Carbanion-Induced Base-Catalyzed Synthesis of 1*H*-Isothiochromenes, Benzo[*c*]thiochromenes, Benzo[*c*]chromenes, and 1-Benzothiophenes through Ring-Transformation Reactions of 6-Aryl-2*H*-pyran-2-ones†

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An innovative approach to the one-pot synthesis of highly functionalized 3,4-dihydro-1*H*-isothiochromenes (**3**), 6*H*-benzo[*c*]thiochromenes (**5**, **6**), 6*H*-benzo[*c*]chromenes (**8**), and 2,3-dihydro-1-benzothiophenes (**10**, **11**) is delineated from the reaction of a suitably functionalized 6-aryl-3-carbomethoxy-4-methylthio-2*H*-pyran-2-one (**1**) and a carbanion generated from tetrahydrothiopyran-4-one, 4-thiochromanone, 4-chromanone, and tetrahydrothiophene-3-one through ring-transformation reactions.

Introduction

The need of an efficient and convenient route for the construction of an annulated heteroaryl system of therapeutic importance is greatly realized in natural product synthesis. Such unsymmetrical biaryls with electron-acceptor and electron-donor substituents are recognized as molecular subunits for expression of nonlinear optical properties, which require high polarizability in the molecules constituting the material.[1] These compounds not only exhibit optical properties but also display diverse pharmacological activities.[2−6]

Though numerous procedures are known for the synthesis of complex biaryls, many of them suffer from harshness or functional-group intolerance of the condition required. Among various reported procedures,[7] palladium-catalyzed coupling of aryl halides with phenols has been found to be mild, highly selective, and easy in workup.[8,9] Various benzothiopyran derivatives have been synthesized either from the reaction of benzylmercaptans and haloacetic acid followed by Friedel−Crafts cyclization[10−12] or by reacting homoxylylene dibromide with potassium sulfide.[13] These compounds have also been prepared[14] by photocycloaddition of thiobenzophenone with propiolic acid. An improved synthesis of 2-benzoyl derivatives of 3,4-dihydro-1*H*-isothiochromenes is also reported by Pummerer cyclization[15] with trifluoroacetic acid.

A survey of the literature revealed that the synthesis of 6*H*-benzo[*c*]thiochromenes has not been explored extensively. Earlier, compounds of this ring system were prepared via Pschorr cyclization[2] and Pummerer rearrangement. Later on, these compounds were synthesized[16] from the reaction of Grignard reagents with 2*H*-1-benzothiopyran-2-one. Further, these compounds were prepared[17] either photochemically from diverse phenoxybenzyl alcohols or from the reaction[18] of 4-substituted bis-(3-alkoxybenzoyl)peroxide and phenol. Anion-accelerated, palladium-catalyzed intermolecular coupling of phenols with aryl halide is one of the mild procedures[10] that yield benzo[*c*]chromenes[19] in high yield. Recently, these were prepared[3] by starting from 3-hydroxy-4-methoxybenzaldehyde after a sequence of reactions.

2,3-Dihydro-1-benzothiophenes were synthesized[20] by ring contraction of *cis*-3-bromo-7-chloro-3,4-dihydro-2*H*-benzothiopyran-4-ol in the presence of imidazole. The reductive ring opening of the **6a** and **11a** dihydro-6*H*-benzothieno[3,2-*c*]benzopyrans[21] with $LiAlH_4$ also yielded 2-aryl-2,3-dihydrobenzo[*b*]thiophene derivatives (**6**).

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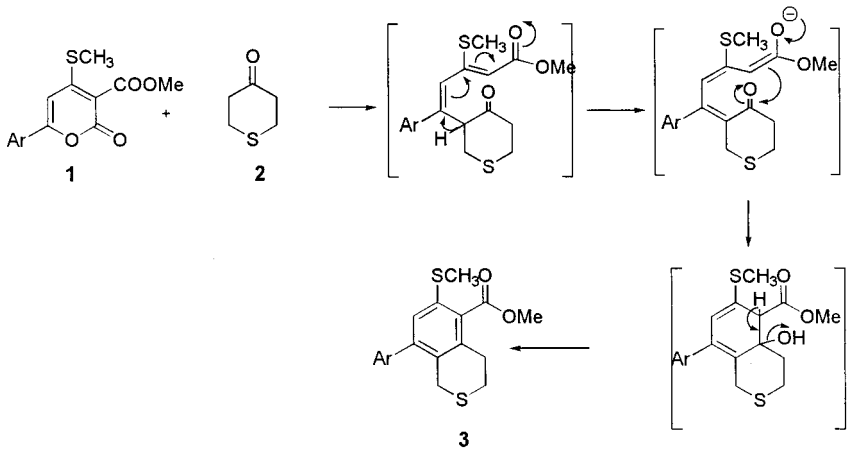
Scheme 1



3	Ar	Yield (%)
a	C_6H_5	70
b	4-FC_6H_4	73
c	4-ClC_6H_4	71
d	4-BrC_6H_4	65
e	1-Naphthyl	68
f	2-Naphthyl	50
g	2-Thienyl	60

Our approach to the synthesis of a functionalized aryl-heteroaryl system is entirely different and is based on base-catalyzed ring-transformation reactions of 6-aryl-3-carbomethoxy-4-methylthio-2*H*-pyran-2-one **1** using aryl- and heteroaryl methyl ketones as a source of carbanions. The precursor **1** was prepared from the base-catalyzed reaction of methyl 2-cyano-3,3-dimethylthioacrylate and aryl methyl ketone as described earlier.[22]

