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Substituted 3-*E*-Styryl-2*H*-chromenes and 3-*E*-Styryl-2*H*-thiochromenes: Synthesis, Photophysical Studies, Anticancer Activity, and Exploration to Tricyclic Benzopyran Skeleton

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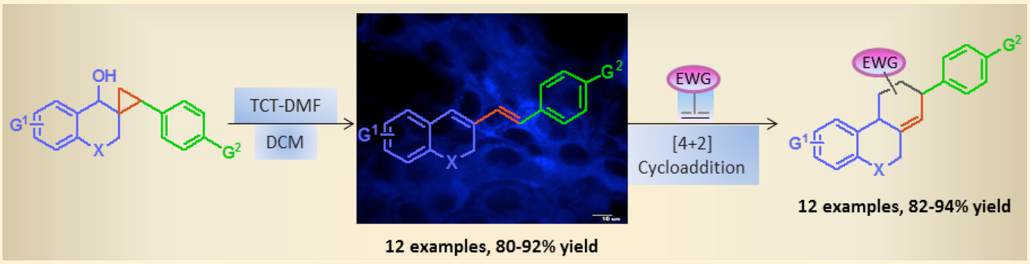
Supporting Information



ABSTRACT: A series of densely substituted 2*H*-chromenes and 2*H*-thiochromenes were synthesized in good yield through cyanuric chloride-dimethylformamide mediated cleavage of different spiro-4-hydroxychroman-3,1′-cyclopropanes and similar thiochroman analogues. This protocol involves operationally very simple, facile and cost-effective reactions using easily accessible reagents under mild reaction condition with tolerance of a variety of sensitive moieties. Results of steady state and time-resolved absorption and emission spectroscopy highlighted the potential of these compounds as fluorescence probes and designated the suitability for subcellular bioimaging. The prepared 2*H*-chromenes demonstrated profound cytotoxic activity against MCF-7 cell line. DFT calculations were done on a representative compound where the results indicated promising reactivity of the title compounds as electron-donating dienes. As a continuation, some of these compounds underwent [4 + 2] Diels–Alder cycloaddition with electron-deficient dienophiles in the absence of any activator or catalyst, which provided an easy access to an array of hitherto unreported molecular frameworks related to bioactive cannabinoid skeletons. These newly constructed Diels–Alder adducts also bear substantial antiproliferative properties.

INTRODUCTION

Substituted 2*H*-chromenes (2*H*-1-benzopyran derivatives), 2*H*-thiochromenes and their analogues constitute a significant family of scaffolds found in a myriad of physiologically active naturally occurring and artificial molecules.[1] Because of a rich array of functionalities these motifs are acknowledged as expedient building blocks in a wide range of bioactive heterocyclic compounds having anticancer, anti-HIV, anti-inflammatory, antioxidant, antitubercular, antiviral, antitumor, antibacterial/antimicrobial, antidiabetic, anticoagulant, antianaphylatic, diuretic, fungicidal, sex-pheromone and many other activities.[2] Because of their intense photophysical behavior,[3] these compounds have also been applied in diverse fields including laser dyes, organic light emitting devices (OLEDs), optical brighteners, organic scintillators, triplet sensitizer, fluorescence probes and exhibit outstanding photochromic properties.[4] They play a pivotal role as a regulator of numerous biopolymers.[5] Therefore, construction of these important molecular skeletons has elicited a great deal of interest in the field of organic synthesis and chemical biology.[6] Different protocols toward the synthesis of multifunctionalized 2*H*-1-benzopyran derivatives have been developed in the recent past, which include transition metal-catalyzed[7] and organocatalytic reactions.[8] However, many of the reported methods employ exotic and expensive metal catalysts, entail costly and complicated starting materials, suffer from severe drawbacks such as poor product yield, harsh reaction condition, use of stoichiometric amount of reagents and limited applicability to specific substitution pattern. Over the past decade, cyanuric chloride (2,4,6-trichloro-1,3,5-triazine or TCT) has emerged as a convenient solid reagent for a number of important organic transformations and been utilized as a mild chlorinating agent[9] for the conversion of alcohols to alkyl chloride, as a coupling agent[10] during the synthesis of hydroxamic acids from carboxylic acids, as a catalyst[11] for Pictet–Spengler reaction with electron-releasing aldehydes and as an activator[12] of DMSO during structure dependent conversion of various

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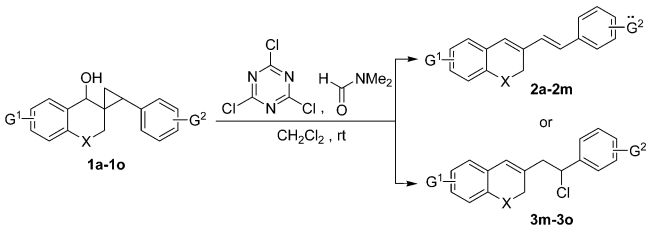
alcohols to methylene acetal or methyl thioether or methyl enethioether. Continuing on this theme, we report herein highly selective, convenient, and cost-effective synthesis of a variety of substituted 2*H*-chromenes from easily accessible and inexpensive starting materials utilizing TCT in combination with DMF (TCT-DMF) as the potent reagent.

RESULTS AND DISCUSSION

At the outset, chroman-4-ones and 1-thiochroman-4-ones were treated with aryl aldehydes bearing a variety of substituents in the presence of alcoholic HCl[13] under refluxing condition to afford the corresponding *E*-3-arylidene derivatives in good yield. Cyclopropanation of the resulting chromanochalcones with dimethylsulfoxonium methylide, generated in situ by phase transfer catalyst ($^{n}Bu_4N^+Br^-$) mediated deprotonation of trimethylsulfoxonium iodide under alkaline condition[14] followed by reduction with methanolic sodium borohydride at room temperature furnished differently substituted spiro-4-hydroxychroman-3,1′-cyclopropanes **1** as inseparable 1:1 diastereomeric mixtures, which were used as the substrates. Compounds **1a**−**1o** reacted with TCT-DMF[9] in anhydrous condition (Scheme 1). The results are summarized in Table 1.

Scheme 1. Synthesis of 3-Substituted 2*H*-chromenes with TCT-DMF Adduct



As evident in Table 1, spiro-4-hydroxychroman-3,1′-cyclopropanes with cyclopropyl moiety bearing aromatic ring with mesomerically electron-releasing group at *p*-position (**1a**−**1h**) furnished substituted 3-*E*-styryl-2*H*-chromenes (**2a**−**2h**) exclusively on treatment with TCT-DMF adduct in anhydrous dichloromethane under stirring condition in good yield (80−92%, entries 1−8 in Table 1). Similar trend was also observed for the thiochroman analogues (**1i**−**1k**) where the corresponding substituted 3-*E*-styryl-2*H*-thiochromenes (**2i**−**2k**) were obtained (yield 84−88%, entries 9−11 in Table 1). Likewise 2*H*-thiochromene **2l** was acquired from **1l** with OMe substituent at the *o*-position (yield 91%, entry 12 in Table 1). The structures of all the products were assigned from ^{1}H NMR, ^{13}C NMR and HRMS analyses (see Supporting Information). In all the products **2**, the exocyclic double bond had *E*-configuration, which was confirmed by the ^3J values (16.1−16.5 Hz) between the exocyclic olefinic protons. X-ray crystallographic study of the compound **2i** corroborated further with the *E*-configuration of both the olefinic linkages along with *s-trans* conformation of the conjugated diene framework (Figure 1). To the best of our knowledge, all these compounds **2** did not have any literature precedence until date.

In this connection it was interesting to note that the spiro-4-hydroxychroman-3,1′-cyclopropane **1m** substituted with the Me group at the *p*-position of the aromatic ring at the carbinol center produced a mixture of the diene **2m** and the corresponding homoallylic chloride **3m** in a ratio of 1:2 under identical condition (entry 13 Table 1). The diene **2m** was isolated by fractional crystallization, whereas the homoallylic chloride **3m** could not be purified from the mother liquor despite several attempts. Therefore, it is evident that a substituent at *p*-position with +R effect preferentially promotes the formation of the diene in comparison to the substituent at the same location with only +I effect. For the substrate **1n**, where an electron-donating substituent (OMe) was placed at the *m*-position of the aromatic ring connected to the carbinyl carbon, the homoallylic chloride **3n** was obtained as the sole product with high yield (95%, entry 14 in Table 1). When the aromatic ring at carbinol carbon carried an electron-withdrawing substituent (Cl) in **1o**, homoallylic chloride **3o** was formed exclusively (yield 94%, entry 15 in Table 1). Homoallylic chlorides have been a subject of consistent interest due to their appearance as a key structural element in a large number of natural and unnatural products,[15] found an extensive use as pharmaceutically active substrates,[16] as well as functional molecules in a variety of organic conversions.[17] As shown in Table 1, the present protocol was compatible with acid-labile functional groups like benzyl (entry 7, Table 1) and methylenedioxy (entries 3, 6, 11, Table 1) and they were well tolerated during the process. Differently substituted 2*H*-chromenes synthesized by this protocol bear the promise of having important functional attributes.

A plausible mechanistic proposition for this reaction is outlined in Figure 2. The substrates **1** initially react with TCT-DMF adduct[9] to generate **4** and the byproduct of TCT as **5**. The cleavage of cyclopropane ring in **4** leads to release of angle strain and the carbocationic intermediate **6** is produced as an intimate ion pair. Attainment of extended conjugation with the aromatic moiety seems to facilitate this process. Substituents at the *p*-position of the aryl moiety (G^2) with electron-donating mesomeric effect render additional stabilization to the carbocationic intermediates through canonical **6′**. Facile deprotonation from the acidic $-CH_2-$ moiety in **6** with mildly basic compound **5** leads to the formation of **2** with extended conjugation. In **1n** (where the electron-releasing substituent is at *m*-position) and **1o** (where an electron-withdrawing substituent is located at the *p*-position), the homoallylic chlorides **3n** and **3o** were obtained as the exclusive products through internal capture of Cl^- by **6**.

