Efficient Synthesis of New 2H-Chromene Retinoids Hybrid Derivatives by Suzuki Cross-coupling Reactions

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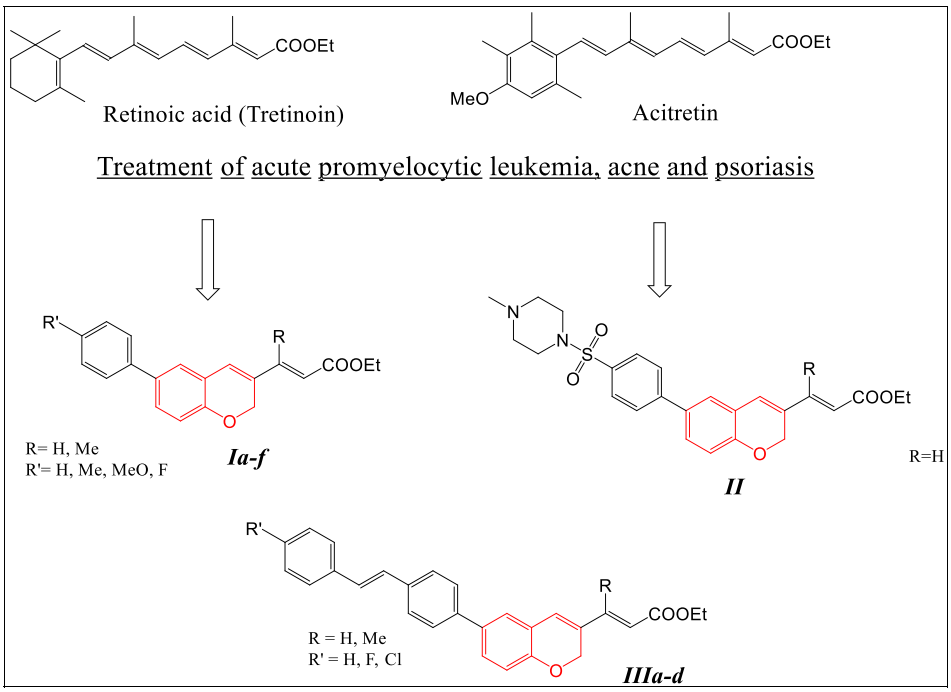


In an attempt to improve anticancer activity, a series of retinoids–chromene hybrids was described. The novel heterocyclic chromene–retinoids hybrid including oxygen as a heteroatom in a six-membered cyclic ring (2H-chromene or 2H-1-benzopyran) was designed and synthesized by introducing different groups such as an aromatic or styrylphenyl ring in 6-position of 2H-chromene. These novel compounds were synthesized by using the efficient cascades one-pot process involving Wittig–Horner–Emmons reaction and Suzuki–Miyaura cross-coupling pallado-catalyzed reactions with 60% to 90% overall yields. These new compounds were tested against glioblastoma multiforme brain cancer, medulloblastoma, neuroblastoma cell lines, and breast cancer MCF-7 cell lines. Two of them exhibited an appreciable anti-tumor activity in the low micromolar range, which opens new perspectives for therapeutic application on humans.

INTRODUCTION

Retinoids are analogs of all-trans-retinoic acid (ATRA), a powerful hormone that mediates many fundamental biological processes. Most of the physiological actions of retinoids can be accounted by the transcriptional regulatory activity of ATRA and 9-cis RA (9-CRA) through their nuclear receptors, known as RA receptors (RARs), (bind ATRA and 9-CRA), and retinoid X receptors (bind 9-CRA) [1], which associate with RA response elements within the promoters of retinoid-responsive genes [2].

A number of synthetic retinoids that interact selectively with their receptors have been synthesized [3–6]. These ATRA analogs have been synthesized with the aim of improving the therapeutic efficacy, to toxicity index as well as to secure better selectivity for various therapeutic applications. These analogs involve changes in the lipophilic or the hydrophilic part, the spacer, or a combination of changes in the parent compound ATRA [7].

Cancer and other serious hyperproliferative diseases are attractive therapeutic targets for retinoids [8–11]. However, the therapeutic use of retinoids is limited due to their severe

toxicity. ATRA is the first clinically useful cyto-differentiating agent, being employed in the treatment of acute promyelocytic leukemia [12]. For this purpose, there is interest in expanding the therapeutic use of ATRA and derivatives to breast cancer [13].

The selectivity, the high receptor binding affinity, and the ability of retinoids to directly modulate gene expression programs present a distinct pharmacological opportunity for cancer treatment and prevention [14]. Therefore, the ATRA and retinoids derivatives (Fig. 1) are largely exploited for therapy of malignant diseases [15–26].

Despite the richness of pharmacological benefits of retinoids, the toxicity represents the main limitation to their chronic use. Therefore, it is imperative to develop a new strategy to minimize the toxicity effect without compromising their therapeutic effectiveness [27–29].

Indeed, systemic retinoid toxicity in adults is similar to hypervitaminosis A, which manifests in skin dryness, conjunctivitis, and hair loss. The cutaneous and metabolic side effects of retinoid treatment are dose-dependent and reversible. It should be noted that only a low percentage of acute promyelocytic leukemia patients receiving RA (14–16%) develop RA syndrome, encompassing dyspnea, fever, pulmonary hemorrhage, and renal and respiratory failures [11,30].

Several studies that have been described in the literature suggest that the toxicity of structural analogs of RAs may be considerably reduced if a heterocyclic is incorporated in the structure of the product. For instance, the presence of a substituted chromene moiety in RA backbone, such as in the oxaretinoids, has reduced considerably the toxicity of compound [31–35].

Indeed, chromene (benzopyran) is one of the privileged medicinal pharmacophore that appears as an important structural component in various natural compounds and generated great attention because of its interesting biological activity [36,37]. The potency of these clinically useful pharmacophores in the treatment of cancer and inflammation and other activities encouraged the development of some more potent and significant compounds. The derivatives of chromene moiety can be able of interacting with a variety of cellular targets that leads to their wide ranging biological activities [36–38], such as anticancer agents [39–44] and as a human aldose reductase like protein inhibitors [45,46], and chromene derivatives with antiviral activity [47].

For this purpose, the chromene ring constitutes an important pharmacophore in retinoids drug discovery. Examples of oxaretinoids were reported recently bearing the 2H-chromene motif with boron-containing derivative of the RARα specific agonist Am-580 [31]. This new derivative, BD4, binds to the RARα receptor with a higher affinity and exhibits less cellular toxicity than Am-580 and ATRA. Other authors have described the synthesis of novel monofluoro lead compound 2-fluoro-4-[8-bromo-2,2-dimethyl-4-(4-methylphenyl)-chromen-6-yl]-4-aminocarbonylbenzoic acid as selective RARα antagonist. Antagonist effects of this fluoro compound were evaluated on the classical ligand-sensitive promoter activation by RARα in MCF7 breast cancer cells [48].

Based on these findings and considering the importance of the therapeutic potential of retinoids, we were interested in designing and synthesizing a small library of new chromene–retinoids hybrid derivatives (**I–III**) that included a combination of changes in the lipophilic part and spacer in the parent compound ATRA (Fig. 2). These chromene–retinoids hybrid analogs were designed to present variable electron density, lipophilicity, and steric bulk in the heterocyclic ring. These compounds were screened for bioactivity in glioblastoma multiforme brain cancer and in breast cancer MCF-7 cells.

RESULTS AND DISCUSSIONS

The main for the preparation of these new chromene–retinoids hybrid compounds (**I–III**) was based on the previously mentioned work described by Brion *et al.* [49]. These new compounds have been produced by

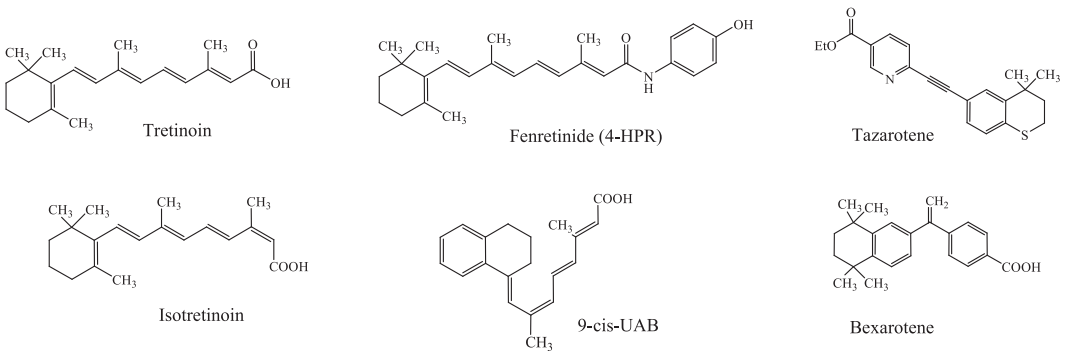


Figure 1. Retinoids derivatives exploited for therapy of cancer diseases.