The topography of pyran-2-ones **1** may be considered as being a cyclic ketenemethylthiohemiacetal with three electrophilic positions (2, 4, and 6) in which the latter is highly susceptible to nucleophiles due to extended conjugation and the presence of an electron-withdrawing carbomethoxy substituent at position 3 of the pyran ring. Thus, carbanions generated in situ from heterocyclic ketones **2**, **4**, **7**, and **9** attack at position 6 by alkali in DMF with ring opening and decarboxylation, followed by condensation-cyclization involving the keto functionality and position 3 of the pyran ring with elimination of water, afford various heterocycles such as **3**, **5**, **6**, **8**, **10**, and **11**. This is a one-pot reaction in which an equimolar mixture of pyran-2-one **1**, a heterocyclic ketone, and powdered KOH in DMF was stirred at ambient temperature for 15−20 h. After the reaction mixture was poured into ice/water, the solution was neutralized with 10% HCl. The precipitate thusly obtained was filtered and purified by column chromatography as unsymmetrical biaryl in which one-half is an annulated heteroaryl and the other half is a substituted aryl group. To our observations, the quantity of alkali and the ring size of ketones influence the course of the reaction. A reaction of **1** and tetrahydrothiopyran-4-one (**2**) regioselectively yielded 3,4-dihydro-1*H*-isothiochromenes (**3**) even using >2 equiv of KOH (Scheme 1). However, a cyclocondensation of **1** with thiochroman-4-one (**4**) using 1 equiv of powdered KOH provided the expected methyl 7-aryl-9-(methylsulfanyl)-6*H*-benzo[*c*]thiochromene-10-carboxyl-ate (**5**); while the use of 2 equiv of the base unexpectedly yielded a hydroxylated product, the production of methyl 7-aryl-9-hydroxy-6*H*-benzo[*c*]thiochromene-10-carboxyl-ate (**6**) through Michael addition is favored in the presence of an excess of alkali (Scheme 2). It was conspicuous that reaction of **1** and chroman-4-one (**7**), using either 1 or 2 equiv of KOH, exclusively yielded a hydroxylated product, methyl 7-aryl-9-hydroxy-6*H*-benzo[*c*]chromene-10-carboxylate (**8**). In this reaction also, Michael addition of the hydroxyl ion is preferred over a cyclocondensation process that is hindered due to the steric effect of benzo-fused ketones, **4** and **7** (Scheme 3). A reaction of **1** with tetrahydrothiophene-3-one (**9**), using 1 equiv of KOH as a base, yielded methyl 7-aryl-5-(methylsulfanyl)-2,3-dihydro-1-benzothiophene-4-carboxylate (**10**), while in the presence of 2 mol of base, 7-aryl-5-(methylsulfanyl)-2,3-dihydro-1-benzothiophene-4-carboxylic acid (**11**) was isolated (Scheme 4). In this reaction, more than 1 equiv of alkali hydrolyzes the ester to an acid without any formation of the hydroxylated product. On the contrary, under similar reaction conditions, no ester hydrolysis was observed when ketones **2**, **4**, and **7** were used as a source of carbanions.

These reactions are superior in many ways to the existing procedures for the construction of various heterocyclic systems with respect to their (a) versatility and compatibility, (b) mild reaction condition, (c) use of inexpensive reagents, (d) moderate-to-high yield and easy workup, and (e) easy access to the synthesis of a biaryl system in which one of the aromatic halves is an annulated sulfur or oxygen heterocycle.

In a nut shell, this is an innovative one-pot synthesis of 3,4-dihydro-1*H*-isothiochromenes (**3**), 6*H*-benzo[*c*]thiochromenes (**5**, **6**), 6*H*-benzo[*c*]chromenes (**8**), and 1-benzthiophene derivatives (**10**, **11**). Our procedure provides

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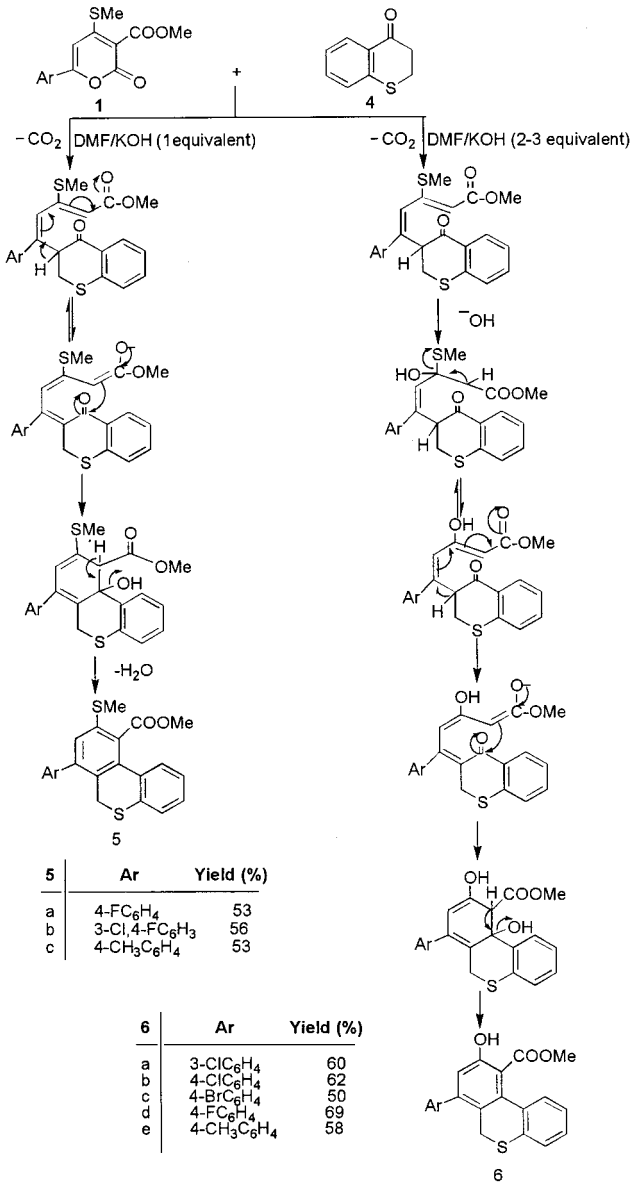
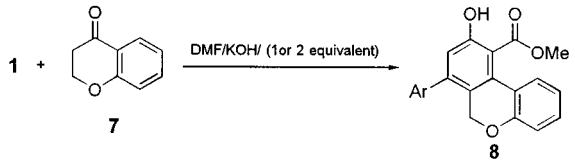
Scheme 2