Photophysical Studies. Of late, 2*H*-chromenes have attracted considerable attention due to their wide range of photophysical activities.[3] Therefore, we have measured the UV−vis absorption, steady state and time-resolved fluorescence to investigate the optical behavior of these 2*H*-chromenes containing various substituents at different positions. The fluorescence studies of all the compounds were performed in 1,4-dioxane (a polar aprotic solvent) at 1×10^{-4} M concentration. The results are listed in Table 2. From the UV spectroscopic studies, it was observed that the longest absorption maxima of these derivatives (**2a**−**2l**) appeared between 359 and 373 nm and they were attributed mainly to $\pi \rightarrow \pi^*$ transition. There is no detectable change in absorption maxima (359−365 nm) irrespective of the locations of the substituents like OMe and Me in either chromene or styryl aromatic ring. Apparently, the thiochromene analogues (**2i**−**2l**) displayed broad absorption bands with peaks in the 361 and 373 nm interval, due to the presence of electron-releasing sulfur in the heterocyclic ring. The fluorescence spectra were recorded using the right-angle configuration, by exciting the compounds at their wavelengths of maximum longest absorption. The compounds (**2a**−**2c**) exhibited longer emission at 421−426 nm

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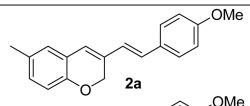
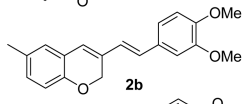
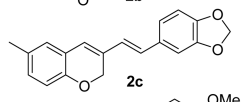
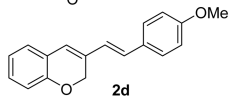
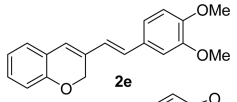
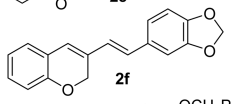
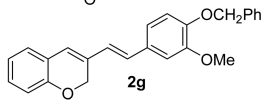
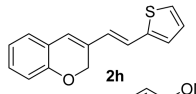
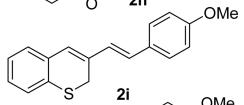
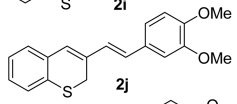
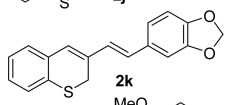
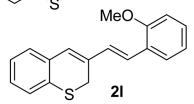
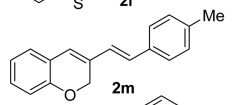
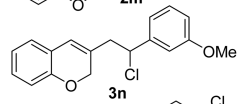
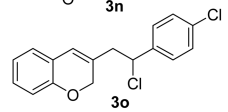
Table 1. Reaction of 1 with TCT-DMF for the Synthesis of 3-Substituted 2*H*-Chromenes

Entry	G^1, G^2	X	Substrate	Product (**2**/**3**)	Time(h)/ Yield(%)[a]
1.	4-Me, 4-OMe	O	**1a**	 **2a**	18/92
2.	4-Me, 3,4-$(OMe)_2$	O	**1b**	 **2b**	14/85
3.	4-Me, 3,4-OCH_2O-	O	**1c**	 **2c**	14/80
4.	H, 4-OMe	O	**1d**	 **2d**	16/90
5.	H, 3,4-$(OMe)_2$	O	**1e**	 **2e**	13/86
6.	H, 3,4-OCH_2O-	O	**1f**	 **2f**	17/90
7.	H; 3-OMe, 4-OCH_2Ph	O	**1g**	 **2g**	11/82
8.	H, 	O	**1h**	 **2h**	18/83
9.	H, 4-OMe	S	**1i**	 **2i**	16/88
10.	H, 3,4-$(OMe)_2$	S	**1j**	 **2j**	14/84
11.	H, 3,4-OCH_2O-	S	**1k**	 **2k**	14/85
12.	H, 2-OMe	S	**1l**	 **2l**	12/91
13.	H, 4-Me	O	**1m**	 **2m**	15/32[b]
14.	H, 3-OMe	O	**1n**	 **3n**	6/95
15.	H, 4-Cl	O	**1o**	 **3o**	5/94

[a]Yield of the isolated pure product characterized spectroscopically. [b]1:2 mixture of diene **2m** and homoallylic chloride **3m** was obtained, out of which the diene **2m** was isolated by crystallization.

because of mildly electron-donating Me substituent in the chromene moiety. Among the 2*H*-chromenes (**2d**−**2h**), the compound **2h** with a thiophene ring showed emission at 429 nm. Likewise, the emissions for the 2*H*-thiochromenes (**2i**−**2l**) were found in a range from 430 to 445 nm. It was quite noticeable that in polar aprotic solvent the fluorescence quantum yields (Φ) of 2*H*-chromenes (**2a**−**2h**) were relatively higher than those of thiochromenes (**2i**−**2l**). Fluorescence lifetime measurements revealed biexponential decays for all the compounds (**2a**−**2l**) when excited near their absorption maximum (359−373 nm) in dioxane (Figure 3). For the chromenes (**2a**−**2l**) it is assumed that the biexponential decay in dioxane may be attributed to two different local environments due to solvent reorganization and collisional deactivation with the solvent. Lifetime values range from 0.30 to 0.54 ns

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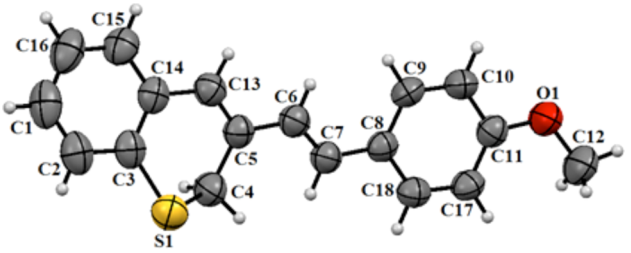

Figure 1. ORTEP drawing of compound **2i**[18]

(Table 3). Quantum yield and lifetime values established their potential application as new fluorescence probes.

Cell Imaging. To evaluate the practical utility of the compounds as fluorescent probes for in vivo cellular imaging, MCF-7 breast cancer cells were used as a model to envisage its cell uptake and imaging. We selected compounds **2b** and **2f** with sufficiently higher fluorescence quantum yields and another representative thiochromene **2i** with relatively lower fluorescence quantum yield for comparison. As shown in Figure 4, intense intracellular blue fluorescence was observed throughout the cell cytosol after being incubated with the probes **2b**, **2f** and **2i** (10 μM) for 30 min. The intense fluorescence might be originated mainly because the probes internalize in the MCF-7 cell cytoplasm and the distribution of the probes in the nucleus is significantly lower (the cell nuclei appear as dark black spots in the fluorescence images). The results clearly demonstrate that the probes **2b**, **2f** and **2i** are capable of penetrating the cell membrane and can specifically label cytosol. This prominent feature should render the prepared 2*H*-chromenes as useful biological tools to examine subtle subcellular biochemical processes.

Construction of Tricyclic Benzopyran Skeletons. To explore the synthetic utility of the prepared dienes **2**, attempts were made to use them in [4 + 2] cycloaddition with various dienophiles in order to achieve a molecular framework related to cannabinoids. Classical cannabinoids belong to a well-known group of approximately 70 terpenophenolic secondary metabolites found in Indian hemp (*Cannabis sativa* var. *indica*).

Table 2. Photophysical Parameters of 3-Substituted 2*H*-Chromenes 2 in 1,4-Dioxane

compound	λ_{abs}^{max} (nm)	λ_{em} (nm)	ε^a (M^{-1} cm^{-1})	Δv^b (cm^{-1})	Φ^c
2a	363	426	3461.9	158 730.16	0.37
2b	364	421	4489.6	175 438.59	0.46
2c	364	425	3152.2	163 934.42	0.44
2d	359	414	3544.6	181 818.18	0.30
2e	361	417	3343.3	178 571.43	0.31
2f	363	417	3452.2	185 185.18	0.35
2g	364	413	3659.2	204 081.63	0.27
2h	365	429	4090.9	156 250.00	0.31
2i	361	430	3440.8	144 927.53	0.09
2j	373	434	3651.6	163 934.42	0.12
2k	369	431	2736.3	161 290.32	0.11
2l	361	445	2925.4	119 047.62	0.10

[a]Molar extinction coefficient ($\times$ 10^{-4}). [b]Stoke's shift. [c]Fluorescence quantum yield.

Among these psychotropic compounds (−)-Δ^9-tetrahydrocannabinol (Δ^9-THC) is the most eminent because it is the key psychoactive constituent of marijuana and consists of a tricyclic 6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromene core structure.[19] A survey of the literature reveal that Δ^9-THC and other cannabinoids provide pharmacochemical benefits for cancer and AIDS patients by acting as appetite stimulants, mitigating nausea and vomiting during chemotherapy.[20] Besides, it has also been applied to alleviate neuropathic pain, to treat spasticity in multiple sclerosis[21] and found to aid glaucoma patients by reducing ophthalmic pressure. Other naturally existing *privileged structured* cannabinoids are the Δ^8-isomer, cannabinol. The identification of two distinct cannabinoid receptors CB_1[22] and CB_2[23] and their selective binding of THC analogues have led to a resurgence of interest to provide efficient synthetic routes. Because of their intriguing bioactivity it is worthwhile to generate a collection of natural product-like small molecular probes with diverse benzopyran-embedded core skeletons. However, there are only a few synthetic routes reported in the literature.[24]

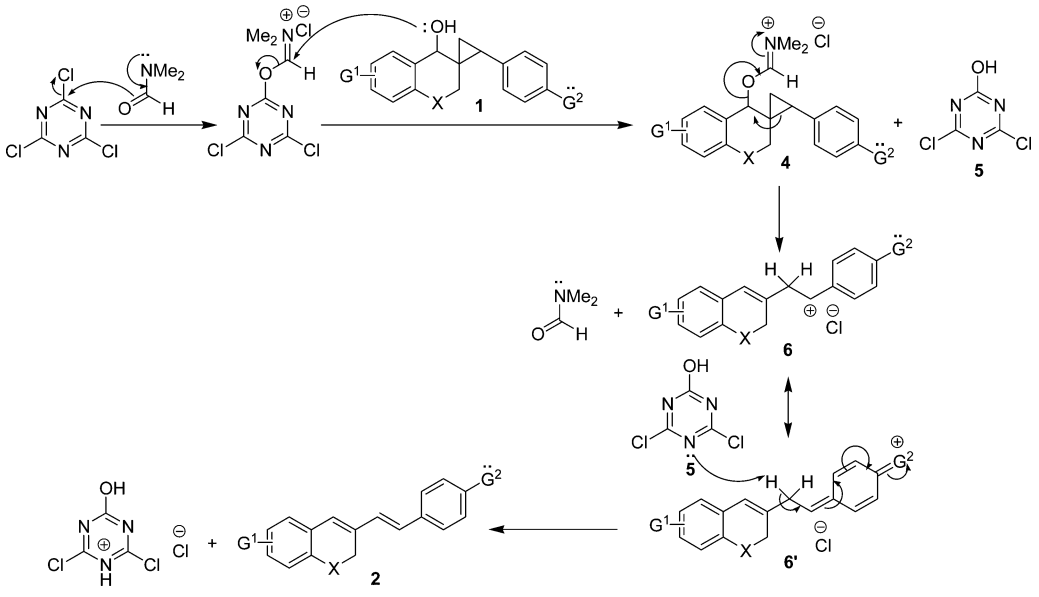

Figure 2. Proposed mechanistic explanation of the substituent effect.