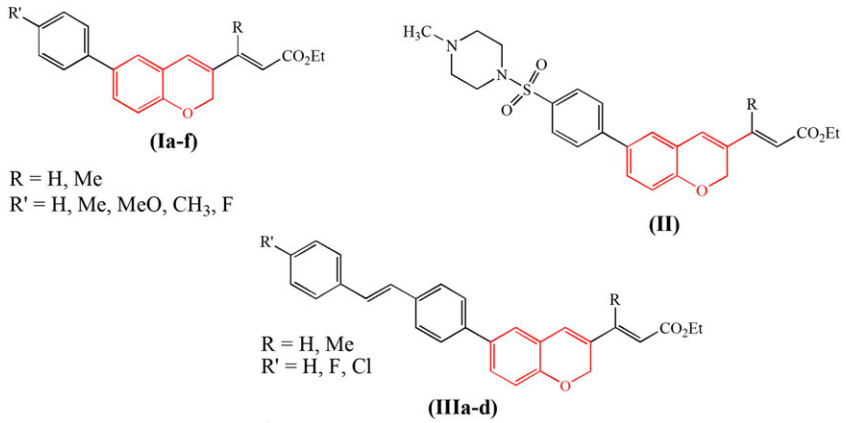


Figure 2. Structures of the new 2H-chromene retinoids hybrid derivatives. [Color figure can be viewed at wileyonlinelibrary.com]

incorporation of the oxygen atom and by substitution of one of the trans double bond of ATRA in the 2H-chromene ring. These compounds have shown the absence of toxicity, and they have shown an anti-resorbant, anti-proliferative, and proapoptotic properties in preliminary experiments. Indeed, the presence of an oxygen atom in the heterocyclic ring changes the lipophilic nature of the molecule and provides new opportunities for interaction with the target zones of receptors. Furthermore, the SAR studies showed that the incorporation of oxygen atom decrease the toxicity by retarding metabolic oxidation, and the substitution in the 6-position of chromene ring moiety has an important role in the activity [50]. This work was also inspired by the works more recently mentioned in the literature [51,52].

The novel chromene–retinoids hybrid compounds (**Ia–f**) were designed with shortening of the chain and introducing the phenyl groups in the 6-position; novel compound (**II**) was designed with 1-methyl-4-(phenyl)sulfonyl)piperazine as bioisostere and in compounds (**IIIa–d**), changes in the lipophilic part, phenyl in 6-position was replaced by substituted stilbenylgroup as bioisostere ring.

Traditionally, polyene chain construction for the total synthesis of ATRA and analogs was accomplished using Wittig reaction [53], Horner–Wadsworth–Emmons, Julia, and Stobbe reactions [54]; more recently, palladium-catalyzed cross-coupling reactions were applied [55–57].

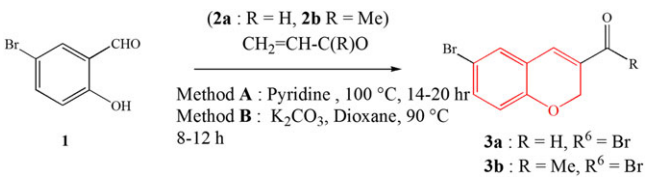
In order to prepare these new chromene–retinoids hybrid derivatives (**I–III**), we decided to develop an efficient synthetic concept, which was based on heterocyclization reaction for the synthesis of heterocyclic, the one-pot cascade process Wittig–Horner reaction [58,59] and Suzuki–Miyaura palladium-catalyzed Csp^2–Csp^2 cross-coupling reactions [60–63].

The heterocyclic intermediates 6-bromo-2*H*-chromenes carboxaldehyde **3a** and ethanone **3b** have been synthesized from commercially available 5-bromosalicylaldehyd **1**, and acrolein **2a** (or methylvinylketone **2b**) by oxa-Michael/aldol reactions using organic or inorganic bases (piperidine, pyridine, DABCO, potassium carbonate, etc.) in dioxane or toluene. The best results were obtained by using potassium carbonate as base and dioxane as solvent (85% yield with acrolein and 65% yield with methylvinylketone) [31,51,64], as shown in Scheme 1.

In our retrosynthetic perspective, we first envisaged that the target molecules chromene retinoid hybrid analogs (**Ia–d**) could be achieved from precursors **3a–b**, **4a–b**, and **5** according to the following retrosynthetic analysis represented in the Figure 3.

Phosphonate esters [58] and phosphonium salts [7,59] have often been used in the assembly of retinoid spacers. We first sought to synthesize the heterocyclic intermediate with bromide in 6-positions **6a** and **6b** *via* Wittig–Horner reactions between commercially available ethoxycarbonylmethylphosphonium bromide **4a** or ethyl phosphonoacetate **4b** and 6-bromo-3-formyl-2*H*-chromene **3a** or 6-bromo-3-acylchromene **3b** by two methods: first,

Scheme 1. Synthesis of 6-bromo-2*H*-chromenes carboxaldehyde and ethanone **3a–b**. [Color figure can be viewed at wileyonlinelibrary.com]



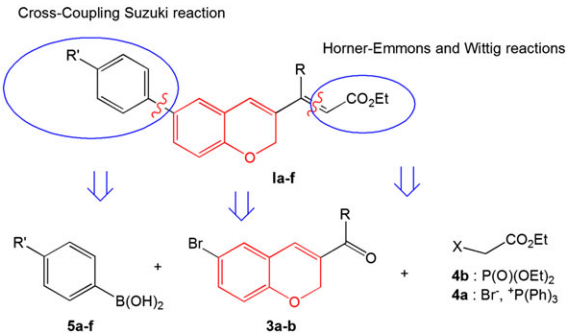


Figure 3. Retrosynthetic analysis for access to new chromene–retinoids hybrid analogs (**Ia–f**). [Color figure can be viewed at wileyonlinelibrary.com]

using BuLi in THF or sodium hydride in toluene as deprotonating agent at −78°C under nitrogen atmosphere for 48 h. The Compounds ethyl (2*E*)-3-(6-bromo-2*H*-1-benzopyran-3-yl)propenoate **6a** were isolated and purified by chromatography with good overall yields (70%) as mixture of *E* and *Z* isomers in the ratio of 95:05 (Table 1, entry 1) (Scheme 2). Unfortunately, this reaction using 6-bromochromene with 3-acyl group **3b** produced ethyl (2*E*)-[3-(6-bromo-2*H*-1-benzopyran-3-yl]butenoate **6b** in an overall moderate yield (45%) (Table 1, entry 2) as mixture of geometric isomers cis and trans in the ratio of 90/10, based on the chemical shift of ethylenic proton at 5.65 and 5.85 ppm for the *E* and *Z* isomers, respectively. (Only the trans isomer is drawn).

The analysis of the intermediates synthesis results **6a–b** shows that the method using the butyllithium (*n*-BuLi, 2 mol in hexane) as base is more efficient and more stereoselective using phosphonium salt **4a** than phosphonate **4b**.

Palladium-catalyzed Suzuki–Miyaura cross-coupling reactions of aryl halides with arylboronic acids are among the most efficient methods to selectively construct biaryl compounds in organic synthesis [60], [65–70]. To date, Suzuki reactions have been extensively used for the synthesis of natural products, herbicides, pharmaceuticals, and other products [60,71].

To synthesize the new compounds (**Ia–f**), we tested two strategies based on palladium-catalyzed Suzuki coupling reactions under homogenous catalysis reaction [72]. The first strategy that operates two successive and independent steps applying the Suzuki cross-coupling of the brominated compounds **6a–b**, serving as the key intermediates, which have been obtained by the Wittig–Horner reaction after isolation and purification of a chemical intermediate. The intermediate is then coupled with phenylboronic acid derivative in the presence of the catalyst Pd $(OAc)_2$ (8 mol %) and $P(C_6H_5)_3$ (30 mol %), lithium chloride (1 equiv) and potassium carbonate (2 equiv) in THF at 60°C, to give the target molecules in moderate yields (45% to 55%). During the Suzuki cross-coupling reaction, monitoring of the progress of the reaction by TLC revealed that some of the reactants are still present in the mixture. Increasing the amount of the catalyst (Pd $(OAc)_2$, 15 mol %) and prolonging the reaction time (48 h) did not improve the yields.

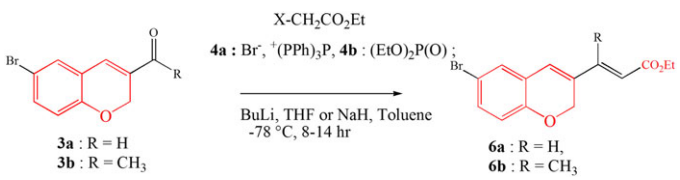
In the second strategy and in order to optimize the experimental conditions and improve the yields, we

Table 1

Results of the preparation of the compounds **6a–b** by two methods.

Entry	Compound	R^6	R	Reagents and conditions *n*-BuLi (1.3 eq), **4a**/**4b** (2 equiv) THF, −78°C then 50°C; NaH (3 eq), **4a**/**4b** (4 equiv) toluene, −78°C then 65°C (base/time)	Yields (%) with **3a** or **3b** at mixture of isomers (*E*:*Z* ratio)
1	**6a**	Br	H	*n*-BuLi/8 h	78 (98:02)/75 (96:04)
				NaH/10 h	65 (96:04)/60 (95:05)
2	**6b**	Br	CH_3	*n*-BuLi/10 h	55 (92:08)/50 (93:07)
				NaH/20 h	50 (92:08)/45 (90:10)

Scheme 2. Synthesis of ethyl (2*E*)-3-[(6-bromo)-2*H*-1-benzopyran-3-yl]propenoate **6a** (or butenoate) **6b**. [Color figure can be viewed at wileyonlinelibrary.com]



decided to develop an alternative methodology for the preparation of the novel compounds (**Ia–f**) based on the new concept one-pot cascades that exploit the Wittig–Horner reaction and Suzuki–Miyaura cross-coupling reaction without isolation of intermediates **6a–b**. First, ethoxycarbonylmethylphosphonium bromide **4a** was condensed with aldehyd **3a** (or ketone **3b**) in the presence of *n*-BuLi (2 equiv), in THF at −78°C, and solvent were evaporated and DMF (10 mL), Pd $(OAc)_2$ (2 mol %), phenylboronic acid and potassium carbonate (2 equiv) have been added under nitrogen without using lithium chloride and triphenylphosphine. The mixture was heated at 90°C for 4 h. The progress of reaction was monitored by TLC. Surprisingly, after only 4 h of heating, all the reagents were consumed. Usual post-reaction treatment by extraction of mixture and chromatography leads to the expected purified coupling product **Ia** with a good yield (85%).