5	Ar	Yield (%)
a	4-FC_6H_4	53
b	3-Cl,4-FC_6H_3	56
c	4-$CH_3C_6H_4$	53

6	Ar	Yield (%)
a	3-ClC_6H_4	60
b	4-ClC_6H_4	62
c	4-BrC_6H_4	50
d	4-FC_6H_4	69
e	4-$CH_3C_6H_4$	58

Scheme 3



8	Ar	Yield (%)
a	C_6H_5	60
b	4-FC_6H_4	58
c	3-Cl,4-FC_6H_3	57
d	3-ClC_6H_4	48
e	4-ClC_6H_4	56
f	4-BrC_6H_4	59
g	3-Pyridyl	78
h	2-Thienyl	51

a new avenue for introducing functionality into the molecule at a specific position.

Experimental Section

Melting points are uncorrected. The reagent-grade reaction solvent DMF was further purified and dried following literature procedures. Both cyclic ketones were purchased from Aldrich. TLC was performed on precoated silica gel plastic plates and visualized by UV irradiation, exposure to iodine vapors, or spraying with $KMnO_4$ solution. IR spectra of liquid samples were run neat and with KBr pellets as solids. ^{1}H NMR spectra were recorded at 200 MHz in $CDCl_3$ with tetramethylsilane as the internal reference. Chemical shifts and coupling constants (J) were reported in δ (ppm) and Hz, respectively. Mass spectra were collected at 70 eV by electron impact. Elemental analyses (C, H, and N) were performed at RSIC, Central Drug Research Institute, Lucknow 226001, India.

Synthesis of Methyl 8-Aryl-3,4-dihydro-6-methylsulfanyl-1*H*-isothiochromene-5-carboxylate (3a−g): General Procedure. A mixture of 6-aryl-3-carbomethoxy-4-methylthio-2*H*-pyran-2-one **1** (1 mmol), tetrahydro-thiopyran-4-one **2** (1 mmol), and KOH (1 mmol) in dry DMF (12 mL) was stirred at room temperature for 15 h. After completion, the reaction mixture was poured into ice water and neutralized with 10% HCl. The solid that was obtained was filtered and purified on a silica gel column by eluting with 1:1 $CHCl_3$/hexane.

Methyl 3,4-Dihydro-6-methylsulfanyl-8-phenyl-1*H*-isothiochromene-5-carboxylate (3a). Mp: 113−115 °C. IR (KBr): ν 1726 cm^{-1} (CO). MS m/z: 330 (M^+). ^{1}H NMR: 2.45 (s, 3H, SCH_3), 2.80 (m, 4H, $2CH_2$), 3.59 (s, 2H, CH_2), 3.97 (s, 3H, OCH_3), 7.19 (s, 1H, ArH), 7.28 (m, 3H, ArH), 7.40−7.49 (m, 2H, ArH). Anal. Calcd for $C_{18}H_{18}O_2S_2$: C, 65.42; H, 5.49. Found: C, 65.34; H, 5.35.

Methyl 3,4-Dihydro- 8-(4-fluorophenyl)-6-methylsulfanyl-1*H*-isothiochromene-5-carboxylate (3b). Mp: 114−115 °C. IR (KBr): ν 1732 cm^{-1} (CO). MS m/z: 348 (M^+, 100). ^{1}H NMR: 2.45 (s, 3H, SCH_3), 2.88−2.98 (m, 4H, $2CH_2$), 3.54 (s, 2H, CH_2), 3.97 (s, 3H, OCH_3), 6.98−7.36 (m, 5H, ArH). Anal. Calcd for $C_{18}H_{17}FO_2S_2$: C, 62.04; H, 4.92. Found: C, 62.32; H, 4.79.