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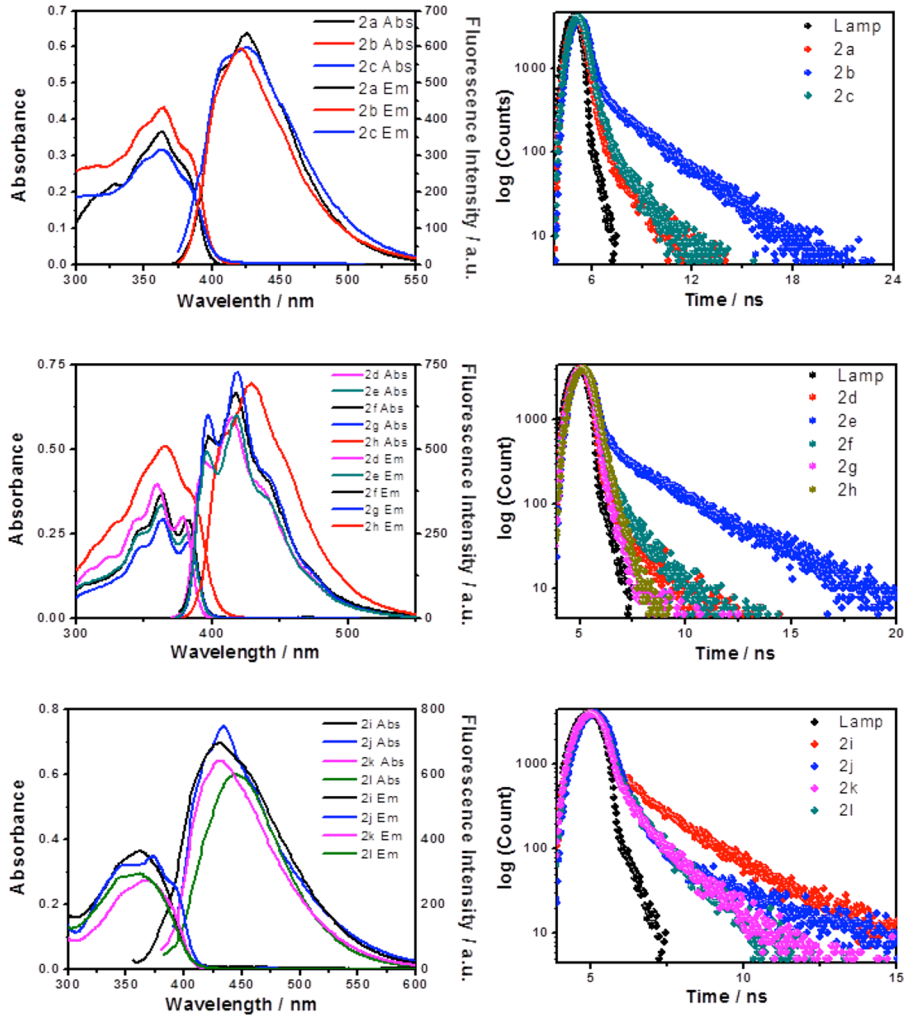

Figure 3. Absorption, emission spectra and fluorescence decay curve of **2a**–**2l** in dioxane.

Table 3. Fluorescence Lifetimes (τ) of 3-Substituted 2*H*-Chromenes 2 in 1,4-Dioxane

compound	a_1[a]	a_2[a]	τ_1 (ns)[b]	τ_2 (ns)[b]	τ_{avg} (ns)	χ^2
2a	0.98	0.02	0.36	2.14	0.39	1.02
2b	0.93	0.07	0.36	2.86	0.54	1.01
2c	0.97	0.03	0.43	2.03	0.49	1.02
2d	0.90	0.10	0.22	1.71	0.37	1.01
2e	0.92	0.08	0.35	3.18	0.33	1.02
2f	0.97	0.03	0.29	1.47	0.33	1.01
2g	0.80	0.20	0.20	0.72	0.30	1.03
2h	0.92	0.08	0.36	1.08	0.42	1.01
2i	0.90	0.10	0.33	2.11	0.51	1.04
2j	0.98	0.02	0.32	2.71	0.37	1.01
2k	0.94	0.06	0.34	1.52	0.41	1.01
2l	0.92	0.01	0.33	1.36	0.45	1.04

[a]The corresponding pre-exponential coefficients. [b]The short (τ_1) and long (τ_2) lived decay times.

Theoretical Calculation. Diels–Alder reaction is one of the most fundamental reactions to form carbocyclic and heterocyclic frameworks and represents an efficient tool for the stereocontrolled access to a plethora of organic compounds.[25] Quantum calculations have been performed by density functional theory (DFT) method using the Gaussian 09 program to find out the feasibility of [4 + 2] cycloaddition

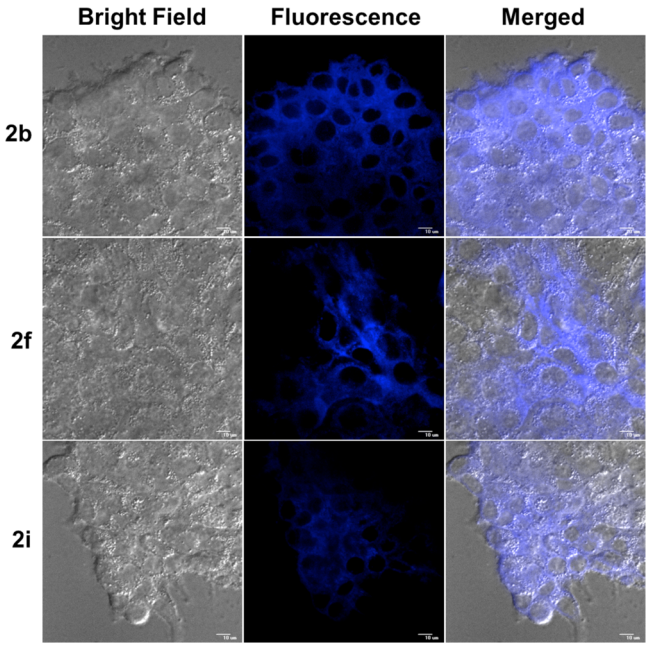

Figure 4. Confocal fluorescence images of living MCF-7 cells with **2b**, **2f** and **2i** (10 μM).

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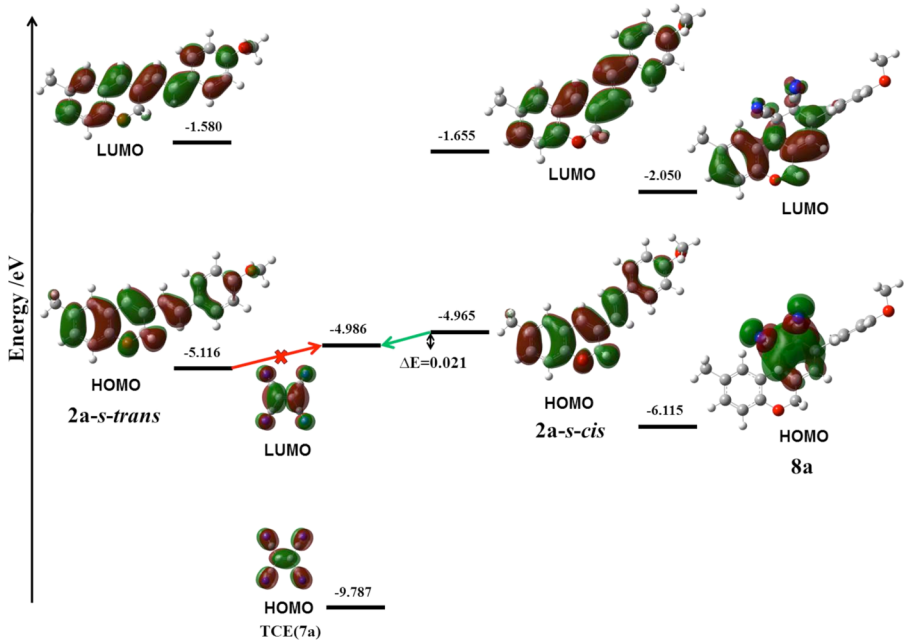


Figure 5. DFT-computed (B3LYP functional, 6-31G(d,p) basis set) HOMO and LUMO pictures of **2a**, **7a** and **8a**.

reaction of the dienes **2** with dienophiles **7**. For this purpose, the diene **2a** and the dienophile tetracyanoethylene (**7a**) were chosen as the representative examples (Figure 5). The ground states of chromenes and cannabinoids were optimized using the restricted correlation function B3LYP with 6-31G(d,p) basis set. As discussed before, the dienes **2** exist exclusively in *s-trans* conformation, but in order to participate in [4 + 2] cycloaddition they must assume *s-cis* conformation. Therefore, HOMO and LUMO energies of **2** in both *s-trans* and *s-cis* conformations as well as of **7a** were calculated and listed in Table 4. From Figure 5, it is evident that the HOMO energy is

Table 4. HOMO and LUMO Energies for the 3-Substituted 2*H*-Chromene Derivatives 2[a]

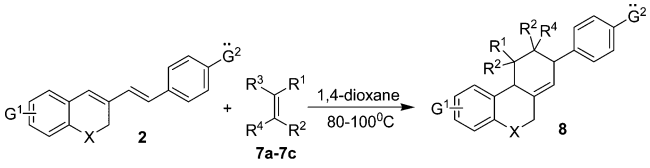
diene **2**	*s-trans* HOMO/LUMO (eV)	*s-cis* HOMO/LUMO (eV)	ΔE_1[b]	ΔE_2[c]
2a	−5.116/−1.580	−4.965/−1.655	0.021	8.132
2d	−5.197/−1.616	−4.967/−1.644	0.019	8.143
2e	−5.242/−1.667	−5.002/−1.685	0.016	8.102
2f	−5.126/−1.719	−4.830/−1.716	0.156	8.071
2g	−5.044/−1.605	−4.892/−1.575	0.094	8.212

[a]Tetracyanoethylene (**7a**): HOMO −9.787 eV, LUMO −4.986 eV. [b]$\text{Diene}_{\text{HOMO}}$(*s-cis*)-$\text{dienophile}_{\text{LUMO}}$. [c]$\text{Dienophile}_{\text{HOMO}}$-$\text{diene}_{\text{LUMO}}$(*s-cis*).

increased with decrease in LUMO energy when the conformation of **2a** is changed from *s-trans* to *s-cis*. It was also found that the energy gap between the LUMO of dienophile (**7a**) and the HOMO of diene (**2a**) is smaller than that between the LUMO of diene (**2a**) and the HOMO of dienophile (**7a**) in *s-cis* conformer. Moreover, the energy of HOMO-diene in *s-cis* conformation is slightly higher than that of LUMO-dienophile and the energy difference is quite small (ΔE = 0.021). Hence, it was concluded that the Diels−Alder reaction would smoothly proceed by the normal electron-demand pathway. As the frontier orbitals are of comparable energies, no catalyst might be essential.

[4 + 2] Cycloaddition of 2*H*-Chromenes and 2*H*-Thiochromenes with Dienophiles. Inspired by the aforementioned theoretical studies, we have exploited Diels−Alder cycloaddition reaction for the synthesis of a series of compounds containing benzopyran embedded moiety analogous to classical cannabinoids starting from the synthesized 2*H*-chromenes **2** as model precursors. Indeed, the compounds **2** underwent facile intermolecular [4 + 2] cycloaddition with electron-deficient dienophiles, for example, tetracyanoethylene (**7a**), maleic anhydride (**7b**) and *N*-phenylmaleimide (**7c**), in 1,4-dioxane at 80−100 °C without any metal or metal−organic framework as catalyst (Scheme 2) to produce compounds **8** containing potentially bioactive tricyclic benzopyran core. Results of the cycloaddition reaction are reported in Table 5.