Moreover, we have already carried out successfully similar concept based on the cascades one-pot, Sonogashira reaction, heterocyclization, and Heck cross-coupling without the isolation of the intermediates in previous work with good yields for the preparation of new chromenimines and furanimines [73] but never tested for Wittig–Horner reaction and Suzuki cross-coupling reaction.

To further explore the factors that influence of this one-pot cascade process Wittig–Horner reaction and Suzuki–Miyaura cross-coupling reaction, which is followed by Suzuki coupling reaction without isolation of the ethylenic intermediate, we examined various bases and solvents. When *n*-BuLi was replaced by LDA, NaH or EtONa or BuOK (Table 2, entries 3, 4, and 5) as bases in THF for the Wittig reaction, we observed that the Suzuki reaction by evaporation of THF and addition of DMF in the mixture as solvent, phenylboronic acid, Pd $(OAc)_2$, and K_2CO_3 did not accomplished (Table 2), but interestingly, when BuLi or LDA was used as base in THF, the one-pot cascade process Wittig–Horner reaction and Suzuki–Miyaura cross-coupling reaction was successfully achieved, and coupling product was obtained with 80% to 90% yield (Table 2, entry 2). These observations indicate that the bases with lithium cation participate in the transmetallation during the mechanism of the catalytic cycle of palladium and triphenylphosphine present in the mixture play an important role in the reduction of Pd (II) to Pd (0), which is the active form in catalysis. For this purpose, only 2 mol % of the catalyst Pd $(OAc)_2$ was required to carry out Suzuki coupling reaction. In order to validate this hypothesis of the participation of the species present in the mixture during the cascades one-pot to the catalytic mechanism of palladium, Suzuki coupling reaction was carried out between the 6-brominated compound **6a** and the phenylboronic acid under catalysis by Pd $(OAc)_2$ (2 mol %) without lithium chloride and triphenylphosphine; the monitoring of the reaction by TLC

Table 2

Study of base effects of cascade one-pot Horner and Suzuki reaction.

Entry	Experimental conditions[a] of the one-pot cascades process **4a** or **4b** (1.3 equiv), THF, −78°C to 25°C, and the solvent (THF) was evaporated and replaced by DMF, phenylboronic acid (1.1 equiv), K_2CO_3 (2 equiv): with **3a** without PPh_3 or LiCl, 90°C; with **3b**, Pd $(OAc)_2$ (2 mol %), PPh_3 (8 mol %), 90°C (Base, 2 equiv/time)	Product yield (%)
1	*n*-BuLi	
	with **4a**, 8 h	**Ia** (90)
	with **4b**, 16 h	(30)
	with **4b**, 6 h, and PPh_3 (8 mol %) was added, 24 h	(65)
2	LDA	
	with **4a**, 6 h	**Ia** (85)
	with **4b**, 24 h	(15)
	with **4a**, and PPh_3 (8 mol %) was added, 6 h	(55)
3	NaH	
	with **4a**, 20 h	**Ia** (25)
	with **4b**,, 24 h	(05)
	with **4b**, and PPh_3 (8 mol %) was added, 24 h	(15)
4	MeONa	
	with **4a**, 20 h	**Ia** (20)
	with **4b**, 24 h	(05)
	with **4b**, and PPh_3 (8 mol %) was added, 24 h	(12)
5	t-BuOK	
	with **4a**, 16 h	**Ia** (15)
	with **4b**, 24 h	(03)
	with **4b**, and PPh_3 (8 mol %) was added, 20 h	(10)

[a]All reactions were performed using THF for Horner–Wittig reactions. THF was evaporated and replaced by DMF under nitrogen atmosphere.

showed that the starting products are always present in the mixture, and no trace of coupling product is detected. In the case where the one-pot cascade Horner reaction and Suzuki coupling reaction is carried out with the phosphonates **4b** without isolation of ethylenic intermediate **6a**, in the presence of butyllithium, without lithium chloride and triphenylphosphine, no trace of coupling product was detected (Table 2, entry 1). The addition of triphenylphosphine (8 mol %) to the mixture with the catalyst Pd $(OAc)_2$ (2 mol %) allows the formation of the coupling product **Ia** in (Table 2, entry 1). These results confirm our hypothesis of the role of lithium ions in the transmetallation and participation of triphenylphosphine in the reduction of Pd (II) to Pd (0).

Analysis of the results in Table 2 shows very different yields depending on the bases used. The BuLi and LDA lithium bases clearly lead to the highest yields confirming the role of lithium ions in transmetallation during Suzuki cross-coupling reaction. Sodium and potassium ions do not perform this role effectively.

In fact, the one-pot approach of synthesis has shown several practical advantages: the lithium bases BuLi and LDA allow both the Wittig condensation and the lithium and triphenylphosphine participate to the reduction of palladium (II) to palladium (0) and transmetallation. Furthermore, the synthesis can be performed within a short reaction time and without using lithium chloride or triphenylphosphine, which is the conventional reagent in these processes. Furthermore, it is known that the presence of triphenylphosphine in the mixture makes the purification of the coupling product more difficult. With this one-pot cascade process Wittig reaction Suzuki cross-coupling reaction does not require adding triphenylphosphine and lithium chloride, which are usually added in the Suzuki coupling reaction. Secondly, this one-pot cascade process Wittig reaction and Suzuki cross-coupling reaction has several practical advantages: it avoids the separation and purification of the ethylenic intermediate and therefore saves solvents and silica for chromatography and energy and avoids the risks of loss of valuable materials during the purification. To confirm the advantages of this one-pot cascade process, we carried out a comparative study between this concept and the one in two successive and independent steps, namely, the Wittig reaction, and then, separation and purification of the heterocyclic ethylenic bromine compounds **6a**–**b**, and Suzuki cross-coupling reaction under the conventional conditions in the presence of 8 mol % of catalyst Pd $(OAc)_2$, lithium chloride (1.2 equiv), triphenylphosphine (40 mol %) and potassium carbonate (4 equiv). The Suzuki cross-coupling reaction efficiency was about 60–75% overall yield, but over a longer reaction time of 26 h to observe the complete disappearance of the starting reagents (monitored by chromatography TLC). On the other hand, the Suzuki cross-coupling reaction that was carried out using the same substrates of phenylboronic acid and the heterocyclic ethyl compound **6b**, using Pd $(OAc)_2$ 8 mol % as catalyst, but in the absence of lithium chloride and triphenylphosphine, does not make it possible to obtain the expected C–C catalyzed coupling product, and the monitoring of the reaction by TLC chromatography shows that only the starting reagents are present in the reaction mixture.

For this purpose, we applied successfully the optimized one-pot cascades process Wittig reaction and Suzuki cross-coupling reaction by condensing compounds **3a**–**b** with ethoxycarbonylmethylphosphonium bromide **4a**. The bromide compounds **6a**–**b** formed is not isolated but reacts with various boronic phenyl acids to give a diversified corresponding new chromene–retinoids hybrid analogs (**Ia**–**f**) with good yields (75–95%), as illustrated in Scheme 3.

Compounds **Ia**–**f** were prepared by two methods (Table 3) and fully characterized by their ^1H and ^{13}C NMR and IR, and their mass were checked by HRMS (Supporting Information).

Although those overall results are not easy to explain, as are the differences between the reactivity of the phosphonium salts **4a** and the phosphonates **4b**, and the link with the palladium catalytic activity, one possible explanation could be that the presence of triphenylphosphine in the reaction mixture would promote *in situ* the reduction of palladium (II) to palladium (0) and maintain this reduced form of the catalyst and increases its catalytic activity. When phosphonates are used, the triphenylphosphine (8 mol %) must be added with the catalyst (2 mol %) to promote its reduction. On the other hand, the lithium ions that originate from *n*-BuLi still present in the mixture promote the transmetallation step to the Suzuki cross-coupling reaction. In fact, it may be assumed that in this one-pot concept, the experimental conditions of the Wittig reaction are consistent with the Suzuki cross-coupling step and the reagents used for the Wittig reaction can also be used to carry out the Suzuki cross-coupling reaction. Therefore, a smaller amount of the catalyst Pd (0) form (2 mol %) become sufficient to achieve the C–C cross-coupling reaction without lithium chloride and triphenylphosphine that are usually used in this type of reactions [60], [61,62,74].