Methyl 8-(4-Chlorophenyl)-3,4-dihydro-6-methylsulfanyl-1*H*-isothiochromene-5-carboxylate (3c). Mp: 109−110 °C. IR (KBr): ν 1733 cm^{-1} (CO). MS m/z: 364 (M^+). ^{1}H NMR: 2.45 (s, 3H, SCH_3), 2.80−3.00 (m, 4H, $2CH_2$), 3.55 (s, 2H, CH_2), 3.97 (s, 3H, OCH_3), 7.14 (s, 1H, ArH), 7.21−7.25 (d, 2H, J = 8.0 Hz, ArH), 7.40−7.44 (d, 2H, J = 8.0 Hz, ArH). Anal. Calcd for $C_{18}H_{17}ClO_2S_2$: C, 59.25; H, 4.69. Found: C, 59.06; H, 4.38.

Methyl 8-(4-Bromophenyl)-3,4-dihydro-6-methylsulfanyl-1*H*-isothiochromene-5-carboxylate (3d). Mp: 114−115 °C. IR (KBr): ν 1719 cm^{-1} (CO). MS m/z: 410 (M^+), 409(100), 408. ^{1}H NMR: 2.45 (s, 3H, SCH_3), 2.88−2.97 (m, 4H, $2CH_2$), 3.55 (s, 2H, CH_2), 3.96 (s, 3H, OCH_3), 7.09 (s, 1H, ArH), 7.17−7.19 (d, 2H, J = 8.0 Hz, ArH), 7.57 (d, 2H, J = 8.0 Hz, ArH). Anal. Calcd for $C_{18}H_{17}BrO_2S_2$: C, 52.80; H, 4.18. Found: C, 52.63; H, 4.13.

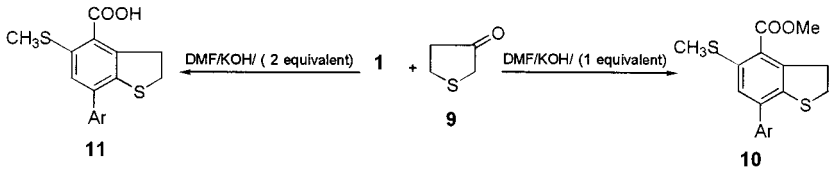
Methyl 3,4-Dihydro-6-methylsulfanyl-8-(1-naphthyl)-1*H*-isothiochromene-5-carboxylate (3e). The product was recovered as a semisolid. IR (neat): ν 1714 cm^{-1} (CO). MS m/z: 380 (M^+). ^{1}H NMR: 2.50 (s, 3H, SCH_3), 2.85−2.97 (m, 4H, $2CH_2$), 3.63 (s, 2H, CH_2), 3.98 (s, 3H, OCH_3), 7.20 (s, 1H, ArH), 7.51−7.57 (m, 4H, ArH), 7.89−7.93 (m, 3H, ArH). Anal. Calcd for $C_{22}H_{20}O_2S_2$: C, 69.43; H, 5.29. Found: C, 69.20; H, 5.25.

Methyl 3,4-Dihydro-6-methylsulfanyl-8-(2-naphthyl)-1*H*-isothiochromene-5-carboxylate (3f). The product was recovered as an oil. IR (neat): ν 1726 cm^{-1} (CO). MS m/z: 380 (M^+). ^{1}H NMR: 2.47 (s, 3H, SCH_3), 2.86−3.03 (m, 4H, $2CH_2$), 3.88 (s, 2H, CH_2), 3.98 (s, 3H, OCH_3), 7.28 (s, 1H, ArH), 7.51−7.56 (m, 3H, ArH), 7.76 (m, 1H, ArH), 7.85−7.93 (m, 3H, ArH). Anal. Calcd for $C_{22}H_{20}O_2S_2$: C, 69.43; H, 5.29. Found: C, 69.23; H, 5.35.

Methyl 3,4-Dihydro-6-methylsulfanyl-8-(2-thienyl)-1*H*-isothiochromene-5-carboxylate (3g). Mp: 103−105 °C. IR (KBr): ν 1718 cm^{-1} (CO). MS m/z: 336 (M^+). ^{1}H NMR: 2.46 (s, 3H, SCH_3), 2.89−2.97 (m, 4H, $2CH_2$), 3.76 (s, 2H, CH_2), 3.96 (s, 2H, OCH_3), 7.01 (s, 1H, ArH), 7.12 (m, 1H, ArH), 7.39 (d, 1H, J = 7. 3 Hz, ArH), 7.57 (d, 1H, J = 7.2 Hz, ArH). Anal. Calcd for $C_{16}H_{16}O_2S_3$: C, 57.11; H, 4.79. Found: C, 56.95; H, 4.55.

Synthesis of Methyl 7-Aryl-9-methylsulfanyl-6*H*-benzo[*c*]thiochromene-10-carboxylate (5a−c): General Pro-

Scheme 4



11	Ar	Yield (%)
a	4-ClC$_6$H$_4$	60
b	4-BrC$_6$H$_4$	58

10	Ar	Yield (%)
a	C$_6$H$_5$	73
b	4-FC$_6$H$_4$	60
c	3-ClC$_6$H$_4$	58
d	4-ClC$_6$H$_4$	72
e	4-BrC$_6$H$_4$	65
f	4-CH$_3$C$_6$H$_4$	60
g	3-Pyridyl	60
h	2-Thienyl	80

cedure. A mixture of **1** (1 mmol), thiochroman-4-one **4** (1 mmol), and KOH (1 mmol) in dry DMF (12 mL) was stirred at room temperature for 15−20 h, and thereafter the reaction mixture was poured into ice/water and neutralized with 10% HCl. The solid that was obtained was filtered and purified on a silica gel column by eluting with 1:1 $CHCl_3$/hexane.