Scheme 2. Diels−Alder Reaction of 3-Substituted 2*H*-Chromenes 2 with Various Dienophiles 7



Cycloaddition reaction of **2d** with **7a** afforded **8b** in 94% yield. The structure of **8b** was deciphered easily with ^{1}H NMR analysis, where the peaks due to olefinic protons C_6−H and C_7−H (at δ 6.73 and δ 6.39) of **2d** disappeared, indicating that the Diels−Alder reaction occurred on the electron rich C_{13}−C_5−C_6−C_7 diene system. The ^{1}H NMR spectrum of **8b** displayed signals for methine protons (i.e., C_7−H and C_{13}−H) at δ 4.74 and δ 4.66 respectively, along with the singlet of olefinic proton C_6−H at δ 6.25 clearly demonstrating formation of an annulated scaffold resembling cannabinoid. To widen the scope of reaction, dienes **2** were allowed to react with other dienophiles (**7b**, **7c**), and in all cases good yields of the product were obtained. However, at lower temperature, a substantial decrease in the conversion was noted. Hence, a good number of

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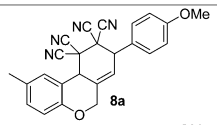
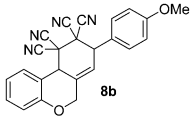
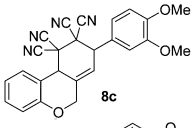
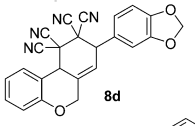
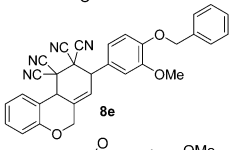
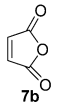
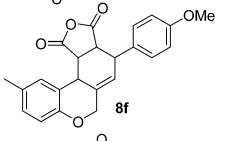
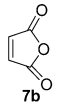
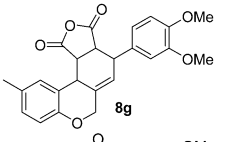
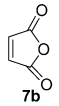
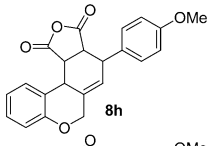
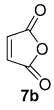
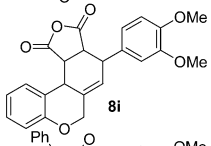
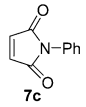
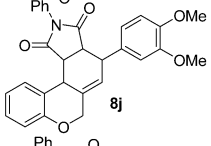
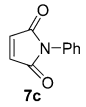
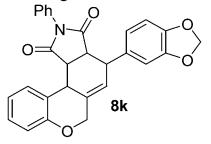
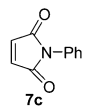
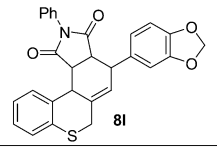
Table 5. Synthesis of Cannabinoid Derivatives 8 by Diels–Alder Reaction of 2*H*-Chromenes 2 with Various Dienophiles 7

Entry	Diene 2	Dienophile (7a-7c)	Product 8	Time(h)/ Yield(%)[a]
1.	**2a**			2/82
2.	**2d**			2/94
3.	**2e**			2/92
4.	**2f**			2/93
5.	**2g**			2/89
6.	**2a**			6/82
7.	**2b**			6/90
8.	**2d**			6/87
9.	**2e**			6/94
10.	**2e**			5/93
11.	**2f**			5/94
12.	**2k**			5/91

[a]Yield of the isolated and purified product characterized spectroscopically.

compounds were synthesized through the aforesaid investigation with a tricyclic benzopyran core related to cannabinoids.

Pharmacology. The significant cytotoxic activity showed by several members of benzopyran family prompted us to investigate in vitro antiproliferative activity of compounds **2** and **8** against MCF-7 (human breast adenocarcinoma) cell line employing the standard MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) reduction assay[26] and compared with the standard drug Doxorubicin. To this end, MCF-7 line was treated for different time intervals 24, 48 and 72 h with various concentrations (20–80 μM/mL) of some of the selected compounds **2** and **8**. The calculated IC_{50} values suggested that these compounds inhibited the growth of the above-mentioned leukemic cell compared with the control cell in a time- and concentration-dependent manner. The results of the cell viability assay are presented in Table 6. As it could be noticed that the compounds **2f**, **2k** and **8l** carrying methylenedioxy functionality on aromatic ring had the distinct tendency to escalate in vitro antitumor efficacy and exhibited slightly better cytotoxicity against MCF-7 (entries 3, 7, 11 in Table 6), while the others unveiled moderate cytotoxic activity. Figure 6 shows the inhibition of cell proliferation for MCF 7 cells incubated with **2f**, **2k**, **8h** and **8l** at different concentrations for 24, 48 and 72 h. The results clearly revealed that the synthesized 3-substituted 2*H*-chromenes and the cannabinoid analogues derived from them came out as excellent scaffolds for further biomolecular study in the arena of cancer chemotherapy.

Table 6. Inhibition of Cell Viability (IC_{50}, μM/mL)[a] of 3-Substituted 2*H*-Chromenes 2 and Cannabinoid Derivatives 8 against MCF-7 Cell Line in Comparison with Standard Drug Doxorubicin

entry	compound	IC_{50} (24 h)	IC_{50} (48 h)	IC_{50} (72 h)
1	**2d**	52.79	51.32	51.04
2	**2e**	65.95	55.43	51.16
3	**2f**	30.54	22.91	21.30
4	**2g**	45.15	43.69	43.11
5	**2h**	68.14	63.97	57.73
6	**2j**	54.29	54.21	54.18
7	**2k**	29.20	28.94	28.78
8	**8d**	43.71	40.06	39.33
9	**8g**	43.19	34.79	33.33
10	**8h**	45.52	36.21	33.26
11	**8l**	25.80	21.86	19.67
12	doxorubicin	ND[b]	ND[b]	1.8

[a]The IC_{50} value corresponded to the compound concentration causing 50% mortality in carcinoma after 24, 48 and 72 h incubation, respectively. The data is a mean value of three independent experiments. [b]Not determined.

CONCLUSION

During this investigation we have found that variably substituted spiro-4-hydroxychroman-3,1′-cyclopropanes and the thiochroman analogues underwent facile reaction with TCT-DMF adduct to afford novel 3-*E*-styryl-2*H*-chromenes and 3-*E*-styryl-2*H*-thiochromenes respectively with good to excellent yield, which serve as the useful precursors for the synthesis of widely substituted tricyclic benzopyran skeletons. Furthermore, the photophysical properties manifested by the

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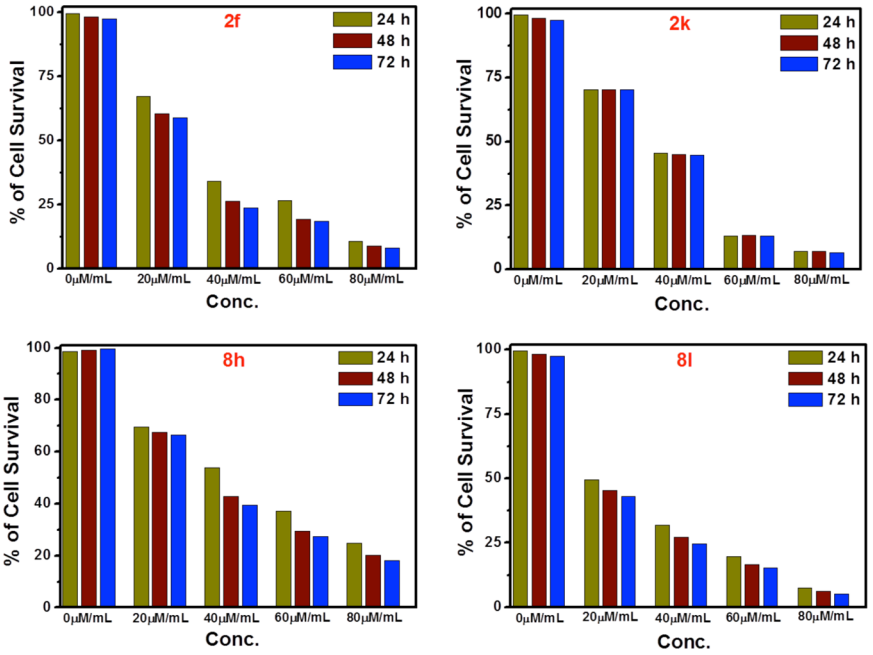

Figure 6. Inhibition of cell proliferation by compounds **2f**, **2k**, **8h** and **8l** on MCF-7 cell line.

chromenes revealed that they were very suitable for in vivo high-resolution microscope imaging. So they can provide remarkable tools to investigate subtle biochemical processes in the cell environment. Finally, cytotoxicity tests (in vitro) indicated that the 2*H*-chromenes and the cannabinoid derivatives are cytotoxic against MCF-7 cell line, which would widen the structural diversity of these anticancer targets and confirm the perspectives of further investigations in this area. Simple execution, easy accessibility of the substrates, good yields, and immense synthetic potential of the products along with important photophysical properties make this protocol highly attractive and utilitarian. We believe that these structural motifs would further augment the engineering of more compounds tailored to specific applications because of the significance and prevalence of these functionalities.

EXPERIMENTAL SECTION

General Methods. All reagents were used without further purification as received from commercial suppliers unless otherwise noted. All solvents were dried and distilled prior to use according to the standard protocols. The ^{1}H NMR spectra were recorded on a 300 or 400 MHz spectrometer, in $CDCl_3$ or DMSO-d_6 solutions and resonances (δ) are given in parts per million (ppm) relative to the singlets at δ 0.0 and δ 7.26 for tetramethylsilane and chloroform, respectively. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet, br = broad, integration, and all coupling constants (J) are absolute values given in hertz (Hz). ^{13}C NMR spectra were recorded at 75 MHz with complete proton decoupling. Chemical shifts are reported in ppm relative to the central line of the heptalet at 77.0 ppm for $CDCl_3$, 39.5 ppm for DMSO-d_6. High resolution mass spectra (HRMS) were acquired using an electron spray ionization time-of-flight (ESI-TOF) mass spectrometer in positive mode in acetonitrile or methanol solvent. The molecular fragments are quoted as the relation between mass and charge (m/z). UV−vis and fluorescence spectroscopy measurements were carried out using matched quartz cells with a slit width of 2.5 mm. The fluorescence quantum yields (Φ) were estimated by comparison of the integrated area of the corrected emission spectra of samples with a reference. Specifically, using quinine sulfate (Φ = 0.54, 0.1 N H_2SO_4) as reference. The concentration of the standard was adjusted to give the same absorbance, which is around 0.1 as the sample at the excitation wavelength. Fluorescence decay measurements were performed using time correlated single photon counting method and using a nanosecond diode laser at 370 nm as light source. The decays were analyzed using IBH DAS-6 decay analysis software. All the experiments were performed at ambient temperature (298 K) with air-equilibrated solutions. The IR spectra were recorded as thin films with KBr and reported in wavenumbers (cm^{-1}). The conversion of starting materials was monitored by thin layer chromatography (TLC) using silica gel (60−120 mesh) coated glass slides and precoated Al plates, which were analyzed with iodine. Melting points were determined with a commercially available melting point apparatus. All reactions involving moisture-sensitive reactants were executed with oven-dried glassware.