Encouraged by the aforementioned results and the importance of the bioisostere 1-methyl-4-(phenyl) sulfonyl)piperazine in increasing the activity of bioactive molecules [75], we applied the same one-pot cascade process successfully to extend the bioisosterie in 6-position of the chromene by introducing the 1-methyl-4-(phenyl)sulfonyl)piperazine to give new chromene retinoid hybrid **II**. For this purpose, the access to

Scheme 3. Reagents and reaction conditions: Way A: (i) $(EtO)_2OPCH_2COOEt$ or ethoxycarbonylmethylphosphonium bromide, BuLi (1.3 equiv), THF, −78°C then 50°C during 4 h; (ii) K_2CO_3, LiCl (1 equiv), Pd $(OAc)_2$ (8 mol %), PPh_3 (20 mol %) toluene/EtOH (8:2), 70°C, 14–16 h. Way B: (iii) first ethoxycarbonylmethylphosphonium bromide **4a** or $(EtO)_2OPCH_2COOEt$ **4b**, appropriate base (2 equiv), THF, −78°C then 50°C for 4 h, and the solvent was evaporated and replaced by DMF (10 mL), and Pd $(OAc)_2$ (2 mol %), (PPh_3 (8 mol %) with **3b**), and appropriate phenyl boronic acid derivative were added under nitrogen, 90°C, 4–10 h. [Color figure can be viewed at wileyonlinelibrary.com]

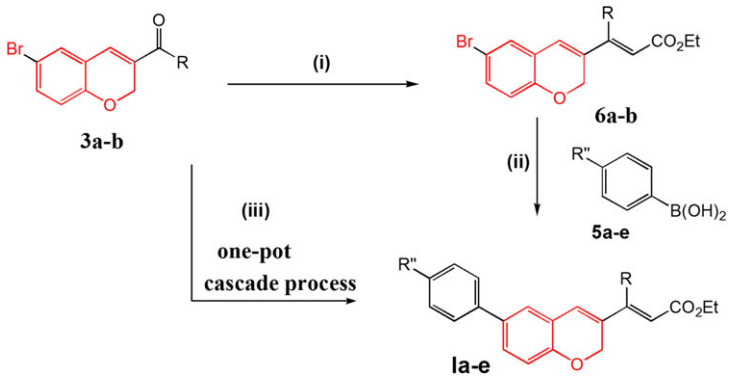


Table 3

Results of the preparation of new compounds **Ia–f** by two ways.

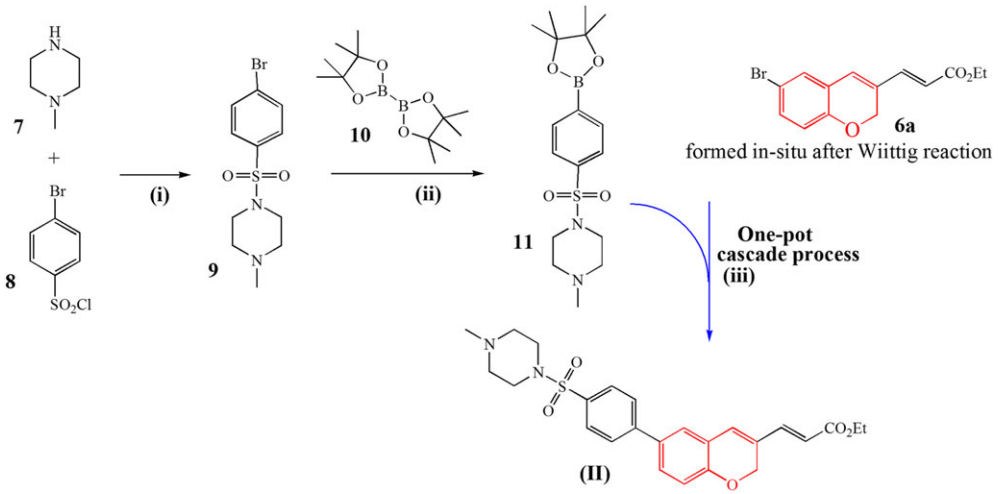
Entry	Compound	R	R″	Time t_1 for two successive steps/t_2 for the one-pot cascade process	Yield (%) in two successive steps; catalyst (8 mol %)/yield (%) by the one-pot cascade process
1	**Ia**	H	H	24/8	50/85
2	**Ib**	H	OMe	36/8	45/90
3	**Ic**	H	F	36/8	40/80
4	**Id**	H	CH_3	30/8	50/75
5	**Ie**	H	Cl	36/7	45/90
6	**If**	CH_3	H	32/10	40/75

Way A: Time t_1 for two successive steps, Pd $(OAc)_2$ catalyst (8 mol %). Way B: t_2 for the one-pot cascade process Pd $(OAc)_2$ catalyst (2 mol %) without LiCl or $P(C_6H_5)_3$ with **4a**.

compound **II** through the one-pot concept has been explored using the Suzuki cross-coupling reaction between compound **6a**, phosphonium salt **4a**, and 1-methyl-4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl]sulfonyl)piperazine **11** in which the synthesis has already been described in the literature [76]. The first step involved the preparation of the 1-[(4-bromophenyl) sulfonyl)-4-methylpiperazine precursor **9**, which was prepared from 1-methylpiperazine **7** and 4-[(4-bromobenzene)]sulfonylchloride **8** in THF with quantitative yield. The 1-methyl-4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)piperazine **11** was obtained from the intermediate compound **9** and pinacolatodiboron **10** using potassium carbonate K_2CO_3 and $PdCl_2(dppf)_2$ (2 mol %) as catalyst in THF/DMSO solvents mixture to afford compound **11** in 50% yield. Next step implies the one-pot cascade process involving Wittig and Suzuki cross-coupling reactions that was described previously between the brominated heterocyclic derivative **6a** and 1-methyl-4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl)piperazine **11** to afford the novel chromene–retinoids hybrid **II** in 85% yield as shown in Scheme 4.

This concept of the one-pot cascade process involving Wittig reaction and cross-coupling Suzuki reaction has again been proved very effective for the preparation of the new hybrid analog (**II**). The product was characterized by ^1H and ^{13}C proton NMR spectroscopy, and its chemical structure was confirmed by mass spectroscopy. The characteristic signals of the ethylenic protons H^2 and H^3 appear at chemical shifts of 5.80 and 7.38 ppm respectively in the form of two doublets. The coupling constant $J^{1,3}$ = 16 Hz coupling of the ethylenic protons is in favor of the trans configuration of the double bond. The protons of the piperazine ring appear at 2.48 ppm ($2CH_2$) and 3.07 ppm ($2CH_2$–N) in the form of two triplets with a 6.5 Hz coupling constant. The four aromatic protons of the phenyl at 6-position of the chromene heterocycle appear at 7.65 and 7.78 ppm as a doublet with a coupling constant $J^{1.3}$ = 8 Hz. The proton signals at 2-position of the heterocycle appear in their usual zone at 5.02 ppm as a singlet. The signal of the

Scheme 4. Reagents and reaction conditions: (i) THF, RT, 4 h, 95% yield; (ii) KOAc, $PdCl_2(dppf)_2$, dioxane, DMSO, 100°C, 16 h, 50% yield; (iii) Pd $(OAc)_2$, 2 mol %, PPh_3 4 mol %, DMF, 90°C, 8 h, 80% yield. [Color figure can be viewed at wileyonlinelibrary.com]



methyl group in piperazine appears at 2.27 ppm as a singlet. The H^4 and H^5, H^7 and H^8 proton signals appear at 6.79 ppm (singlet), 7.29 ppm (d, $J^{1.4}$ = 1.8 Hz), 7.38 ppm (doublet of doublet, $J^{1.3}$ = 7 Hz and $J^{1.4}$ = 1.8 Hz), and 6.93 ppm (doublet, $J^{1.3}$ = 7 Hz), respectively.

Analysis of the ^{13}C NMR spectrum of the product revealed the characteristic signals of the carbon atoms of the piperazine heterocycle at 45.69, 45.97, and 54.03 ppm. The signal of the carbon atom at 2-position of the heterocycle appears at 65.37 ppm, and the carbonyl signal of the ester appears at 166.64 ppm. The signals from the ethyl group of the ester appear at 14.30 and 60.66 ppm. The chemical formula of the product was confirmed by mass spectroscopy (calcd for $C_{25}H_{29}N_2O_5S$ $[M + H]^+$, 469.17983; found, 469.17686).

Analysis of the FTIR spectrum showed the presence of the elongation vibration bands of the sulfone group 1172.65, 1311.17, and 1346.92 cm^{-1} and a deformation band at 613.20 cm^{-1}. The vibrating band of the carbonyl ester group appears in its usual zone at 1711 cm^{-1}.

Moreover, we considered extending the bioisostere by the elongation of the skeleton in its lipophilic part, to access to the new chromene–retinoids hybrid analogs (**III**) by introducing the styryl group on the phenyl to which we have attached various substituents from precursors **3a–b**, **12a–c**, and phenylboronic acid **13** according to the following retrosynthetic analysis as shown in Figure 4.

According to the strategy based in the one-pot cascade Wittig–Horner reaction and Suzuki–Miyaura cross-coupling reaction described previously and the heterocyclic bromide compounds **3a–b**, phosphonium salt **4a**, and 4-formylphenylboronic acid **13** as the substrates, the aldehyde **Ie** containing heterocyclic ring system was prepared with 80% yield as a yellow solid.