Methyl 7-(4-Fluorophenyl)-9-methylsulfanyl-6*H*-benzo[*c*]thiochromene-10-carboxylate (5a). Mp: 178−180 °C. IR (KBr): ν 1670 cm^{-1} (CO). Ms *m*/*z*: 396 (M$^+$). ^{1}H NMR: 2.45 (s, 3H, SCH_3), 3.44 (s, 2H, CH_2), 3.67 (s, 3H, OCH_3), 7.06 (s, 1H, ArH), 7.20 (m, 8H, ArH). Anal. Calcd for $C_{22}H_{17}FO_2S_2$: C, 66.64; H, 4.32. Found: C, 66.91; H, 4.56.

Methyl 7-(3-Chloro-4-fluorophenyl)-9-methylsulfanyl-6*H*-benzo[*c*]thiochromene-10-carboxylate (5b). Mp: 219−220 °C. IR (KBr): ν 1650 cm^{-1} (CO). MS *m*/*z*: 430 (M$^+$). ^{1}H NMR: 2.52 (s, 3H, SCH_3), 3.64 (s, 2H, CH_2), 3.69 (s, 3H, OCH_3), 7.11 (s, 1H, ArH), 7.27 (m, 6H, ArH), 7.85 (s, 1H, ArH). Anal. Calcd for $C_{22}H_{16}ClFO_2S_2$: C, 61.30; H, 3.74. Found: C, 61.49; H, 3.92.

Methyl 7-(4-Methylphenyl)-9-methylsulfanyl-6*H*-benzo[*c*]thiochromene-10-carboxylate (5c). Mp: 168−170 °C. IR (KBr): ν 1650 cm^{-1} (CO). MS *m*/*z*: 392 (M$^+$, 100). ^{1}H NMR: 2.43 (s, 3H, CH_3), 2.47 (s, 3H, SCH_3), 3.67 (s, 2H, CH_2), 8.71 (s, 3H, OCH_3), 7.16 (s, 1H, ArH), 7.23 (m, 6H, ArH), 7.48 (m, 2H, ArH). Anal. Calcd for $C_{22}H_{20}O_2S_2$: C, 70.37; H, 5.14. Found: C, 70.61; H, 5.38.

Synthesis of Methyl 7-Aryl-9-hydroxy-6*H*-benzo[*c*]-thiochromene-10-carboxylate (6a−e): General Procedure. A mixture of **1** (1 mmol), ketone **4** (1 mmol), and powdered KOH (2−3 mmol) in dry DMF (12 mL) was stirred at room temperature for 18 h, and thereafter the reaction mixture was poured into ice/water and acidified with 10% HCl. The precipitate that was obtained was filtered and purified on a silica gel column using 4:1 $CHCl_3$/hexane as the eluent.

Methyl 7-(3-Chlorophenyl)-9-hydroxy-6*H*-benzo[*c*]thiochromene-10-carboxylate (6a). Mp: 149−150 °C. IR (KBr): ν 3392 (OH), 1670 cm^{-1} (CO). MS *m*/*z*: 382 (M$^+$), 307 (100). ^{1}H NMR: 3.58 (s, 2H, CH_2), 3.59 (s, 3H, OCH_3), 6.92 (s, 1H, ArH), 7.30 (8H, ArH), 9.32 (s, 1H, OH). Anal. Calcd for $C_{21}H_{15}ClO_3S$: C, 65.88; H, 3.94. Found: C, 65.58; H, 3.79.

Methyl 7-(4-Chlorophenyl)-9-hydroxy-6*H*-benzo[*c*]thiochromene-10-carboxylate (6b). Mp: 158−160 °C. IR (KBr): ν 3392 (OH), 1650 cm^{-1} (CO). MS *m*/*z*: 382 (M$^+$, 100), 351 (85). ^{1}H NMR: 3.58 (s, 2H, CH_2), 3.59 (s, 3H, OCH_3), 6.91 (s, 1H, ArH), 7.22 (m, 5H, ArH), 7.48 (m, 3H, ArH), 9.42 (s, 1H, OH). Anal. Calcd for $C_{21}H_{15}ClO_3S$: C, 65.88; H, 3.94. Found: C, 65.67; H, 3.73.

Methyl 7-(4-Bromophenyl)-9-hydroxy-6*H*-benzo[*c*]thiochromene-10-carboxylate (6c). Mp: 154−155 °C. IR (KBr): ν 3390 (OH), 1670 cm^{-1} (CO). MS *m*/*z*: 428 (M$^+$), 426, 154 (100). ^{1}H NMR: 3.58 (s, 2H, CH_2), 3.65 (s, 3H, OCH_3), 7.18 (s, 1H, ArH), 7.23 (m, 6H, ArH), 7.63 (d, 2H, J = 8.3 Hz, ArH). Anal. Calcd for $C_{21}H_{15}BrO_3S$: C, 59.01; H, 3.53. Found: C, 59.32; H, 3.59.

Methyl 7-(4-Fluorophenyl)-9-hydroxy-6*H*-benzo[*c*]thiochromene-10-carboxylate (6d). Mp: 208−210 °C. IR (KBr): ν 3380 (OH), 1651 cm^{-1} (CO). MS *m*/*z*: 366 (M$^+$, 100). ^{1}H NMR: 3.56 (s, 2H, CH_2), 3.74 (s, 3H, OCH_3), 7.09 (s, 1H, ArH), 7.20 (m, 8H, ArH). Anal. Calcd for $C_{21}H_{15}FO_3S$: C, 68.84; H, 4.12. Found: C, 69.10; H, 4.32.