General Procedure for the Synthesis of 3-Substituted 2*H*-Chromene Derivatives. To a round-bottomed flask containing cyanuric chloride (277 mg, 1.5 mmol), anhydrous *N*,*N*-dimethylformamide (0.4 mL, 5.2 mmol) was added in drops at 5−10 °C under stirring condition. After 20 min of stirring at that temperature, a white curdy precipitate was obtained (if the precipitate turned pale yellow, then it failed to react further and was discarded). To this mixture a solution of the suitable spiro-4-hydroxychroman-3,1′-cyclopropanes (**1**, 1 mmol) in dry dichloromethane (2 mL) was added dropwise with stirring under cold condition. After complete addition of the substrate **1**, the reaction mixture was allowed to attain the ambient temperature, and the stirring was continued for the stipulated period of time (as mentioned in Table 1) until the completion of the reaction (progress of the reaction was monitored with TLC). After the reaction was complete, the resulted mixture was diluted with ether (30 mL), and the precipitate was filtered off. The organic layer was then washed with 10% Na_2CO_3 solution followed by water and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by purification gave the product **2** in good yields.

*3-(4-Methoxystyryl)-6-methyl-2H-chromene (**2a**).* Light yellow solid (255.2 mg, 92%): mp 170−172 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, J = 8.6 Hz, 2H), 6.91−6.71 (m, 6H), 6.43 (s, 1H), 6.37 (s, 1H), 5.04 (s, 2H), 3.83 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 151.4, 131.1, 130.7, 129.7, 129.3, 127.6, 127.4, 127.1, 124.7, 123.0, 122.8, 115.1, 114.2, 65.6, 55.3, 20.5; HRMS (ESI-TOF, m/z) calcd for $C_{19}H_{18}NaO_2$ [M + Na^+] 301.1205, found 301.1204.

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*3-(3,4-Dimethoxystyryl)-6-methyl-2H-chromene (**2b**).* Yellow solid (261.7 mg, 85%): mp 130−131 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99−6.71 (m, 7H), 6.45 (s, 1H), 6.38 (d, J = 16.4 Hz, 1H), 5.04 (s, 2H), 3.93 (s, 3H), 3.90 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4, 149.1, 149.0, 130.9, 130.6, 130.0, 129.3, 127.6, 127.1, 124.8, 123.2, 122.7, 119.8, 115.1, 111.2, 108.5, 65.5, 55.9, 55.8, 20.5; HRMS (ESI-TOF, m/z) calcd for $C_{20}H_{21}O_3$ [M + H$^+$] 309.1485, found 309.1486.

*3-((E)-2-(Benzo[d][1,3]dioxol-6-yl)vinyl)-6-methyl-2H-chromene (**2c**).* Light yellow solid (233.6 mg, 80%): mp 157−158 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.91−6.66 (m, 6H), 6.43 (s, 1H), 6.35 (d, J = 16.4 Hz, 1H), 5.97 (s, 2H), 5.02 (s, 2H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4, 148.2, 147.4, 131.5, 130.7, 129.4, 127.4, 127.2, 125.0, 123.4, 122.7, 121.5, 115.1, 108.4, 105.2, 101.1, 65.5, 29.7, 20.5; HRMS (ESI-TOF, m/z) calcd for $C_{19}H_{17}O_3$ [M + H$^+$] 293.1172, found 293.1171.

*3-(4-Methoxystyryl)-2H-chromene (**2d**).* Light yellow solid (237.1 mg, 90%): mp 134−136 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, J = 8.7 Hz, 2H), 7.12−6.81 (m, 6H), 6.73 (d, J = 16.5 Hz, 1H), 6.46 (s, 1H), 6.39 (d, J = 16.5 Hz, 1H), 5.07 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 153.6, 130.9, 129.7, 128.8, 127.7, 127.5, 126.7, 124.6, 122.9, 122.8, 121.5, 115.4, 114.2, 65.6, 55.3; HRMS (ESI-TOF, m/z) calcd for $C_{18}H_{17}O_2$ [M + H$^+$] 265.1223, found 265.1222.

*3-(3,4-Dimethoxystyryl)-2H-chromene (**2e**).* Yellow solid (253.0 mg, 86%): mp 111−113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13−6.82 (m, 7H), 6.74 (d, J = 16.4 Hz, 1H), 6.49 (s, 1H), 6.39 (d, J = 16.4 Hz, 1H), 5.08 (s, 2H), 3.94 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 149.2, 130.9, 130.1, 128.9, 127.8, 126.8, 124.8, 123.1, 122.9, 121.5, 119.9, 115.4, 111.3, 108.7, 65.7, 56.0, 55.9; HRMS (ESI-TOF, m/z) calcd for $C_{19}H_{18}NaO_3$ [M + Na$^+$] 317.1154, found 317.1153.

*3-((E)-2-(Benzo[d][1,3]dioxol-6-yl)vinyl)-2H-chromene (**2f**).* Yellow solid (250.4 mg, 90%): mp 128−130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12−6.76 (m, 7H), 6.68 (d, J = 16.2 Hz, 1H), 6.46 (s, 1H), 6.34 (d, J = 16.5 Hz, 1H), 5.96 (s, 2H), 5.05 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 153.2, 147.9, 147.2, 131.4, 131.3, 128.8, 128.3, 126.8, 124.6, 122.8, 122.5, 121.8, 121.5, 115.2, 108.5, 105.2, 101.2, 65.0; HRMS (ESI-TOF, m/z) calcd for $C_{18}H_{14}NaO_3$ [M + Na$^+$] 301.0841, found 301.0840.

*3-(4-(Benzyloxy)-3-methoxystyryl)-2H-chromene (**2g**).* Light yellow solid (303.6 mg, 82%): mp 132−133 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−6.81 (m, 12H), 6.73 (d, J = 16.5 Hz, 1H), 6.48 (s, 1H), 6.37 (d, J = 16.5 Hz, 1H), 5.17 (s, 2H), 5.07 (s, 2H), 3.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 149.7, 148.2, 136.9, 130.8, 130.5, 128.9, 128.5, 127.9, 127.7, 127.2, 126.7, 124.9, 123.1, 122.8, 121.5, 119.7, 115.4, 113.9, 109.2, 70.9, 65.6, 55.9; HRMS (ESI-TOF, m/z) calcd for $C_{25}H_{22}NaO_3$ [M + Na$^+$] 393.1467, found 393.1467.

*3-((E)-2-(Thiophen-2-yl)vinyl)-2H-chromene (**2h**).* Yellow solid (199.4 mg, 83%): mp 123−124 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21−6.81 (m, 7H), 6.68 (distorted AB quartet, J = 16.1 Hz, 1H), 6.59 (distorted AB quartet, J = 16.3 Hz, 1H), 6.49 (s, 1H), 5.04 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 142.6, 130.3, 129.1, 127.8, 126.9, 126.4, 126.2, 124.8, 123.7, 122.8, 121.6, 121.1, 115.5, 65.4; HRMS (ESI-TOF, m/z) calcd for $C_{15}H_{13}OS$ [M + H$^+$] 241.0687, found 241.0688.

*3-(4-Methoxystyryl)-2H-thiochromene (**2i**).* Light yellow solid (246.8 mg, 88%): mp 120−122 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, J = 6.9 Hz, 2H), 7.26−7.08 (m, 4H), 6.90 (d, J = 6.9 Hz, 2H), 6.85 (d, J = 16.1 Hz, 1H), 6.62 (d, J = 16.2 Hz, 1H), 6.55 (s, 1H), 3.83 (s, 3H), 3.72 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 133.1, 131.9, 131.2, 129.7, 128.4, 128.2(2), 127.7, 127.5, 127.4, 126.6, 125.6, 114.2, 55.2, 24.9; HRMS (ESI-TOF, m/z) calcd for $C_{18}H_{17}OS$ [M + H$^+$] 281.0995, found 281.0996.

*3-(3,4-Dimethoxystyryl)-2H-thiochromene (**2j**).* Light yellow semisolid (260.7 mg, 84%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25−6.82 (m, 8H), 6.61 (d, J = 16.5 Hz, 1H), 6.57 (s, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.72 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0(2), 133.0, 131.7, 131.1, 130.0, 128.4, 127.5, 126.6, 125.5, 119.9, 111.1, 108.5, 55.8, 55.7, 24.9; HRMS (ESI-TOF, m/z) calcd for $C_{19}H_{18}KO_2S$ [M + K$^+$] 349.0665, found 349.0666.

*5-((1E)-2-(2H-Thiochromen-3-yl)vinyl)benzo[d][1,3]dioxole (**2k**).* Orange yellow solid (250.0 mg, 85%): mp 100−101 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26−6.54 (m, 10H), 5.97 (s, 2H), 3.70 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 147.5, 133.1, 131.7, 131.5, 131.3, 128.6, 128.5, 128.3, 127.9, 127.7, 126.7, 125.6, 121.7, 108.5, 105.4, 101.2, 24.9; HRMS (ESI-TOF, m/z) calcd for $C_{18}H_{14}KO_2S$ [M + K$^+$] 333.0352, found 333.0352.

*3-(2-Methoxystyryl)-2H-thiochromene (**2l**).* Yellow solid (255.0 mg, 91%): mp 111−113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59−6.90 (m, 10H), 6.59 (s, 1H), 3.89 (s, 3H), 3.79 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 133.1, 132.3, 131.4, 129.7, 128.8(2), 128.4, 127.6, 126.6, 126.1, 125.9, 125.5, 123.2, 120.7, 110.8, 55.4, 24.9; HRMS (ESI-TOF, m/z) calcd for $C_{18}H_{16}KOS$ [M + K$^+$] 319.0559, found 319.0558.

*3-(4-Methylstyryl)-2H-chromene (**2m**).* Pale yellow solid (80.0 mg, 32%): mp 118−120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, J = 8.0 Hz, 2H), 7.21−7.06 (m, 4H), 6.95−6.83 (m, 3H), 6.52 (s, 1H), 6.46 (d, J = 16.5 Hz, 1H), 5.12 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 137.9, 134.2, 130.9, 129.5, 129.0, 128.0, 126.9, 126.4, 125.7, 123.4, 122.9, 121.5, 115.5, 65.7, 21.3; HRMS (ESI-TOF, m/z) calcd for $C_{18}H_{17}O$ [M + H$^+$] 249.1280, found 249.1279.

*3-(2-Chloro-2-(3-methoxyphenyl)ethyl)-2H-chromene (**3n**).* Light yellow semisolid (285.7 mg, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (t, J = 8.3 Hz, 1H), 7.12−6.87 (m, 6H), 6.82 (d, J = 8.0 Hz, 1H), 6.28 (s, 1H), 5.00 (t, J = 7.7 Hz, 1H), 4.68 (distorted AB quartet, J = 14.4 Hz, 1H), 4.57 (distorted AB quartet, J = 14.4 Hz, 1H), 3.83 (s, 3H), 2.99−2.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 152.9, 142.4, 130.2, 129.7, 128.7, 126.3, 122.7, 122.4, 121.3, 119.1, 115.3, 113.9, 112.6, 67.9, 61.0, 55.2, 44.1. Elemental analysis calculated (%) for $C_{18}H_{17}ClO_2$: C 71.88, H 5.70, Cl 11.78, O 10.64. Found: C 71.92, H 5.75.