The required primary phosphonium salts **12a–c** were readily obtained by the treatment of the benzyl bromide

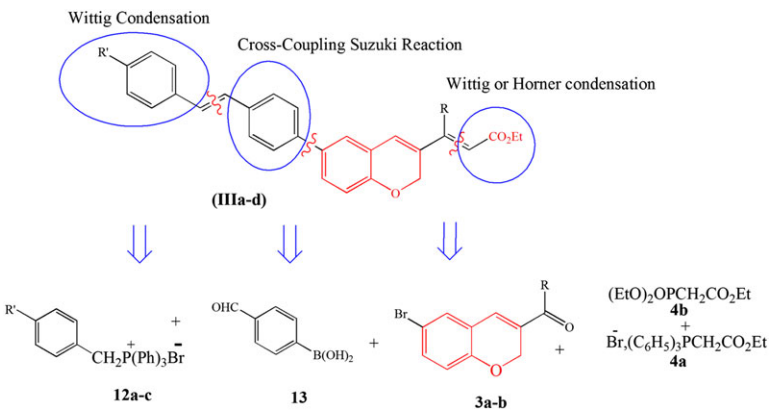


Figure 4. Retrosynthetic analysis to access to chromene–retinoids hybrid compounds (**IIIa–d**). [Color figure can be viewed at wileyonlinelibrary.com]

with triphenylphosphine in THF at 60°C for 12 h with a quantitative yield.

According to a convergent strategy, the Wittig reaction between the phosphonium salt **12a–c** and the aldehyde **Ig** in THF is performed in the presence of BuLi as base at −78°C to give the corresponding ethylenic compounds **IIIa–d** (Table 2) with good yields in the form of a mixture of isomer in which the trans isomer has a large majority (*E*/*Z*: 98/02) and readily separated by chromatography. (Only the trans isomer is drawn).

Encouraged by the success of this strategy, we have synthesized, in the same experimental conditions, a series of analogs with different substituents (R = H, R′ = H, F, Cl, Table 3, entries 1, 2, 3, and R = CH_3, R = H, entry 4) in good yields. When R^3 = CH_3 (Table 3, entry 4), the compound **IIId** was isolated with 85% yield as (85/15) (*E*/*Z*) ratio, and (*E*) isomer was successfully separated by column chromatography using SiO_2 and mixture hexane/dichloromethane (80/20 ratio) as eluent. The general scheme for access to the new chromene–retinoids hybrid derivatives **IIIa–d** is presented in Scheme 5.

The analysis of the experimental results described in Table 4 makes it possible to conclude that the Wittig condensation reactions for access to the chromene–retinoids hybrid **IIIa–d** analogs are carried out with satisfactory overall yields (Table 4, entries 2 and 3, R″ = F or Cl, 85% yield, during a shorter time 14 h). This Wittig reaction was shown to be fairly stereoselective for all ethyl propenoate analogs (**IIIa**,**c**). On the other hand, for the ethyl butenoate heterocyclic derivative (**IIId**) (R^3 = Me), the Wittig reaction is less stereoseletive (Table 4, entry 4, mixture of isomers ratio *E*/*Z* 85/15). In this case, a mixture of stereoisomers containing about 15% of the *Z* isomer is obtained (the *Z* isomer is not described in this paper). All these products have been characterized by NMR spectroscopy of ^{1}H proton and ^{13}C carbon and by FTIR spectroscopy. Their chemical formulas have been confirmed by mass spectroscopy. For example, the proton H^4 signal of compound **IIIa** appears as 6.55 ppm as a singlet, and the ethylenic protons H^2 and H^3 appear at 6.47 and 7.65 ppm as a doublet with a coupling constant $J^{1.3}$ = 15 Hz (trans configuration of double bond). The phenyl protons at the 6-position of the chromene appear at 8.12 and 7.53 ppm as a doublet ($J^{1.3}$ = 8 Hz). The signal of the protons in 2-position of the heterocycle appears in their usual zone at 5.11 ppm. The FTIR spectrum of product **IIIa** shows the carbonyl group elongation vibration band of the ester function at 1716 cm^{-1} and the vibration bands of aromatics (C=C) and (=CH) at 3028 cm^{-1} between 1368 and 1639 cm^{-1}, respectively, thus confirm the existence of the phenyl groups.

Scheme 5. Reagents and reaction conditions: (i) first Br, $(C_6H_5)_3PCH_2COOEt$ **4a**, BuLi (2 equiv), THF, −78°C, then 50°C for 12 h; (ii) the solvent was evaporated, and DMF, Pd $(OAc)_2$ (2 mol %), K_2CO_3 (2 equiv) were added, 90°C, 10 h; (iii) phosphonium salts and *n*-BuLi (1.2 equiv) in THF, −78°C then 25°C, 8 h. [Color figure can be viewed at wileyonlinelibrary.com]

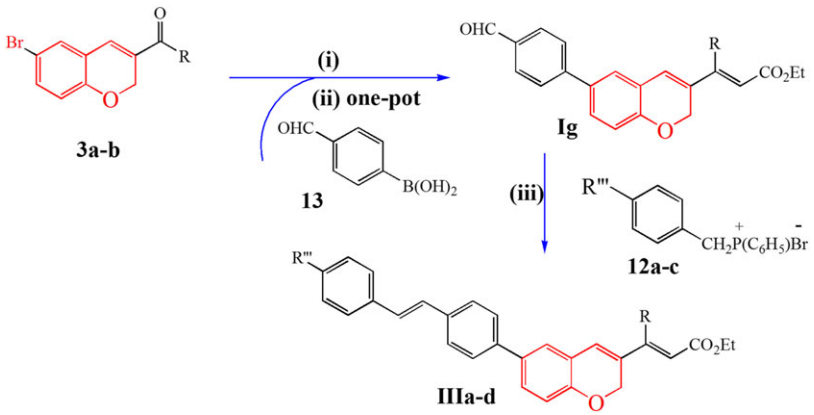


Table 4

Results of synthesis of chromene–retinoids hybrid derivatives **IIIa–d**.

Entry	Compound	R	R″	Time of reaction (h)	Yield (%)	Ratio (*E*/*Z*)
1	**IIIa**	H	H	16	80	95/05
2	**IIIb**	H	Cl	14	85	96/04
3	**IIIc**	H	F	14	85	95/05
4	**IIId**	CH_3	H	18	70	85/15

Table 5

Results of preparation of 6-bromo-2*H*-chromenes carboxaldehyde and ethanone **3a–b** by two methods.

Entry	Compound	R	R^5	Reagents conditions: Method A—pyridine, 100°C; Method B—K_2CO_3, (2 eq) dioxane, 90°C	Yields (%)
1	**3a**	H	Br	With acrolein (2 eq)	
				Method A, 16 h	55
				Method B, 6 h	85
2	**3b**	CH_3	Br	With methylvinylketone (3.5 eq) and:	
				Method A, 24 h	50
				Method B, 20 h	65

Table 6

Cytotoxic activity (tests in brain cancer cell).

		Cell line IC_{50} (μM)		
Entry	Compound	IC_{50} (U87)	IC_{50} (U251)	IC_{50} (U118)
1	**Ia**	>1000	NI[a]	NI[a]
2	**Ib**	>150	>100	>150
3	**Ic**	10	10	10
4	**Id**	100	100	100
5	**Ie**	10	10	10
6	**If**	>100	>100	>100
7	**Ig**	>100	>100	>100
8	**II**	ND[b]	ND[b]	ND[b]
9	**IIIa**	>100	>100	>100
10	**IIIb**	>100	>100	>100
11	**IIIc**	10	10	10
12	**IIId**	>100	>100	>100

[a]NI, non inhibition.
[b]Not determined.

PHARMACOLOGY

Preliminary evaluation of these 2H-chromene retinoids hybrid analogs concerning their ability to inhibit the proliferation of human brain cancer cell and human breast cancer MCF-7 cells. First provisionally, these new compounds were tested in glioblastoma multiforme brain cancer (U87, U251, and U118 cell lines). According to the results described in Table 6, the compounds **Ie** and **IIIc** showed a cytotoxic activity at 10 μM after 72 h, which inhibits cell growth (Table 6, entries 3 and 11). In contrast, the other compounds **Ia–d** (Table 5, entries 1–4), **If**,**g**, and **IIIa**,**b**,**d** showed a moderate antiproliferative activity (Table 6, entries 9–10, 12). However, the compound **Ia** proved inactive against these three malicious cancer cell lines.

Then, the target-to-hit compounds **Ie** and **IIIc** were tested in other two brain cancers medulloblastoma and neuroblastoma cell lines, and we found that **IIIc** is active at 10 μM against these two brain cancers (Table 7, entry 2). In contrast, the compound **Ie** showed a moderate cytotoxicity (Table 7, entry 1).

Table 7

Cytotoxic activity (tests in medulloblastoma and neuroblastoma cell).

		Cell line IC_{50} (μM)	
Entry	Compound	IC_{50} (medulloblastoma cell)	IC_{50} (neuroblastoma cell)
1	**Ie**	100	100
2	**IIIc**	10	10

Further studies are now in progress in order to develop more active compounds and also to determine the mechanisms through which analogs **Ie** and **IIIc** exerts its antiproliferative and cytotoxic activities. The results of these studies will be published subsequently.

