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ORIGINAL PAPER

Efficient synthesis of methyl 4-chloro-6-fluoro-3-formyl-2*H*-chromene-2-carboxylate and its derivatives

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Abstract Methyl 4-chloro-6-fluoro-3-formyl-2*H*-chromene-2-carboxylate was synthesized conveniently using Vilsmeier reagent. A series of new 2*H*-chromenes was prepared in high yields by introducing a corresponding *β*-halovinylaldehyde into condensation and cyclization reactions with active methylene compounds.

Keywords Chromanes · Chromenes · *β*-Halovinylaldehydes · Hetarylacetonitriles · Condensation

Introduction

Chromanes and 2*H*-chromenes constitute two important classes of oxygen-containing heterocycles which have attracted significant synthetic interest due to their reactivity and biological activity of naturally occurring representatives [1, 2]. Members of these classes, such as sorbinil (**1**) [3] and **2** [4], have demonstrated aldose reductase inhibition properties which can be used in the treatment of complications of diabetes; others such as antioxidants **3** [5] or insulin secretion inhibitors **4** [6] possess the potential to be biological "response modifiers" (Fig. 1). All of these compounds contain the benzopyran moiety, but the limited number of reported compounds prohibits an assessment of how their key functional groups influence inhibitory activity.

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Results and discussion

In this paper, we report our results regarding the synthesis of novel methyl 4-chloro-6-fluoro-3-formyl-2*H*-chromene-2-carboxylate (**6**) from methyl 6-fluoro-4-oxochromane-2-carboxylate (**5**) and studying its reactions with active methylene compounds. It is well known that *β*-halovinylaldehydes have been extensively employed as versatile reactive intermediates in the synthesis of a large variety of aliphatic, aromatic, and heterocyclic compounds [7]. It should be noted that carboxylate **5** and its corresponding carboxylic acid were used as key intermediates in the synthesis of fidarestat, a potent inhibitor of aldose reductase used to treat incurable complications of diabetes [8, 9].

Methyl 6-fluoro-4-oxochromane-2-carboxylate (**5**) [10] reacted with Vilsmeier reagent to afford the corresponding novel *β*-chlorocarboxyaldehyde derivative **6** only (Scheme 1).

Transformation via Vilsmeier's methodology has already been described for other simple benzopyranones, but examples are scarce [11–13]. Literature sources also contain data about the Vilsmeier formylation of 7-methoxy-2,2,-dimethyl-4-chromanones, which were readily converted into 4-chloro-6-formyl-7-methoxy-2,2-dimethyl-2*H*-chromenes with high yields (up to 80%) [14, 15].

Methyl 4-chloro-6-fluoro-3-formyl-2*H*-chromene-2-carboxylate (**6**) was then introduced into the reaction, with malononitrile and hetarylacetonitriles **8a–8i** acting as 1,3-*C,N*-binucleophiles.

In each case, mild conditions were used (heating during 20–30 min in *i*-PrOH or DMF), and products of condensation **7** and **9a–9i** were obtained with good yields (Scheme 2, Table 1). Continuous reflux of product **9a** in DMF for 2 h led to the intramolecular nucleophilic substitution of the chlorine atom and resulted in a heterocyclization product **10** (Scheme 3). Based on the

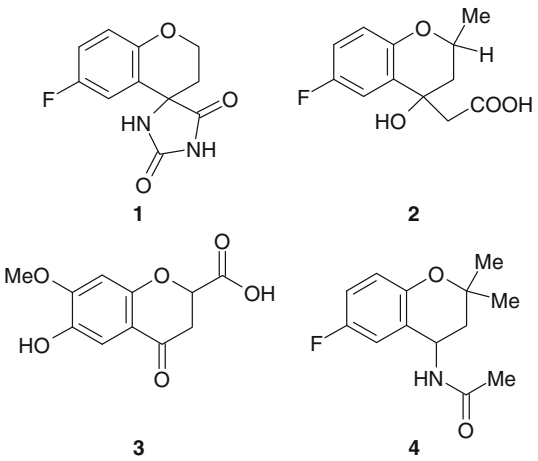
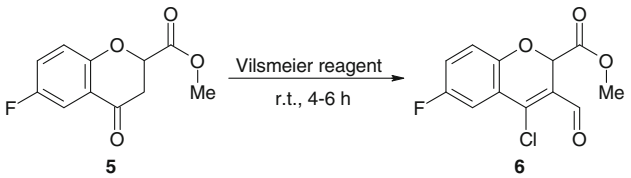
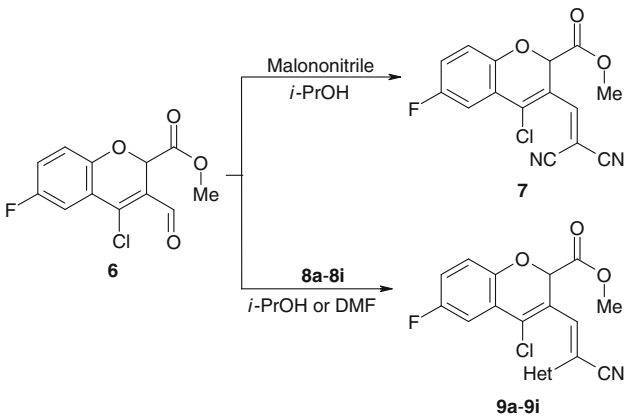