Methyl 7-(4-Methylphenyl)-9-hydroxy-6*H*-benzo[*c*]thiochromene-10-carboxylate (6e). The product was recovered as an oil. IR (neat): ν 3392 (OH), 1681 cm^{-1} (CO). MS *m*/*z*: 362 (M$^+$). ^{1}H NMR: 2.33 (s, 3H, CH_3), 3.53 (s, 2H, CH_2), 3.67 (s, 3H, OCH_3), 6.96 (s, 1H, ArH), 7.20 (m, 8H, ArH). Anal. Calcd for $C_{22}H_{18}O_3S$: C, 72.91; H, 5.00. Found: C, 72.71; H, 4.78.

Synthesis of Methyl 7-Aryl-9-hydroxy-6*H*-benzo[*c*]-chromene-10-carboxylate (8a−g): General Procedure. A mixture of **1** (1 mmol), ketone **7** (1 mmol), and powdered KOH (1 mmol) in dry DMF (15 mL) was stirred at ambient temperature for 20 h and then poured into ice/water while the solution was stirring. The solution was acidified with 10% HCl, and the solid that was obtained was filtered and purified on a silica gel column using 4:1 $CHCl_3$/hexane as the eluent.

Methyl 9-Hydroxy-7-phenyl-6*H*-benzo[*c*]chromene-10-carboxylate (8a). Mp: 109−110 °C. IR (KBr): ν 3398 (OH), 1647 cm^{-1} (CO). MS *m*/*z*: 332 (M$^+$, 100). ^{1}H NMR: 3.69 (s, 3H, OCH_3), 4.99 (s, 2H, CH_2), 6.89 (s, 1H, ArH), 7.03 (m, 2H, ArH), 7.28 (m, 2H, ArH), 7.41 (m, 5H, ArH). Anal. Calcd for $C_{21}H_{16}O_4$: C, 75.89; H, 4.85. Found: C, 76.39; H, 5.15.

Methyl 7-(4-Fluorophenyl)-9-hydroxy-6*H*-benzo[*c*]chromene-10-carboxylate (8b). Mp: 174−175 °C. IR (KBr): ν 3390 (OH), 1637 cm^{-1} (CO). MS *m*/*z*: 350 (M$^+$). ^{1}H NMR: 3.75 (s, 3H, OCH_3), 4.83 (s, 2H, CH_2), 6.90 (s, 1H, ArH), 7.19 (m, 8H, ArH), 9.39 (s, 1H, OH). Anal. Calcd for $C_{21}H_{15}FO_4$: C, 71.99; H, 4.32. Found: C, 72.28; H, 4.39.

Methyl 7-(3-Chloro-4-flurophenyl)-9-hydroxy-6*H*-benzo[*c*]chromene-10-carboxylate (8c). Mp: 159−160 °C. IR (KBr): ν 3425 (OH), 1662 cm^{-1} (CO). MS *m*/*z*: 384 (M$^+$). ^{1}H NMR: 3.75 (s, 3H, OCH_3), 4.82 (s, 2H, CH_2), 6.88 (s, 1H, ArH), 7.33 (m, 7H, ArH), 9.42 (s, 1H, OH). Anal. Calcd for $C_{21}H_{14}FClO_4$: C, 65.54; H, 3.67. Found: C, 65.74; H, 3.92.

Methyl 7-(3-Chlorophenyl)-9-hydroxy-6*H*-benzo[*c*]chromene-10-carboxylate (8d). Mp: 168−170°. IR (KBr): ν 3398 (OH), 1691 cm^{-1} (CO). MS *m*/*z*: 366 (M$^+$), 154 (100). ^{1}H NMR: 3.79 (s, 3H, OCH_3), 4.90 (s, 2H, CH_2), 6.88 (s, 1H, ArH), 7.03 (d, 2H, J = 8.4 Hz, ArH), 7.14 (m, 2H, ArH), 7.24 (d, 2H, J = 8.3 Hz, ArH), 7.56 (m, 2H, ArH), 9.36 (s, 1H, OH). Anal. Calcd for $C_{21}H_{15}ClO_4$: C, 68.73; H, 4.12. Found: C, 68.65; H, 4.23.

Methyl 7-(4-Chlorophenyl)-9-hydroxy-6*H*-benzo[*c*]chromene-10-carboxylate (8e). Mp: 179−180 °C. IR (KBr): ν 3413 (OH), 1664 cm^{-1} (CO). MS *m*/*z*: 366 (M$^+$), 154 (100). ^{1}H NMR: 3.74 (s, 3H, OCH_3), 4.83 (s, 2H, CH_2), 6.89 (s, 1H, ArH), 7.03 (m, 2H, ArH), 7.22 (m, 4H, ArH), 7.43 (d, 2H, J = 8.2 Hz, ArH). Anal. Calcd for $C_{21}H_{15}ClO_4$: C, 68.76; H, 4.12. Found: C, 68.55; H, 4.00.