CONCLUSION

We report for the first time the success at synthesizing novel chromene–retinoids hybrid derivatives. The concept that was based on the one-pot cascade process involving

Wittig reaction and Suzuki cross-coupling reaction without isolation of the intermediate and using the existing species in the reaction mixture such as triphenylphosphine for reduction of Pd (II) and lithium ions for transmetallation showed more advantage than successive multistep synthesis because of faster method and provides better overall yields. In addition, the one pot cascade process was carried out without lithium chloride and triphenylphosphine, which is the usual reagent of the Suzuki cross-coupling reaction, and using lesser amount of the catalyst (2 mol %), and it was possible to economize on the solvents and purification materials of intermediates. The preliminary evaluation of these chromene–retinoids hybrid products to inhibit the proliferation of human brain cancer cell have shown very encouraging results.

EXPERIMENTAL

All reactions were carried out under inert atmosphere, unless mentioned otherwise. Solvents were dried and purified by standard methods. All reagents were purchased from commercial sources unless otherwise indicated. The progress of all reactions was monitored by TLC using glass plates precoated with silica gel 60 F254 to a thickness of 0.5 mm. Column chromatography was performed on a silica gel (60 mesh) using ethyl acetate and hexane as eluents. IR spectra were recorded on a Perkin-Elmert FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 and 75 MHz respectively, using TMS as an international standard in $CDCl_3$. Mass spectra were recorded on a Micromass VG-7070H for IE.

Synthesis of (6-bromo-2*H*-chromene-3-yl)-carboxaldehyde (3a). ***Way A.*** A mixture of 5-bromosalicylaldehyde **1** (10 mmol), acrolein **2a** (15 mmol), and potassium carbonate (30 mmol) in a dry dioxane (30 mL) was stirred at 90°C for 8 h under nitrogen atmosphere. After completion of the reaction as indicated by TLC, the reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (3 × 15 mL). The organic layer was washed with aqueous solution of sodium hydrogenocarbonate (5%) (20 mL) and brine solution (20 mL), respectively, then dried under anhydrous Na_2SO_4. Evaporation of the solvent followed by purification on silica gel column chromatography using hexanes/ethyl acetate (9:1) as eluent afforded pure 6-bromo-2*H*-chromene-3-carbaldehyde **3a**. 85% yield, $C_{10}H_7O_2$ Br, Mr: 239 g/mol; mp 95–97°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm): 9.61 (s, 1H), 7.31–7.40 (dd, 1H, $J^{1.3}$ = 8 and $J^{1.4}$ = 1.2 Hz), 7.35 (d, 1H, $J^{1.4}$ = 1.2 Hz), 7.19 (s, 1H), 6.65 (d, 1H, 8 Hz), 5.08 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 189.36, 154.0, 139.49, 135.48, 132.55, 131.37 122.19, 118.49, 113.96, 63.33. IR (KBr): ν (cm^{-1}): 2928–2857, 1670, 1275, 750.

Way B. A mixture of 5-bromosalicylaldehyde **1** (10 mmol) and acrolein **2a** (20 mmol) in a dry pyridine (20 mL) was stirred at 90°C for 12 h under nitrogen atmosphere. After completion of the reaction as indicated by TLC, the reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (3 × 15 mL). The organic layer was washed with aqueous solution of sodium hydrogenocarbonate (5%) (20 mL) and brine solution (20 mL), respectively, then dried under anhydrous Na_2SO_4. Evaporation of the solvent followed by purification on silica gel column chromatography using hexanes/ethyl acetate (9:1) as eluent afforded pure (6-bromo-2*H*-chromen-3-yl)-carboxaldehyde **3a** in 65% yield.

Synthesis of 2-(6-bromo-2*H*-chromen-3-yl)-ethanone (3b). To a mixture of 5-bromosalicylaldehyde **1** (10 mmol) and methylvinylketone **2b** (35 mmol) in a dry dioxane (30 mL) and potassium carbonate (40 mmol) was added, and the reaction mixture was stirred at 90°C for 24 h under nitrogen atmosphere. After completion of the reaction as indicated by TLC, the reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (3 × 15 mL). The organic layer was washed with aqueous solution of sodium hydrogenocarbonate (5%) (20 mL) and brine solution (20 mL), respectively, then dried under anhydrous Na_2SO_4. Evaporation of the solvent followed by purification on a silica gel column chromatography using hexanes/ethyl acetate (9:1) as eluent afforded pure 2-(6-bromo-2*H*-chromen-3-yl)-ethanone **3b**. 60% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.35–7.39 (m, 2H), 7.18 (d, 1H, $J^{1.4}$ = 1.5 Hz), 6.68 (s, 1H), 5.03 (s, 2H), 2.48 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): 152.0, 138.47, 134.48, 130.56, 129.37, 121.19, 116.49, 111.96, 66.6, 62.4. R_f: 0.40 (hexane/dichloromethane 80:20) Rdt: 75%; mp 92–94°C, $C_{11}H_9O_2Br$, Mr: 253 g/mol, IR (KBr): ν (cm^{-1}): 2925–2857, 1662, 1205, 716.

Standard procedure for preparation of ethyl 6-bromo-3-[2*H*-chromen-3-yl]propenoate 6a and but-2-enoate 6b. ***Processed in two successive steps.*** A mixture of 6-bromo-2*H*-chromene-3-carboxaldehyde **3a** (10 mmol) and THF (30 mL) was taken in a three-necked flask. To this solution, 12 mmol of phosphonium salt **4a** or ethyl phosphonoacetate **4b** was added with magnetic stirring under nitrogen atmosphere. The mixture was allowed to cool at −78°C, and then butyllithium in hexane (24 mmol) was added dropwise. After 2 h at room temperature, the reaction mixture was stirred at 60°C for 12 h. After completion of the reaction as indicated by TLC, the reaction mixture was quenched with NaCl solution (15 mL) and extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried

over Na_2SO_4. Evaporation of the solvent followed by purification on a silica gel column chromatography using hexanes/ethyl acetate (9:1) as eluent afforded pure ethyl (2*E*)-6-bromo-3-[2*H*-chromen-3-yl]propenoate **6a** as a yellow solid: mp 166–168°C, in 75% yield, $C_{14}H_{13}O_3Br$, Mr: 309 g/mol. R_f = 0.3 (hexane/ethyl acetate 8:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.32 (1H, d, $J^{1.3}$ = 15.5 Hz), 7.20–7.10 (2H, m), 6.75 (1H, s), 6.61 (1H, d, $J^{1.3}$ = 7.2 Hz), 5.72 (1H, d, $J^{1.3}$ = 15.5 Hz), 4.95 (2H, s), 4.24 (2H, q, $J^{1.3}$ = 7 Hz), 1.29 (3H, t, $J^{1.3}$ = 7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 168.7, 154.0, 149.05, 140.49, 135.48, 132.55, 131.37 122.19, 118.49, 113.96, 63.33, 60.05, 16.87. IR (KBr): ν (cm^{-1}): 3050–2910, 1705, 1240, 1311, 1184, 750; HRMS (EI, *m/z*): $[M + H]^+$, calcd for $C_{14}H_{14}BrO_3$: 310.16372, found: 310.16204.

Similarly, we prepared ethyl (2*E*)-6-bromo-3-[2*H*-chromen-3-yl]but-2-enoate **6b** from 2-(3-bromo-2*H*-chromen-3-yl)ethanone **3b** and phosphonium salt **4a** or ethyl phosphonoacetate **4b**. Reaction times and temperatures are given in Table 1. mp 152–156°C, in 55% yield, $C_{15}H_{15}O_3Br$, Mr: 323 g/mol. R_f = 0.28 (hexane/ethyl acetate) = 9:1)

^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ (ppm): 7.15 (2H, m), 6.7 (1H, s), 6.6 (1H, d, $J^{1.3}$ = 7.8 Hz), 5.7 (1H, s), 4.92 (2H, s), 4.2 (2H, q, $J^{1.3}$ = 7 Hz), 2.4 (3H, s), 1.3 (3H, t, $J^{1.3}$ = 7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 167.8, 153.5, 149.69, 140.39, 135.45, 132.25, 131.32, 121.99, 116.38, 113.12, 63.02, 60.02, 23.45, 16.87. IR (KBr): ν (cm^{-1}): 3045–2915, 1700, 1311, 1245, 1180, 750. HRMS (EI, *m/z*): $[M + H]^+$, calcd for $C_{15}H_{16}BrO_3$: 324.19034, found: 324.1887.

Procedure for preparation of 1-methyl-4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)sulfonyl) piperazine 11. To a solution of 4-[(4-bromobenzene)] sulfonylchloride **8** (6.00 g, 23.48 mmol) in tetrahydrofuran (40 mL), 1-methylpiperazine **7** (3.9 mL, 35.22 mmol) was added. The resulting reaction mixture was stirred at room temperature for 4 h. After evaporation of the solvent, the residue was dissolved in dichloromethane (100 mL) and washed with saturated sodium hydrogen carbonate aqueous solution (three times), saturated sodium chloride aqueous solution, dried over magnesium sulfate, and concentrated under reduced pressure to give 7.41 g (quantitative yield) of **9** as white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.70–7.64 (m, 2H), 7.64–7.56 (m, 2H), 3.10–2.95 (m, 4H), 2.59–2.38 (m, 4H), 2.26 (s, 3H).