Fig. 1 Biologically active compounds containing the chromane skeleton



Scheme 1



Scheme 2

mild conditions required for the reaction, the *Z*-configuration was assigned to compound **9a**; such heterocyclization reaction would not be so easily possible for an *E*-isomer. The vinyl proton signal in the ^{1}H NMR spectra of **9a–9i** is found at 6.36–6.61 ppm, implying that the configuration is the same for all of these compounds.

The *β*-chlorocarboxyaldehyde derivative **6** also reacted with methyl mercaptoacetate in methanol under reflux in the presence of potassium bicarbonate to give methylthienocarboxylic ester derivative **11** (Scheme 4).

Table 1 Reactions of chloroaldehyde **6** with hetarylacetonitriles **8**

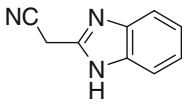
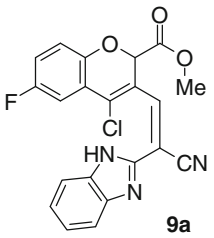
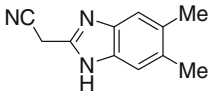
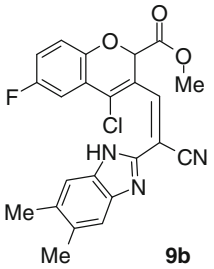
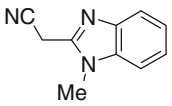
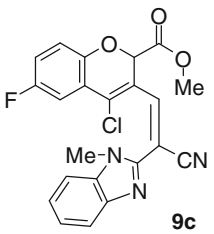
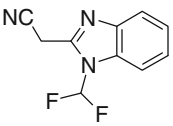
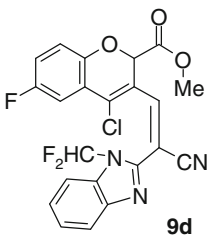
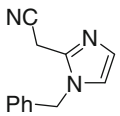
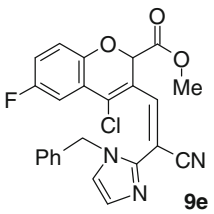
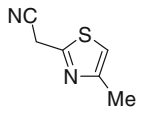
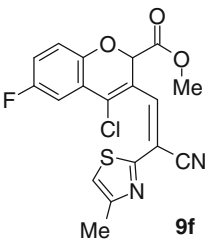
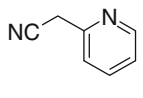
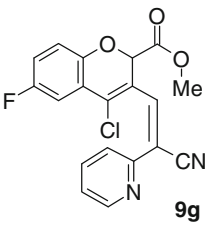
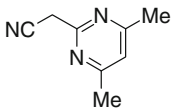
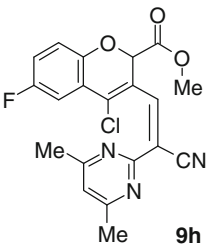
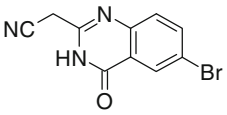
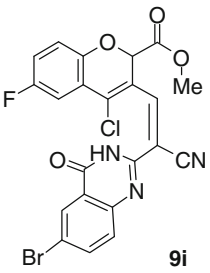
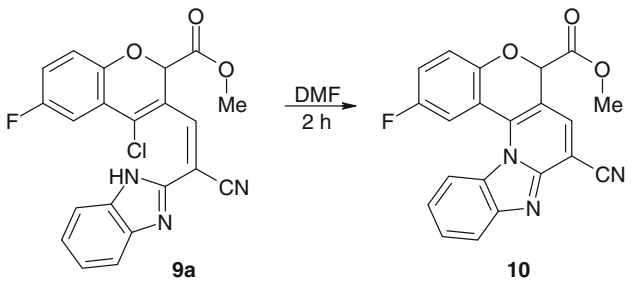
Hetarylacetonitrile **8a–8i**	Product **9a–9i**	Solvent	Time/min
 **8a**	 **9a**	DMF	20
 **8b**	 **9b**	DMF	20
 **8c**	 **9c**	DMF	20
 **8d**	 **9d**	DMF	20
 **8e**	 **9e**	*i*-PrOH	30