Methyl 7-(Bromophenyl)-9-hydroxy-6*H*-benzo[*c*]chromene-10-carboxylate (8f). Mp: 178−180 °C. IR (KBr): ν 3410

(OH), 1664 cm^{-1} (CO). MS *m/z*: 412 (M^+), 410, 307 (100). ^1H NMR: 3.74 (s, 3H, OCH_3), 4.82 (s, 2H, CH_2), 6.88 (s, 1H, ArH), 7.31 (m, 6H, ArH), 7.58 (d, 2H, $J = 8.4$ Hz, ArH), 9.37 (s, 1H, OH). Anal. Calcd for $C_{21}H_{15}BrO_4$: C, 61.32; H, 3.68. Found: C, 61.71; H, 3.97.

Methyl 9-Hydroxy-7-(3-pyridyl)-6*H*-benzo[*c*]chromene-10-carboxylate (8g). Mp: 218−220 °C. IR (KBr): ν 3390 (OH), 1647 cm^{-1} (CO). MS *m/z*: 333 (M^+), 307 (100). ^1H NMR: 3.84 (s, 3H, OCH_3), 4.85 (s, 2H, CH_2), 6.81 (s, 1H, ArH), 7.04 (m, 2H, ArH), 7.24 (m, 2H, ArH), 7.40 (d, 1H, $J = 7.0$ Hz, PyH), 7.64 (m, 1H, PyH), 8.56 (s, 1H, PyH), 8.66 (d, 1H, $J = 7.0$ Hz, PyH), 9.66 (s, 1H, OH). Anal. Calcd for $C_{20}H_{15}O_4N$: C, 72.06; H, 4.54; N, 4.20. Found: C, 72.43; H, 4.72; N, 4.50.

Methyl 9-Hydroxy-7-(2-thienyl)-6*H*-benzo[*c*]chromene-10-carboxylate (8h). Mp: 178−180 °C. IR (KBr): ν 3419 (OH), 1647 cm^{-1} (CO). MS *m/z*: 338 (M^+), 307 (100). ^1H NMR: 3.83 (s, 3H, OCH_3), 5.05 (s, 2H, CH_2), 6.90 (s, 1H, ArH), 7.18 (m, 7H, ArH), 9.39 (s, 1H, OH). Anal. Calcd for $C_{19}H_{14}O_4S$: C, 67.44; H, 4.17. Found: C, 67.73; H, 4.18.

Synthesis of Methyl 7-Aryl-2,3-dihydro-5-methylsulfanyl-1-benzothiophene-4-carboxylate (10a−h): General Procedure. A mixture of **1** (1 mmol), tetrahydrothiophene-3-one **9** (1 mmol), and KOH (1 mmol) in dry DMF (15 mL) was stirred at room temperature for 20 h. The reaction mixture was poured into ice/water and acidified with 10% HCl with stirring. The solid that was obtained was filtered and purified on a silica gel column by eluting with 1:1 $CHCl_3$/hexane.

Methyl 2,3-Dihydro-5-methylsulfanyl-7-phenyl-1-benzothiophene-4-carboxylate (10a). Mp: 104−105 °C. IR (KBr): ν 1641 cm^{-1} (CO). MS *m/z*: 316 (M^+). ^1H NMR: 2.45 (s, 3H, SCH_3), 3.31−3.48 (m, 4H, $2CH_2$), 3.95 (s, 3H, OCH_3), 7.17 (s, 1H, ArH), 7.46 (m, 5H, ArH). Anal. Calcd for $C_{17}H_{16}O_2S_2$: C, 64.53; H, 5.10. Found: C, 64.37; H, 5.04.

Methyl 2,3-Dihydro-7-(4-flurophenyl)-5-methylsulfanyl-1-benzothiophene-4-carboxylate (10b). Mp: 114−115 °C. IR (KBr): ν 1645 cm^{-1} (CO). MS *m/z*: 334 (M^+). ^1H NMR: 2.46 (s, 3H, SCH_3), 3.31−3.46 (m, 4H, $2CH_2$), 3.95 (s, 3H, OCH_3), 7.09 (s, 1H, ArH), 7.16 (m, 2H, ArH), 7.30 (m, 2H, ArH). Anal. Calcd for $C_{17}H_{15}FO_2S_2$: C, 61.05; H, 4.52. Found: C, 61.33; H, 4.81.

Methyl 7-(3-Chlorophenyl)-2,3-dihydro-5-methylsulfanyl-1-benzothiophene-4-carboxylate (10c). Mp: 104−105 °C. IR (KBr): ν 1641 cm^{-1} (CO). MS *m/z*: 350 (M^+). ^1H NMR: 2.46 (s, 3H, SCH_3), 3.31−3.43 (m, 4H, $2CH_2$), 3.95 (s, 3H, OCH_3), 7.13 (s, 1H, ArH), 7.38 (m, 3H, ArH), 7.49 (s, 1H, ArH). Anal. Calcd for $C_{17}H_{15}ClO_2S_2$: C, 58.18; H, 4.30. Found: C, 58.10; H, 4.18.

Methyl 7-(4-Chlorophenyl)-2,3-dihydro-5-methylsulfanyl-1-benzothiophene-4-carboxylate (10d). Mp: 118−120 °C. IR (KBr): ν 1641 cm^{-1} (CO). MS *m/z*: 350 (M^+, 100). ^1H NMR: 2.45 (s, 3H, SCH_3), 3.28−3.45 (m, 4H, $2CH_2$), 3.94 (s, 3H, OCH_3), 7.16 (s, 1H, ArH), 7.46 (m, 4H, ArH). Anal. Calcd for $C_{17}H_{15}ClO_2S_2$: C, 58.18; H, 4.30. Found: C, 58.15; H, 4.10.

