zhi, C. M. Tegley, E. A. Kalle et al., “5-Aryl-1,2-dihydrocro-meno[3,4-f]quinolines: a novel class of nonsteroidal human progesterone receptor agonists,” *Journal of Medicinal Chemistry*, vol. 41, no. 3, pp. 291–302, 1998.

[55] J. M. Schmidt, G. B. Tremblay, M. Pagé et al., “Synthesis and evaluation of a novel nonsteroidal-specific endothelial cell proliferation inhibitor,” *Journal of Medicinal Chemistry*, vol. 46, no. 8, pp. 1289–1292, 2003.

[56] K. Hajela, K. Kapoor, and R. Kapil, “Synthesis and post-coital contraceptive activity of ether and ester analogues of 2,3-diaryl-2H-1-benzopyrans,” *Bioorganic & Medicinal Chemistry*, vol. 3, pp. 1417–1420, 1995.

[57] K. Hajela and R. S. Kapil, “Synthesis and post-coital contraceptive activity of a new series of substituted 2,3-diaryl-2H-1-benzopyrans,” *European Journal of Medicinal Chemistry*, vol. 32, no. 2, pp. 135–139, 1997.

[58] K. Hajela, J. Pandey, A. Dwivedy et al., “Resolution, molecular structure and biological activities of the D- and L-enantiomers of potent anti-implantation agent, DL-2-[4-(2-piperidinoethoxy)phenyl]-3-phenyl-2H-1-benzopyran,” *Bioorganic & Medicinal Chemistry*, vol. 7, no. 9, pp. 2083–2090, 1999.

[59] H. Pechmann and C. Duisberg, “Neue Bildungsweise der Cumarine. Synthese des Daphnetins. I,” *Chemische Berichte*, vol. 17, no. 1, pp. 929–936, 1884.

[60] J. Johnson, “The Perkin reaction and related reactions,” *Organic Reactions*, vol. 1, pp. 210–265, 1942.

[61] G. Jones, “The Knoevenagel condensation,” *Organic Reactions*, vol. 15, pp. 204–599, 1967.

[62] G. Brufola, F. Fringuelli, O. Piermatti, and F. Pizzo, “Simple and efficient one-pot preparation of 3-substituted coumarins in water,” *Heterocycles*, vol. 43, no. 6, pp. 1257–1266, 1996.

[63] R. L. Shriner, “The reformatsky reaction,” in *Organic Reactions*, vol. 1, pp. 1–58, John Wiley & Sons, 1942.

[64] I. Yavar, R. Hekmat-Shoar, and A. Zonouzi, “A new and efficient route to 4-carboxymethylcoumarins mediated by vinyltriphosphonium salt,” *Tetrahedron Letters*, vol. 39, no. 16, pp. 2391–2392, 1998.

[65] J. R. Johnson, “Perkin reaction and related reactions,” *Organic Reactions*, vol. 1, p. 210, 1942.

[66] M. H. Elnagdi, S. O. Abdallah, K. M. Ghoneim, E. M. Ebied, and K. N. Kassab, “Synthesis of some Coumarin derivatives as potential LaserDyes,” *Journal of Chemical Research, Synopses*, no. 2, pp. 44–45, 1997.