*3-(2-Chloro-2-(4-chlorophenyl)ethyl)-2H-chromene (**3o**).* Light yellow semisolid (286.9 mg, 94%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (s, 4H), 7.08 (t, J = 7.7 Hz, 1H), 6.94−6.75 (m, 3H), 6.22 (s, 1H), 4.96 (t, J = 7.6 Hz, 1H), 4.64 (distorted AB quartet, J = 14.4 Hz, 1H), 4.54 (distorted AB quartet, J = 14.4 Hz, 1H), 2.96−2.78 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 139.4, 134.4, 129.8, 129.0, 128.9, 128.3, 126.4, 123.1, 122.3, 121.5, 115.4, 68.0, 60.1, 44.2. Elemental analysis calculated (%) for $C_{17}H_{14}Cl_2O$: C 66.90, H 4.62, Cl 23.24, O 5.24. Found: C 66.83, H 4.68.

General Procedure for the Synthesis of Cannabinoid Derivatives. Compound **2** (1 mmol) and the dienophile **7** (2 mmol) were gently refluxed (at 80−100 °C) in dry dioxane (2 mL) under anhydrous condition for the required period of time (as mentioned in Table 5). After complete consumption of compound **2** (evident from TLC), the solution was cooled to room temperature and was evaporated to obtain a sticky mass, which was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with water and dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 80/20) to afford the product **8** in excellent yield.

*8-(4-Methoxyphenyl)-2-methyl-6H-benzo[c]chromene-9,9,10,10-(8H,10aH)-tetracarbonitrile (**8a**).* Yellow solid (333.5 mg, 82%): mp 125−126 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.40 (d, J = 8.6 Hz, 2H), 7.17 (d, J = 8.3 Hz, 1H), 6.94 (t, J = 8.5 Hz, 3H), 6.24 (s, 1H), 4.70 (d, J = 11.9 Hz, 1H), 4.59 (s, 1H), 4.51−4.47 (m, 2H), 3.82 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0, 154.5, 132.5, 131.8, 130.8, 128.0, 123.9, 123.6, 118.5, 115.7, 114.1, 112.8, 112.1, 109.8, 108.1, 69.8, 55.3, 47.1, 45.2, 42.5, 40.6, 20.8; IR (KBr, cm^{-1}) ν 3426.63, 2931.05, 1611.34, 1514.28, 1502.41, 1464.68, 1427.48, 1246.89, 1182.44, 1032.47, 1000.00, 845.60, 819.53, 737.35; HRMS (ESI-TOF, m/z) calcd for $C_{25}H_{18}N_4NaO_2$ [M + Na$^+$] 429.1328, found 429.1326.

*8-(4-Methoxyphenyl)-6H-benzo[c]chromene-9,9,10,10(8H,10aH)-tetracarbonitrile (**8b**).* Yellow solid (370.0 mg, 94%): mp 118−120 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, J = 7.9 Hz, 1H), 7.41−7.36 (m, 3H), 7.15 (t, J = 7.6 Hz, 1H), 7.07 (d, J = 8.2 Hz, 1H), 6.93 (d, J = 8.6 Hz, 2H), 6.25 (s, 1H), 4.74 (d, J = 11.8 Hz, 1H), 4.66 (s, 1H), 4.55−4.49 (m, 2H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

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161.0, 156.6, 132.5, 130.9, 130.4, 127.9, 123.9, 123.4, 122.9, 118.8, 116.0, 114.1, 112.8, 112.1, 109.8, 108.0, 69.7, 55.3, 47.0, 45.1, 42.3, 40.7; IR (KBr, cm^{-1}) ν 3448.02, 2928.85, 1608.36, 1514.44, 1490.15, 1460.24, 1238.72, 1180.55, 1029.66, 761.61; HRMS (ESI-TOF, m/z) calcd for $C_{24}H_{16}N_4NaO_2$ [M + Na^+] 415.1173, found 415.1171.

*8-(3,4-Dimethoxyphenyl)-6H-benzo[c]chromene-9,9,10,10-(8H,10aH)-tetracarbonitrile (**8c**).* Yellow solid (389.1 mg, 92%): mp 136−138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 7.7 Hz, 1H), 7.37 (t, J = 7.4 Hz, 1H), 7.17−6.86 (m, 5H), 6.25 (s, 1H), 4.73 (d, J = 11.6 Hz, 1H), 4.64 (s, 1H), 4.53−4.49 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 150.5, 148.8, 130.9, 130.6, 128.0, 124.1, 124.0(2), 122.9, 118.8, 116.0, 113.8, 112.8, 112.1, 110.8, 109.8, 108.3, 69.7, 56.0, 55.8, 47.4, 45.2, 42.6, 40.6; IR (KBr, cm^{-1}) ν 3449.01, 2933.95, 1607.30, 1516.65, 1490.27, 1462.97, 1270.54, 1238.15, 1146.40, 1023.85, 760.42; HRMS (ESI-TOF, m/z) calcd for $C_{25}H_{18}N_4NaO_3$ [M + Na^+] 445.1278, found 445.1277.

*8-(Benzo[d][1,3]dioxol-6-yl)-6H-benzo[c]chromene-9,9,10,10-(8H,10aH)-tetracarbonitrile (**8d**).* Light yellow solid (378.3 mg, 93%): mp 167−168 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 7.8 Hz, 1H), 7.38 (t, J = 7.5 Hz, 1H), 7.18−6.82 (m, 5H), 6.23 (s, 1H), 6.01 (s, 2H), 4.73 (d, J = 11.9 Hz, 1H), 4.64 (s, 1H), 4.54−4.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 149.3, 148.0, 131.0, 130.7, 128.0, 125.6, 125.2, 123.8, 123.0, 118.9, 116.0, 112.8, 112.0, 111.0, 109.7, 108.3, 108.2, 101.9, 69.7, 47.3, 45.1, 42.6, 40.6; IR (KBr, cm^{-1}) ν 3424.53, 2915.90, 1608.33, 1504.97, 1489.83, 1447.32, 1256.61, 1239.18, 1103.95, 1039.21, 1003.18, 924.40, 763.70, 668.07; HRMS (ESI-TOF, m/z) calcd for $C_{24}H_{14}N_4NaO_3$ [M + Na^+] 429.0964, found 429.0966.

*8-(4-(Benzyloxy)-3-methoxyphenyl)-6H-benzo[c]chromene-9,9,10,10(8H,10aH)-tetracarbonitrile (**8e**).* Greenish yellow solid (444.2 mg, 89%): mp 104−106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, J = 7.9 Hz, 1H), 7.43−6.88 (m, 11H), 6.24 (s, 1H), 5.14 (s, 2H), 4.73 (d, J = 11.8 Hz, 1H), 4.64 (s, 1H), 4.53−4.47 (m, 2H), 3.87 (s, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 149.7, 149.3, 136.3, 130.9, 130.5, 128.6, 128.0, 127.3, 124.4, 124.0, 123.9, 122.9, 118.8, 116.0, 114.3, 113.0, 112.7, 112.1, 109.8, 108.2, 70.8, 69.7, 56.1, 47.5, 45.2, 42.6, 40.6; IR (KBr, cm^{-1}) ν 3426.62, 2875.17, 1606.66, 1514.30, 1490.06, 1462.43, 1270.72, 1237.56, 1144.89, 1004.70, 758.73, 698.06, 668.03; HRMS (ESI-TOF, m/z) calcd for $C_{31}H_{22}N_4NaO_3$ [M + Na^+] 521.1589, found 521.1588.

*3a,4-Dihydro-4-(4-methoxyphenyl)-10-methyl-6H-isobenzofuro-[5,4-c]chromene-1,3(11bH,11cH)-dione (**8f**).* Orange yellow solid (309.5 mg, 82%): mp 206−207 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.26 (d, J = 8.3 Hz, 2H), 7.20 (s, 1H), 6.98−6.91 (m, 3H), 6.77 (d, J = 8.2 Hz, 1H), 6.30 (s, 1H), 4.56 (d, J = 13.4 Hz, 1H), 4.40 (d, J = 13.3 Hz, 1H), 4.06−3.78 (m, 4H), 3.76 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.0, 170.9, 158.2, 154.5, 138.3, 130.7, 130.4, 129.6, 129.0, 128.3, 123.9, 122.8, 117.1, 113.6, 67.9, 55.0, 48.4, 46.8, 34.4, 20.5; IR (KBr, cm^{-1}) ν 3424.40, 2920.09, 2836.30, 1778.21, 1615.33, 1518.98, 1497.87, 1461.01, 1288.10, 1252.45, 1176.07, 1037.22, 1005.68, 932.19, 835.86, 819.65, 756.68; HRMS (ESI-TOF, m/z) calcd for $C_{23}H_{20}NaO_5$ [M + Na^+] 399.1208, found 399.1207.

*3a,4-Dihydro-4-(3,4-dimethoxyphenyl)-10-methyl-6H-isobenzofuro[5,4-c]chromene-1,3(11bH,11cH)-dione (**8g**).* Orange yellow solid (366.4 mg, 90%): mp 169−170 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.30 (s, 1H), 6.99−6.77 (m, 5H), 6.35 (s, 1H), 4.58 (d, J = 13.1 Hz, 1H), 4.41 (d, J = 13.2 Hz, 1H), 4.04−3.80 (m, 4H), 3.76 (s, 6H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.0, 170.8, 154.5, 148.4, 147.8, 138.2, 131.1, 130.5, 129.0, 128.3, 124.0, 122.8, 120.6, 117.1, 112.6, 111.5, 67.9, 55.5, 55.4, 48.4, 46.8, 34.4, 20.5; IR (KBr, cm^{-1}) ν 3424.71, 2934.70, 2837.52, 1779.24, 1733.89, 1518.04, 1500.05, 1464.63, 1243.82, 1143.40, 1024.98, 931.49, 820.50, 765.74; HRMS (ESI-TOF, m/z) calcd for $C_{24}H_{22}NaO_6$ [M + Na^+] 429.1314, found 429.1315.

*3a,4-Dihydro-4-(4-methoxyphenyl)-6H-isobenzofuro[5,4-c]-chromene-1,3(11bH,11cH)-dione (**8h**).* Light yellow solid (315.8 mg, 87%): mp 213−215 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.41 (d, J = 7.3 Hz, 1H), 7.25 (d, J = 8.6 Hz, 2H), 7.16 (t, J = 7.5 Hz, 1H), 7.02 (t, J = 7.3 Hz, 1H), 6.93−6.86 (m, 3H), 6.32 (s, 1H), 4.60 (d, J = 13.6 Hz, 1H), 4.45 (d, J = 13.5 Hz, 1H), 4.07−3.78 (m, 4H), 3.75 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.0, 170.9, 158.2, 156.6, 138.1, 130.7, 129.7, 128.9, 127.7, 124.1, 123.2, 121.9, 117.3, 113.6, 67.9, 55.0, 48.4, 46.8, 34.4; IR (KBr, cm^{-1}) ν 3421.89, 2935.54, 2839.34, 1777.81. 1614.71, 1584.66, 1519.63, 1489.80, 1460.48, 1257.22, 1179.23, 1005.06, 937.35, 758.03; HRMS (ESI-TOF, m/z) calcd for $C_{22}H_{18}O_5K$ [M + K^+] 401.0791, found 401.0792.