Methyl 7-(4-Bromophenyl)-2,3-dihydro-5-methylsulfanyl-1-benzothiophene-4-carboxylate (10e). Mp: 118−120 °C. IR (KBr): ν 1647 cm^{-1} (CO). MS *m/z*: 396 (M^+), 394, 148 (100). ^1H NMR: 2.45 (s, 3H, SCH_3), 3.30−3.43 (m, 4H, $2CH_2$), 3.95 (s, 3H, OCH_3), 7.08 (s, 1H, ArH), 7.38 (d, 2H, $J = 8.0$ Hz, ArH), 7.56 (d, 2H, $J = 8.0$ Hz, ArH). Anal. Calcd for $C_{17}H_{15}BrO_2S_2$: C, 51.64; H, 3.82. Found: C, 51.88; H, 3.91.

Methyl 2,3-Dihydro-7-(4-methylphenyl)-5-methylsulfanyl-1-benzothiophene-4-carboxylate (10f). Mp: 124−125 °C. IR (KBr): ν 1647 cm^{-1} (CO). MS *m/z*: 330 (M^+). ^1H NMR: 2.39 (s, 3H, CH_3), 2.46 (s, 3H, SCH_3), 3.31−3.43 (m, 4H, $2CH_2$), 3.89 (s, 3H, OCH_3), 7.09 (s, 1H, ArH), 7.32 (d, 2H, $J = 8.0$ Hz, ArH), 7.43 (d, 2H, $J = 8.0$ Hz, ArH). Anal. Calcd for $C_{18}H_{18}O_2S_2$: C, 65.42; H, 5.49. Found: C, 65.71; H, 5.53.

Methyl 2,3-Dihydro-5-methylsulfanyl-7-(3-pyridyl)-1-benzothiophene-4-carboxylate (10g). Mp: 109−110 °C. IR (KBr): ν 1647 cm^{-1} (CO). MS *m/z*: 317 (M^+). ^1H NMR: 2.46 (s, 3H, SCH_3), 3.33−3.48 (m, 4H, $2CH_2$), 3.86 (s, 3H, OCH_3), 7.11 (s, 1H, ArH), 7.40 (m, 1H, PyH), 7.88 (d, 1H, $J = 7.2$ Hz, PyH), 8.69 (d, 1H, $J = 7.1$ Hz, PyH), 8.86 (s, 1H, PyH). Anal. Calcd for $C_{16}H_{15}O_2NS_2$: C, 60.54; H, 4.76; N, 4.41. Found: C, 60.59; H, 4.91; N, 4.78.

Methyl 2,3-Dihydro-5-methylsulfanyl-7-(2-thienyl)-1-benzothiophene-4-carboxylate (10h). Mp: 108−110 °C. IR (KBr): ν 1649 cm^{-1}(CO). MS *m/z*: 322 (M^+). ^1H NMR: 2.46 (s, 3H, SCH_3), 3.34−3.41 (m, 4H, CH_2), 3.39 (s, 3H, OCH_3), 7.19 (s, 1H, ArH), 7.36 (m, 3H, ArH). Anal. Calcd for $C_{15}H_{14}O_2S_3$: C, 55.87; H, 4.37. Found: C, 55.75; H, 4.21.

Synthesis of 7-Aryl-2,3-dihydro-5-methylsulfanyl-1-benzothiophene-4-carboxylic Acid (11a−b): General Procedure. A mixture of **1** (1 mmol), tetrahydrothiophene-3-one **9** (1 mmol), and KOH (2−3 mmol) in dry DMF (15 mL) was stirred at room temperature for 18 h. The reaction mixture was poured into ice/water with stirring and acidified with 10% HCl. The solid that was obtained was filtered and purified on a silica gel column using chloroform as the eluent.

7-(4-Chlorophenyl)-2,3-dihydro-5-methylsulfanyl-1-benzothiophene-4-carboxylic Acid (11a). Mp: >260 °C. IR (KBr): ν 3296 (OH), 1677 cm^{-1} (CO). MS *m/z*: 336 (M^+, 100). ^1H NMR: 2.40 (s, 3H, SCH_3), 3.28−3.49 (m, 4H, $2CH_2$), 7.07 (s, 1H, ArH), 7.39 (m, 4H, ArH). Anal. Calcd for $C_{16}H_{13}ClO_2S_2$: C, 57.04; H, 3.88. Found: C, 57.31; H, 4.15.

7-(4-Bromophenyl)-2,3-dihydro-5-methylsulfanyl-1-benzothiophene-4-carboxylic Acid (11b). Mp: 208−210 °C. IR (KBr): ν 1660 cm^{-1} (CO). MS *m/z*: 382 (M^+), 381, 380. ^1H NMR: 2.46 (s, 3H, SCH_3), 3.30−3.56 (m, 4H, $2CH_2$), 7.09 (s, 1H, ArH), 7.39 (d, 2H, $J = 8.2$ Hz, ArH), 7.58 (d, 2H, $J = 8.2$ Hz, ArH). Anal. Calcd for $C_{16}H_{13}BrO_2S_2$: C, 50.38; H, 3.43. Found: C, 50.61; H, 3.71.

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