1-Methyl-4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl)sulfonyl)piperazine 11. To a solution of 1-((4-bromophenyl)sulfonyl)-4-methylpiperazine **9** (7.4 g, 23.20 mmol) in 1,4-dioxane (89 mL) and DMSO (7.4 mL) pinacolatodiboron **10** (17.67 g, 69.59 mmol), potassium acetate (4.56 g, 46.39 mmol), and $PdCl_2$(dppf) (849 mg, 1.16 mmol) were added under argon atmosphere. The mixture was stirred at 100°C for 16 h. After filtration and evaporation of the solvent, the residue was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride, dried over magnesium sulfate, and concentrated under reduce pressure. The crude product was purified by flash column chromatography using dichloromethane/methanol (95/5) v/v to afford 4.24 g (50% yield) of **11** as a solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.94 (d, *J* = 8.3 Hz, 2H), 7.72 (d, *J* = 8.3 Hz, 2H), 3.03 (s, 4H), 2.47 (s, 4H), 2.26 (s, 3H), 1.35 (s, 12H).

General procedure for the Suzuki cross-coupling reaction of aryl bromide 6a and 6b with aryl boronic acids 5a–e. The aryl bromide (0.5 mmol), arylboronic acid (0.75 mmol), catalyst palladium acetate Pd $(OAc)_2$ (5 mol %), triphenylphosphine (20 mol %), lithium chloride (0.75 mmol), potassium carbonate K_2CO_3 (1.5 mmol), and mixture of solvents—toluene : ethanol : water (0.75:0.15:0.10 v/v) 10 mL—were successively added, under nitrogen, into a 25 mL round bottom flask. The mixture was stirred vigorously at 90°C for the varying specific length of time based on each different substrates. After reaction completion, the solid was filtered off, and the filtrate was extracted with ethyl acetate (3 × 5 mL), washed with water and brine three times, and then dried over anhydrous $MgSO_4$. After removing the solvent, the crude product was purified by column chromatography over a silica gel (eluent : petroleum ether/ethyl acetate, 90/10) to give the desired product and calculate the yield. Reaction times and yield and temperatures are given in Table 2.

General procedure for cascades one-pot Wittig (or Horner Emmons) and Suzuki cross-coupling reactions without isolation of the reaction intermediates. In a three-necked flask, to a solution of (6-bromo-2*H*-chromen-3-yl) carboxaldehyde **3a** (10 mmol) in 20 mL of anhydrous THF was added phosphonium salt **4a** or ethyl phosphonoacetate **4b** (12 mmol) under nitrogen and under stirring. The mixture was allowed to cool to −78°C, and then butyllithium (1.6 M in hexane, 2 equiv, 24 mmol) was added dropwise. The mixture reaction was allowed to return to room temperature for 2 h and stirred at 60°C for the additional time t_1 indicated in Table 3 to complete the reaction (monitored by TLC). Then THF was removed under *vacuo*. Under a nitrogen atmosphere, in the case where the reaction is carried out with ethyl phosphonate **4b**, anhydrous DMF (10 mL), palladium acetate Pd $(OAc)_2$ (2% mol), (triphenylphosphine (8 mol %) and potassium carbonate (2 equiv) and appropriate phenylboronic acid (15 mmol) were sequentially added. When the reaction is carried out with the phosphonium salt **4a**, triphenylphosphine is not added to the mixture. The reaction was stirred at 90°C for the time t_2 indicated in

Table 3. The deep brown color mixture was allowed to cool to 25°C and was poured into water (20 mL). The mixture was filtered and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with water (15 mL) and dried over anhydrous Na_2SO_4, and the solvent was removed. The residue was purified by chromatography on a silica gel using 5% ethyl acetate/hexane as eluent, to afford compounds (**Ia**–**f**) with the yields indicated in Table 2.

Ethyl (2E)-3-(6-phenyl-2H-chromen-3-yl)prop-2-enoate (Ia). mp 142–144°C (hexane/ethyl acetate 8:2), $C_{20}H_{18}O_3$: 306 g/mol. ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ (ppm) 1.33 (t, 3H, $J^{1.3}$ = 7 Hz), 4.17 (q, 2H, $J^{1.3}$ = 7 Hz), 5.01 (s, 2H), 5.7 (d, 1H, $J^{1.3}$ = 15.8 Hz), 6.75 (s, 1H), 6.8 (d, 1H, $J^{1.3}$ = 15.8 Hz), 7.26–7.54 (m, 8H). ^{13}C NMR ($CDCl_3$, 300 MHz): δ (ppm) 14.31, 60.61, 65.25, 116.13, 117.36, 121.94, 126.46, 126.66, 127.03, 128.80, 129.50, 130.68, 134.99, 140.27, 153.94, 166.77. IR (KBr): ν (cm^{-1}): 2982, 1709, 1630, 1620, 1482, 750. HRMS (ESI) *m/z*: Calcd for $C_{20}H_{19}O_3$[M + H]$^+$, 307.13353; found, 307.13108.

Ethyl (2E)-3-(6-(4-methoxyphenyl)-2H-chromen-3-yl)prop-2-enoate (Ib). mp 138–140°C (hexane/dichloromethane 6:4), $C_{21}H_{20}O_4$: 336 g/mol. ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 1.32 (t, 3H, $J^{1.3}$ = 7 Hz), 3.85 (s, 3H), 4.23 (q, 2H, $J^{1.3}$ = 7 Hz), 4.99 (s, 2H), 5.75 (d, 1H, $J^{1.3}$ = 15 Hz), 6.78 (s, 1H), 6.89 (d, 1H, $J^{1.3}$ = 15 Hz), 7.24–7.47 (m, 7H). ^{13}C NMR ($CDCl_3$, 300 MHz): δ (ppm): 14.31, 55.36, 60.60, 65.21, 114.23, 116.07, 117.27, 126.03, 127.68, 128.77, 129.11, 130.79, 141.45, 153.45, 153.49, 158.95, 166.80. IR (KBr): ν (cm^{-1}): 3409, 2954, 1718, 1621, 1517, 1487, 740. HRMS (ESI) *m/z*: calcd for $C_{21}H_{21}O_4$ [M + H]$^+$, 337.1441; found, 337.14136.

Ethyl (2E)-3-(6-(4-fluoro)-2H-chromen-3-yl)prop-2-enoate (Ic). mp 120–122°C (hexane/dichloromethane 8:2), $C_{20}H_{17}FO_3$: 324 g/mol. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.32 (t, 3H, $J^{1.3}$ = 7 Hz), 4.24 (q, 2H, $J^{1.3}$ = 7 Hz), 5 (s, 2H), 5.76 (d, 1H, $J^{1.3}$ = 15 Hz), 6.78 (s, 1H), 6.91 (d, 1H, $J^{1.3}$ = 15 Hz), 7.11–7.50 (m, 7H). ^{19}F NMR ($CDCl_3$, 300 MHz): δ = −115.92. ^{13}C NMR ($CDCl_3$, 300 MHz): δ (ppm) 14.33, 60.65, 65.27, 115.52, 115.80, 116.20, 117.49, 122.00, 126.33, 128.16, 128.16, 130.52, 134.05, 141.05, 153.91, 160.65, 166.77. IR (KBr): ν (cm^{-1}): 3403, 2989, 1706, 1620, 1487, 1232, 820. HRMS (ESI) *m/z*: calcd for $C_{20}H_{18}FO_3$ [M + H]$^+$, 325.12411; found, 325.12147.

Ethyl (2E)-3-(6-(4-methylphenyl)-2H-chromen-3-yl)prop-2-enoate (Id). R_f = 0.40 (hexane/dichloromethane 6:4). mp 160–162°C (hexane/dichloromethane 6:4), $C_{21}H_{20}O_3$:320 g/mol. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm): 1.33 (t, 3H, *J* = 7 Hz), 1.6 (s, 3H), 4.25 (q, 2H, $J^{1.3}$ = 7 Hz), 4.99 (s, 2H), 5.75 (d, 1H, $J^{1.3}$ = 15 Hz), 6.7 (s, 1H), 6.9 (d, 1H, $J^{1.3}$ = 15 Hz), 7.24–7.45 (m, 7H). ^{13}C NMR ($CDCl_3$, 300 MHz): δ (ppm): 14.31, 21.07, 60.60, 65.18, 115.81, 116.07, 117.28, 118.15, 121.75, 126.49, 127.96, 129.51, 10.78, 133.78, 136.79, 137.39, 140.91, 141.45, 166.62. IR (KBr): ν (cm^{-1}): 3414, 2979, 2362, 1705, 1612, 1486, 1317, 1169, 813. HRMS (ESI) *m/z*: calcd for $C_{21}H_{21}O_3$ [M + H]$^+$, 321.14918; found, 321.14674.

Ethyl 3-(6-(4-chlorophenyl)-2H-chromen-3-yl)prop-2-enoate (Ie). mp 156–158°C (hexane/dichloromethane 7:3), $C_{20}H_{17}ClO_3$: 340 g/mol. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm): 1.33 (t, 3H, *J* = 7 Hz), 4.26 (q, 2H, $J^{1.3}$ = 7 Hz), 5 (s, 2H), 5.76 (d, 1H, $J^{1.3}$ = 15.5 Hz), 6.73 (s, 1H), 6.91 (d, 1H, $J^{1.3}$ = 15.5 Hz), 7.02–7.46 (m, 7H). ^{13}C NMR ($CDCl_3$, 300 MHz): δ: 14.02, 43.96, 46.65, 60.38, 71.42, 116.22, 118.35, 122.02, 123.13, 126.23, 127.85, 129.24, 130.29, 133.16, 134.55, 139.09, 141.19, 146.70, 155.32, 165.40. IR (KBr): ν (cm^{-1}): 3413, 2980, 1709, 1622, 1481, 1313, 820. HRMS (ESI) *m/z*: calcd for $C_{20}H_{18}ClO_3$ [M + H]$^+$, 341.09456; found, 341.09207.