*3a,4-Dihydro-4-(3,4-dimethoxyphenyl)-6H-isobenzofuro[5,4-c]-chromene-1,3(11bH,11cH)-dione (**8i**).* Whitish yellow solid (370.0 mg, 94%): mp 190−192 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.41 (d, J = 7.4 Hz, 1H), 7.17 (t, J = 7.7 Hz, 1H), 7.02 (t, J = 7.4 Hz, 1H), 6.94−6.85 (m, 4H), 6.36 (s, 1H), 4.60 (d, J = 13.5 Hz, 1H), 4.45 (d, J = 13.5 Hz, 1H), 4.07−3.80 (m, 4H), 3.75 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.0, 170.9, 156.6, 148.4, 147.8, 138.0, 131.1, 128.9, 127.7, 124.1, 123.2, 121.9, 120.6, 117.3, 112.6, 111.5, 67.9, 55.5(2), 48.4, 46.8, 34.4; IR (KBr, cm^{-1}) ν 3423.10, 2932.22, 2836.88, 1778.13, 1586.01, 1519.79, 1490.61, 1464.78, 1246.36, 1027.85, 1004.46, 954.35, 923.92, 764.64; HRMS (ESI-TOF, m/z) calcd for $C_{23}H_{20}NaO_6$ [M + Na^+] 415.1158, found 415.1157.

*3a,4-Dihydro-4-(3,4-dimethoxyphenyl)-2-phenylchromeno[4,3-e]isoindole-1,3(2H,6H,11bH,11cH)-dione (**8j**).* Yellow solid (435.0 mg, 93%): mp 98−100 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.51−6.76 (m, 12H), 6.37 (s, 1H), 4.62−4.49 (s, 1H), 3.94−3.92 (m, 2H), 3.80−3.70 (m, 8H, containing two singlets at δ 3.75 (s, 3H) and δ 3.74 (s, 3H)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 169.5, 157.0, 148.8, 148.2, 137.8, 134.2, 131.2, 129.1, 128.9, 128.4, 128.2, 128.0, 126.2, 126.1, 124.4, 122.9, 122.2, 120.9, 117.9, 112.1, 111.0, 68.7, 55.9, 55.8, 47.4, 45.9, 41.7, 35.7; IR (KBr, cm^{-1}) ν 3464.64, 2935.34, 2836.59, 1715.00, 1597.70, 1517.46, 1457.14, 1380.98, 1264.95, 1235.80, 1143.86, 1024.90, 758.72, 693.41; HRMS (ESI-TOF, m/z) calcd for $C_{29}H_{26}NO_5$ [M + H^+] 468.1805, found 468.1808.

*4-(Benzo[d][1,3]dioxol-6-yl)-3a,4-dihydro-2-phenylchromeno-[4,3-e]isoindole-1,3(2H,6H,11bH,11cH)-dione (**8k**).* Yellow solid (424.8 mg, 94%): mp 109−110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−6.83 (m, 12H), 6.26 (s, 1H), 5.98 (s, 2H), 4.66 (d, J = 13.6 Hz, 1H), 4.57 (d, J = 13.6 Hz, 1H), 3.89 (brs, 1H), 3.82 (brs, 1H), 3.71 (t, J = 8.4 Hz, 1H), 3.61 (t, J = 7.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 174.3, 169.6, 157.0, 147.8, 146.8, 138.0, 134.2, 131.2, 129.2, 128.9, 128.4, 128.2, 128.0, 126.3, 126.1, 124.1, 123.0, 122.2, 117.9, 109.2, 108.2, 101.1, 68.7, 47.5, 45.9, 41.7, 35.7; IR (KBr, cm^{-1}) ν 3464.16, 2892.64, 1713.97, 1597.83, 1490.07, 1444.72, 1381.45, 1237.09, 1037.17, 930.87, 826.90, 758.09, 693.11; HRMS (ESI-TOF, m/z) calcd for $C_{28}H_{21}NNaO_5$ [M + Na^+] 474.1317, found 474.1315.

*4-(Benzo[d][1,3]dioxol-6-yl)-3a,4-dihydro-2-phenylthio-chromeno[4,3-e]isoindole-1,3(2H,6H,11bH,11cH)-dione (**8l**).* Yellow solid (426.0 mg, 91%): mp 95−97 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−6.78 (m, 12H), 6.25 (s, 1H), 5.93 (s, 2H), 3.90 (brs, 1H), 3.70 (brs, 2H), 3.63−3.35 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 173.5, 169.3, 147.3, 146.3, 138.1, 136.2, 133.9, 132.7, 131.6, 131.0, 129.5, 128.9, 128.6, 128.3, 128.0, 126.2, 126.0, 123.5, 121.5, 109.1, 107.7, 100.8, 66.8, 47.4, 46.8, 40.9, 33.7; IR (KBr, cm^{-1}) ν 3468.78, 2891.89, 1712.95, 1597.02, 1502.56, 1443.08, 1380.89, 1232.34, 1185.64, 1035.99, 931.88, 826.54, 756.23, 698.26; HRMS (ESI-TOF, m/z) calcd for $C_{28}H_{21}NO_4S$ [M + H^+] 468.1264, found 468.1266.

Crystallographic Data Collection and Refinement. Compound **2i** (30 mg) in CH_2Cl_2/petroleum ether (v/v = 1:2) solution was left to evaporate. Light yellow single crystals suitable for X-ray diffraction were obtained. A suitable single crystal was selected and mounted in air onto thin glass fibers. Accurate unit cell parameters were determined by a least-squares fit of 2θ values, and intensity data were measured on a CCD diffractometer with Mo Kα radiation (λ = 0.71073 Å) at 296 K. The detector was placed at a distance 6.03 cm from the crystal. The data were reduced in SAINTPLUS,[27] and empirical absorption correction was applied using the SADABS package.[27] The structures were solved by direct methods and refined with full-matrix least-squares technique using the SHELXTL v.6.14 program package.[28,29] All non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms were added theoretically and riding on the concerned atoms. Molecular structure plots were drawn using Platon.[30]

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■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra, cytotoxicity data, HOMO and LUMO pictures, Cartesian coordinates and energies, crystallographic data and CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Schweizer, E. E.; Meeder-Nycz, O. In *Chromenes, Chromanes, Chromones*; Ellis, G. P., Ed.; Wiley-Interscience: New York, 1977; Vol. *31*, pp 11−139. (b) Hepworth, J. D. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Boulton, A. J., McKillop, A., Eds.; Pergamon Press: Oxford, U.K., 1984; Vol. *3*, pp 737−883. (c) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285−2309. (d) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939−9953. (e) Nicolaou, K. C.; Pfefferkorn, J. A.; Mitchell, H. J.; Roecker, A. J.; Barluenga, S.; Cao, G.-Q.; Affleck, R. L.; Lillig, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 9954−9967. (f) Nicolaou, K. C.; Pfefferkorn, J. A.; Barluenga, S.; Mitchell, H. J.; Roecker, A. J.; Cao, G.-Q. *J. Am. Chem. Soc.* **2000**, *122*, 9968−9976.

(2) (a) Abdel-Aziz, H. A.; Elsaman, T.; Al-Dhfyan, A.; Attia, M. I.; Al-Rashood, K. A.; Al-Obaid, A.-R. M. *Eur. J. Med. Chem.* **2013**, *70*, 358−363. (b) Muna, J.; Jabbar, A. A.; Devi, N. S.; Liu, Y.; Meir, E. G. V.; Goodman, M. M. *Bioorg. Med. Chem.* **2012**, *20*, 4590−4597. (c) Azizmohammadi, M.; Khoobi, M.; Ramazani, A.; Emami, S.; Zarrin, A.; Firuzi, O.; Miri, R.; Shafiee, A. *Eur. J. Med. Chem.* **2013**, *59*, 15−22. (d) Murthy, Y. L. N.; Suhasini, K. P.; Pathania, A. S.; Bhushan, S.; Nagendra Sastry, Y. *Eur. J. Med. Chem.* **2013**, *62*, 545−555. (e) Kumar, J. A.; Saidachary, G.; Mallesham, G.; Sridhar, B.; Jain, N.; Kalivendi, S. V.; Rao, V. J.; Raju, B. C. *Eur. J. Med. Chem.* **2013**, *65*, 389−402. (f) Mun, J.; Jabbar, A. A.; Devi, N. S.; Yin, S.; Wang, Y.; Tan, C.; Culver, D.; Snyder, J. P.; Meir, E. G. V.; Goodman, M. M. *J. Med. Chem.* **2012**, *55*, 6738−6750. (g) Dong, Y.; Nakagawa-Goto, K.; Lai, C.-Y.; Morris-Natschke, S. L.; Bastow, K. F.; Kim, Y.; Lee, E. Y.-H. P.; Lee, K.-H. *J. Nat. Prod.* **2012**, *75*, 370−377. (h) zhi Qiang, D.; Shi, J. B.; Song, B. A.; Liu, X. H. *RSC Adv.* **2014**, *4*, 5607−5617. (i) Sandhya, B.; Giles, D.; Mathew, V.; Basavarajaswamy, G.; Abraham, R. *Eur. J. Med. Chem.* **2011**, *46*, 4696−4701. (j) Hussain, M. K.; Ansari, M. I.; Yadav, N.; Gupta, P. K.; Gupta, A. K.; Saxena, R.; Fatima, I.; Manohar, M.; Kushwaha, P.; Khedgikar, V.; Gautam, J.; Kant, R.; Maulik, P. R.; Trivedi, R.; Dwivedi, A.; Kumar, K. R.; Saxena, A. K.; Hajela, K. *RSC Adv.* **2014**, *4*, 8828−8845. (k) Trenor, S. R.; Shultz, A. R.; Love, B. J.; Long, T. E. *Chem. Rev.* **2004**, *104*, 3059−3078. (l) Coi, A.; Bianucci, A. M.; Calderone, V.; Testai, L.; Digiacomo, M.; Rapposelli, S.; Balsamo, A. *Bioorg. Med. Chem.* **2009**, *17*, 5565−5571. (m) Tahtaoui, C.; Demailly, A.; Guidemann, C.; Joyeux, C.; Schneider, P. *J. Org. Chem.* **2010**, *75*, 3781−3785. (n) Bhavsar, D.; Trivedi, J.; Parekh, S.; Savant, M.; Thakrar, S.; Bavishi, A.; Radadiya, A.; Vala, H.; Lunagariya, J.; Parmar, M.; Paresh, L.; Loddo, R.; Shah, A. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3443−3446. (o) Mukherjee Singh, O.; Devi, N. S.; Singh Thokchom, D.; Sharma, G. J. *Eur. J. Med. Chem.* **2010**, *45*, 2250−2257. (p) Balabani, A.; Hadjipavlou-Litina, D. J.; Litinas, K. E.; Mainou, M.; Tsironi, C.-C.; Vronteli, A. *Eur. J. Med. Chem.* **2011**, *46*, 5894−5901. (q) Reddy, Ch. S.; Devi, M. V.; Kumar, G. R.; Rao, L. S.; Nagaraj, A. *J. Heterocyclic Chem.* **2011**, *48*, 176−182.

(3) (a) Ranjith, C.; Vijayan, K. K.; Praveen, V. K.; Kumar, N. S. S. *Spectrochim. Acta, Part A* **2010**, *75*, 1610−1616. (b) Yi, X.; Zhao, J.; Wu, W.; Huang, D.; Ji, S.; Sun, J. *Dalton Trans.* **2012**, *41*, 8931−8940. (c) Sun, J.; Zhao, J.; Guo, H.; Wu, W. *Chem. Commun.* **2012**, *48*, 4169−4171. (d) Yi, X.; Yang, P.; Huang, D.; Zhao, J. *Dyes Pigm.* **2013**, *96*, 104−115. (e) Lee, K. H.; Park, M. H.; Seo, B. M.; Seo, J. H.; Kim, Y. K.; Yoon, S. S. *Mol. Cryst. Liq. Cryst.* **2011**, *550*, 260−269. (f) Kobayashi, A.; Takehira, K.; Yoshihara, T.; Uchiyama, S.; Tobita, S. *Photochem. Photobiol. Sci.* **2012**, *11*, 1368−1376. (g) Wei, M.; Yin, P.; Shen, Y.; Zhang, L.; Deng, J.; Xue, S.; Li, H.; Guo, B.; Zhang, Y.; Yao, S. *Chem. Commun.* **2013**, *49*, 4640−4642.

(4) (a) Moorthy, J. N.; Venkatakrishnan, P.; Samanta, S.; Kumar, D. K. *Org. Lett.* **2007**, *9*, 919−922. (b) Sousa, C. M.; Pina, J.; Seixas de Melo, J.; Berthet, J.; Delbaere, S.; Coelho, P. J. *Eur. J. Org. Chem.* **2012**, 1768−1773. (c) Moorthy, J. N.; Mandal, S.; Mukhopadhyay, A.; Samanta, S. *J. Am. Chem. Soc.* **2013**, *135*, 6872−6884. (d) Mandal, S.; Parida, K. N.; Samanta, S.; Moorthy, J. N. *J. Org. Chem.* **2011**, *76*, 7406−7414.

(5) (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893−930. (b) Kogan, N. M.; Rabinowitz, R.; Levi, P.; Gibson, D.; Sandor, P.; Schlesinger, M.; Mechoulam, R. *J. Med. Chem.* **2004**, *47*, 3800−3806.

(6) (a) Chang, D.-J.; An, H.; Kim, K.-S.; Kim, H. H.; Jung, J.; Lee, J. M.; Kim, N.-J.; Han, Y. T.; Yun, H.; Lee, S.; Lee, G.; Lee, S.; Lee, J. S.; Cha, J.-H.; Park, J.-H.; Park, J. W.; Lee, S.-C.; Kim, S. G.; Kim, J. H.; Lee, H.-Y.; Kim, K.-W.; Suh, Y.-G. *J. Med. Chem.* **2012**, *55*, 10863−10884. (b) Yoshioka, E.; Kohtani, S.; Miyabe, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 6638−6642. (c) Majumdar, N.; Korthals, K. A.; Wulff, W. D. *J. Am. Chem. Soc.* **2012**, *134*, 1357−1362. (d) Kinfe, H. H.; Mebrahtu, F. M.; Makolo, F. L.; Moshapo, P. T.; Manana, M. M. *J. Org. Chem.* **2014**, *79*, 3111−3118.

(7) (a) Uemura, M.; Watson, I. D. G.; Katsukawa, M.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 3464−3465. (b) Bera, K.; Sarkar, S.; Biswas, S.; Jana, U. *J. Org. Chem.* **2011**, *76*, 3539−3544. (c) Mo, J.; Choi, W.; Min, J.; Kim, C.-E.; Eom, D.; Kim, S. H.; Lee, P. H. *J. Org. Chem.* **2013**, *78*, 11382−11388. (d) Paul, N. D.; Mandal, S.; Otte, M.; Cui, X.; Zhang, X. P.; de Bruin, B. *J. Am. Chem. Soc.* **2014**, *136*, 1090−1096. (e) Mahendar, L.; Satyanarayana, G. *J. Org. Chem.* **2014**, *79*, 2059−2074.

(8) (a) Sundén, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Chem.—Eur. J.* **2007**, *13*, 574−581. (b) Westermann, B.; Ayaz, M.; van Berkel, S. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 846−849. (c) Xu, L.-W.; Li, L.; Shi, Z.-H. *Adv. Synth. Catal.* **2010**, *352*, 243−279. (d) Rueping, M.; Uria, U.; Lin, M.; Atodiresei, I. *J. Am. Chem. Soc.* **2011**, *133*, 3732−3735. (e) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570−1581. (f) Shen, H.; Yang, K.-F.; Shi, Z.-H.; Jiang, J.-X.; Lai, G.-Q.; Xu, L.-W. *Eur. J. Org. Chem.* **2011**, 5031−5038. (g) Xu, D.-Q.; Wang, Y.-F.; Luo, S.-P.; Zhang, S.; Zhong, A.-G.; Chen, H.; Xu, Z.-Y. *Adv. Synth. Catal.* **2008**, *350*, 2610−2616.

(9) (a) Luca, L. D.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2002**, *4*, 553−555. (b) Blotny, G. *Tetrahedron Lett.* **2003**, *44*, 1499−1501.

(10) Giacomelli, G.; Porcheddu, A.; Salaris, M. *Org. Lett.* **2003**, *5*, 2715−2717.

(11) Sharma, A.; Singh, M.; Rai, N. N.; Sawant, D. *Beilstein J. Org. Chem.* **2013**, *9*, 1235−1242.
(12) Chaudhuri, S. K.; Pramanik, A.; Roy, R.; Khan, S.; Ghatak, A.; Bhar, S. *J. Ind. Chem. Soc.* **2013**, *90*, 1773−1780.
(13) Baigrie, L. M.; Cox, R. A.; Slebocka-Tilk, H.; Tencer, M.; Tidwell, T. T. *J. Am. Chem. Soc.* **1985**, *107*, 3640−3645.
(14) Patro, B.; Deb, B.; Ila, H.; Junjappa, H. *J. Org. Chem.* **1992**, *57*, 2257−2263.
(15) (a) Aruna Verma, K. M.; Wadhawa, S. K. *Curr. Sci.* **1981**, *50*, 223−225. (b) Larson, G. L.; Prieto, J. A.; Valle, L. *Synth. Commum.* **1989**, *19*, 1405−1412. (c) Troyanov, S. I.; Popov, A. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 4215−4218. (d) Kitagawa, T.; Lee, Y.; Masaoka, N.; Komatsu, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1398−1401.
(16) Biernacki, W.; Gadula, A. *Polym. J. Chem.* **1981**, *55*, 849−854.
(17) Jung, M. E.; Fahr, B. T.; D'Amic, D. C. *J. Org. Chem.* **1998**, *63*, 2982−2987.
(18) CCDC 990712 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).
(19) Gaoni, Y.; Mechoulam, R. *J. Am. Chem. Soc.* **1964**, *86*, 1646−1647.
(20) (a) Sarfaraz, S.; Adhami, V. M.; Syed, D. N.; Afaq, F.; Mukhtar, H. *Cancer Res.* **2008**, *68*, 339−342. (b) Ware, M. A.; Daeninck, P.; Maida, V. *Ther. Clin. Risk Manage.* **2008**, *4*, 99−107. (c) Pertwee, R. G. *Mol. Neurobiol.* **2007**, *36*, 45−59. (d) Mackie, K. *Annu. Rev. Pharmacol. Toxicol.* **2006**, *46*, 101−122.
(21) (a) Müller-Vahl, K. R.; Schneider, U.; Koblenz, A.; Jöbges, M.; Kolbe, H.; Daldrup, T.; Emrich, H. M. *Pharmacopsychiatry* **2002**, *35*, 57−61. (b) Müller-Vahl, K. R.; Prevedel, H.; Theloe, K.; Kolbe, H.; Emrich, H. M.; Schneider, U. *Neuropsychopharmacology* **2003**, *28*, 384−388.
(22) Matsuda, L. A.; Lolait, S. J.; Brownstein, M. J.; Young, A. C.; Bonner, T. I. *Nature* **1990**, *346*, 561−564.
(23) Munro, S.; Thomas, K. L.; Abu-Shaar, M. *Nature* **1993**, *365*, 61−65.
(24) (a) Shen, Z.; Ni, Z.; Mo, S.; Wang, J.; Zhu, Y. *Chem.—Eur. J.* **2012**, *18*, 4859−4865. (b) He, Y.; Zhang, X.; Cui, L.; Wang, J.; Fan, X. *Green Chem.* **2012**, *14*, 3429−3435. (c) Minuti, L.; Ballerini, E. *J. Org. Chem.* **2011**, *76*, 5392−5403.
(25) (a) Stocking, E. M.; Williams, R. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078−3115. (b) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassili-kogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668−1698. (c) Reymond, S.; Cossy, J. *Chem. Rev.* **2008**, *108*, 5359−5406. (d) Orellana, A.; Pandey, S. K.; Carret, S.; Greene, A. E.; Poisson, J.-F. *J. Org. Chem.* **2012**, *77*, 5286−5296. (e) Fujiwara, K.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2012**, *134*, 5512−5515. (f) Mergott, D. J.; Zuend, S. J.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 745−748. (g) Takao, K.-I.; Munakata, R.; Tadano, K.-I. *Chem. Rev.* **2005**, *105*, 4779−4807. (h) Sanap, K. K.; Samant, S. D. *Synlett* **2012**, *23*, 2189−2194. (i) Petronijevic, F. R.; Wipf, P. *J. Am. Chem. Soc.* **2011**, *133*, 7704−7707. (j) Boonsompat, J.; Padwa, A. *J. Org. Chem.* **2011**, *76*, 2753−2761. (k) Takao, K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, *105*, 4779−4807. (l) Zhao, C. G.; Zheng, H. J.; Jing, P.; Fang, B. W.; Xie, X. G.; She, X. G. *Org. Lett.* **2012**, *14*, 2293−2295. (m) Jiang, X.; Wang, L.; Kai, M.; Zhu, L.; Yao, X.; Wang, R. *Chem.—Eur. J.* **2012**, *18*, 11465−11473.
(26) (a) Mosmann, T. *J. Immunol. Methods* **1983**, *65*, 55−63. (b) Miri, R.; Motamedi, R.; Rezaei, M. R.; Firuzi, O.; Javidnia, A.; Shafiee, A. *Arch. Pharm.* **2011**, *344*, 111−118.
(27) *SMART, SAINT, SADABS, XPREP, SHELXTL*; Bruker AXS Inc.: Madison, WI, 1998.
(28) Sheldrick, G. M. *SHELXS-97, Program for Solution of Crystal Structures*; University of Gottingen: Gottingen, Germany, 1997.
(29) Sheldrick, G. M. *SHELXL-97, Program for Refinement of Crystal Structures*; University of Gottingen: Gottingen, Germany, 1997.
(30) *PLATON for Windows*, v. 1.15; Spek, A. L. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **1990**, *46*, C34.