Ethyl 3-(6-(4-phenyl)-2H-chromen-3-yl)but-2-enoate (If). mp 150–152°C (hexane/dichloromethane 5:5), $C_{21}H_{20}O_3$: 320 g/mol. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm): 1.33 (t, 3H, $J^{1.3}$ = 7 Hz), 2.46 (s, 3H), 4.21 (q, 2H, $J^{1.3}$ = 7 Hz), 5.02 (s, 2H), 5.68 (s, 1H), 6.92–7.54 (m, 9H). ^{13}C NMR ($CDCl_3$, 300 MHz): δ (ppm) 14.32, 60.06, 66.29, 115.07, 115.91, 122.17, 125.54, 125.79, 126.50, 126.66, 128.22, 128.78, 129.06, 132.08, 134.90, 140.41, 149.25, 153.59, 166.85. IR (KBr): ν (cm^{-1}): 3415, 2977, 2364, 1708, 1599, 1165, 762. HRMS (ESI) *m/z*: calcd for $C_{21}H_{21}O_3$ [M + H]$^+$, 321.14918; found, 321.14684.

Ethyl (2E)-3-[6-(4-(4-methylpiperazinyl)sulfonyl)-phenyl)-2H-chromen-3-yl]prop-2-enoate (II). mp 188–190°C (hexane/dichloromethane 6:4), $C_{25}H_{28}N_2O_5S$: 468 g/mol. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.32 (t, 3H, $J^{1.3}$ = 7 Hz), 2.27 (s, 3H), 2.52 (t, 2H, $J^{1.3}$ = 6.8 Hz), 3.07 (t, 2H, $J^{1.3}$ = 6.8 Hz), 4.26 (q, 2H, *J* = 7 Hz), 5.03 (s, 2H), 5.77 (s, 1H), 6.79 (d, 1H), 7.26–7.80 (m, 8H). ^{13}C NMR ($CDCl_3$, 300 MHz), δ (ppm): 14.30, 45.69, 45.97, 51.81, 54.03, 60.66, 65.37, 116.50, 117.30, 122.15, 126.60, 127.04, 128.41, 129.60, 130.06, 130.25, 132.87, 141.12, 141.38, 144.88, 154.87, 166.64. IR (KBr): ν (cm^{-1}): 3415, 2891, 2810, 2361, 1711, 1621, 1311, 943, 755. HRMS (ESI) *m/z*: calcd for $C_{25}H_{29}N_2O_5S$ [M + H]$^+$, 469.17983; found, 469.17686.

Standard procedure for preparation of chromene–retinoids hybrid derivatives (IIIa–d). In a three-necked flask, to a solution of ethyl 3-[6-(4-formylphenyl-2*H*-chromen-3-yl] propenoate **If** (10 mmol) in 10 mL of THF was added appropriate phosphonium salt **12a**–**c** (15 mmol) under stirring and under nitrogen. The mixture was allowed to cool to −78°C, and then butyllithium in hexane (15 mmol) was added dropwise. Then the mixture was stirred at −78°C for 4 h and brought to room temperature for 5 h to room and refluxed at 65°C for 4 h. The mixture was allowed to cool to 25°C, and a saturated NaCl solution was added (15 mL). Next, to extract with ethyl

acetate (2 × 20 mL) and to combine the organic layers that have been dried over $MgSO_4$, and the solvent was removed. The residue was purified by flash chromatography (silica gel, mixture 95:05 hexane/ethyl acetate), to afford compounds **IIIa–d** as a yellow solid in the yields indicated in Table 2.

Ethyl (2E)-3-[6-(4-styryl-phenyl)-2H-chromen-3-yl]prop-2-enoate (IIIa). mp 182–184°C (hexane/dichloromethane 6:4), $C_{28}H_{24}O_3$: 408 g/mol. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm): 1.34 (t, 3H, $J^{1.3}$ = 7 Hz), 4.39 (q, 2H, $J^{1.3}$ = 7 Hz), 5.11 (s, 2H), 6.45 (d, 1H, $J^{1.3}$ = 16 Hz), 6.89 (s, 1H), 6.95 (d, 1H, $J^{1.3}$ = 16 Hz), 7.04 (d, 2H, $J^{1.3}$ = 16 Hz), 7.52–8.15 (m, 8H, J = 8 Hz). ^{13}C NMR ($CDCl_3$, 300 MHz): δ (ppm) 14.36, 29.69, 61, 65.56, 115.51, 121.57, 124.43, 126.69, 126.95, 127.19, 127.56, 129.25, 130.11, 130.23, 131.23, 138.05, 139.02, 144.83, 153.72, 166.50. IR (KBr): ν (cm^{-1}): 3413, 3028, 2922, 2854, 1716, 1276, 1109, 873, 768. HRMS (ESI) *m/z*: calcd for $C_{28}H_{24}O_3$ $[M + H]^+$, 409.168; found, 409.16686.

Ethyl 3-[6-(4-((4-chlorostyryl)-phenyl)-2H-chromen-3-yl] prop-2-enoate (IIIb). M.p:170–172°C (hexane/dichloromethane 7:3), $C_{28}H_{23}ClO_3$: 442 g/mol. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.33 (t, 3H, $J^{1.3}$ = 7 Hz), 4.37 (q, 2H, $J^{1.3}$ = 7 Hz), 5.02 (s, 2H), 5.83 (d, 1H, $J^{1.3}$ = 16 Hz), 6.59 (s, 1H), 6.63 (d, 1H, $J^{1.3}$ = 16 Hz), 6.93 (d, 2H, $J^{1.3}$ = 16 Hz), 7.24–7.45 (m, 8H, J = 8 Hz). ^{13}C NMR ($CDCl_3$, 300 MHz): δ (ppm) 14.33, 60.65, 65.29, 117.42, 121.97, 126.42, 126.87, 127.04, 127.67 (4C), 128.51 (2C), 129.36, 130.24, 130.46, 130.62, 134.32, 135.75, 141.39, 167. IR (KBr): ν (cm^{-1}): 3414, 2957, 2363, 1904, 1710, 1621, 1487, 1168, 1090, 821. HRMS (ESI) *m/z*: calcd for $C_{28}H_{24}ClO_3$ $[M + H]^+$, 443.14151; found, 443.13848.

Ethyl 3-[6-(4-((4-fluorostyryl)-phenyl)-2H-chromen-3-yl] prop-2-enoate (IIIc). mp 166–168°C (hexane/dichloromethane 8:2), $C_{28}H_{23}FO_3$: 426 g/mol. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.34 (t, 3H, $J^{1.3}$ = 7 Hz), 4.32 (q, 2H, $J^{1.3}$ = 7 Hz), 5.02 (s, 2H), 5.83 (d, 1H, $J^{1.3}$ = 16 Hz), 6.61 (s, 1H), 6.80 (d, 1H, $J^{1.3}$ = 16 Hz), 6.98 (d, 2H, $J^{1.3}$ = 16 Hz), 7.25–7.75 (m, 8H, $J^{1.3}$ = 8 Hz). ^{19}F NMR ($CDCl_3$, 300 MHZ): δ (ppm) = −114.55. ^{13}C NMR ($CDCl_3$, 300 MHz): δ (ppm) 14.28, 60.69, 65.18, 113.61, 117.48, 118.16, 123.49, 128.84, 129.14, 129.41, 130.19, 133.16, 140.91, 153.28, 166.55. IR (KBr): ν (cm^{-1}): 3414, 2961, 1895, 1708, 1622, 1600, 1507, 1237, 1181, 1017, 975, 825. HRMS (ESI) *m/z*: calcd for $C_{28}H_{24}FO_3$ $[M + H]^+$, 427.17106; found, 427.16840.

Ethyl 3-[6-(4-styryl-phenyl)-2H-chromen-3-yl]but-2-enoate (IIId). mp 186–188°C (hexane/dichloromethane 8:2), $C_{29}H_{26}O_3$: 422 g/mol. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.31 (t, 3H, $J^{1.3}$ = 7 Hz), 2.50 (s, 3H), 4.21 (q, 2H, $J^{1.3}$ = 7 Hz), 5.00 (s, 2H), 5.67 (s, 1H), 6.87 (s, 1H), 6.92 (d, 2H, J = 16 Hz), 7.01–7.75 (m, 8H, J = 8 Hz). ^{13}C NMR ($CDCl_3$, 300 MHz): δ (ppm) 14.34, 14.49, 60.06, 66.30, 115.10, 115.97, 122.21, 125.51, 126.25, 126.81, 126.97, 127.15, 127.65, 127.86, 128.16, 128.28, 128.71, 128.87, 129.37, 129.76, 130.34, 132.11, 134.33, 136.08, 137.34, 139.51, 149.22, 153.68, 166.84. IR (KBr): ν (cm^{-1}): 3413, 2979, 1714, 1598, 1408, 1168, 1043, 962, 845, 691. HRMS (ESI) *m/z*: calcd for $C_{29}H_{27}O_3$ $[M + H]^+$, 423.19336; found, 423.19336.

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