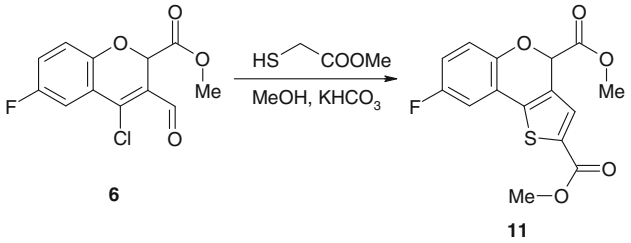
Table 1 continued

Hetarylacetonitrile **8a–8i**	Product **9a–9i**	Solvent	Time/min
 **8f**	 **9f**	*i*-PrOH	30
 **8g**	 **9g**	*i*-PrOH	30
 **8h**	 **9h**	*i*-PrOH	30
 **8i**	 **9i**	DMF	30



9a **10**

Scheme 3



6 **11**

Scheme 4

Conclusions

To summarize, we have developed an efficient synthetic route to novel methyl-4-chloro-6-fluoro-3-formyl-2*H*-chromene-2-carboxylate and have studied its condensation and cyclization reactions with various active methylene compounds. The initial and obtained compounds contain the potentially bioactive 2*H*-chromene skeleton, and a study targeted at learning their biological activity is in progress.

Experimental

Reaction flow and the identity of obtained compounds was controlled by TLC on Merck F_{254} plates using chloroform:methanol (9:1, v/v) as the eluent. Melting points were determined using a Kofler-type Leica Galen III micro hot stage microscope. NMR spectra were recorded on a Mercury-400 spectrometer (spectrometer frequency for ^{1}H: 400 MHz, ^{13}C: 100 MHz) from DMSO-d_6 solutions. The TMS signal was used as an internal standard. Elemental analyses for C, H, and N were conducted using a Perkin-Elmer C, H, N Analyzer; their results were found to be in good agreement (±0.2%) with the calculated values. Mass spectra were recorded on an Agilent 1100 LC/MSD instrument with chemical ionization (CI).

4-Chloro-6-fluoro-3-formyl-2H-chromene-2-carboxylate (**6**, $C_{12}H_8ClFO_4$)

To a mixture of 4.18 g DMF (57 mmol) and 7 g $POCl_3$ (46 mmol) in an ice bath at 0–5 °C, a solution of 6.2 g **5** (28 mmol) in 30 cm^3 CH_2Cl_2 was added dropwise while maintaining the reaction temperature below 20 °C. After addition was completed, the reaction was continued at 50 °C for 2 h and then poured over crushed ice. The aqueous layer was extracted twice with 50 cm^3 CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over sodium sulfate and evaporated under reduced pressure. Purification by recrystallization from MeOH afforded the title compound as an off-white solid (5.8 g, 77%). M.p.: 126–128 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 10.12$ (s, 1H, C*H*O), 7.44 (dd, $^{3}J_{HF} = 8.0$ Hz, $^{4}J_{HH} = 3$ Hz, 1H), 7.30 (td, $^{3}J_{HF} = 8.0$ Hz, $^{4}J_{HH} = 3$ Hz, $^{3}J_{HH} = 8$ Hz,

1H), 7.12 (dd, $^4J_{HF}$ = 4.0 Hz, $^3J_{HH}$ = 8 Hz, 1H), 5.87 (s, 1H), 3.62 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 193.4, 172.6, 155.3, 153.2, 150.1, 137.9, 127.6, 117.4, 115.3, 112.6, 78.4, 54.2 ppm; MS: calcd. for $C_{12}H_8ClFO_4$ 270.64, found 270.64.

*General procedure for the reaction of β-chlorocarboxyaldehyde **6** with nitriles*

To a mixture of 10 cm^3 *i*-PrOH or DMF (see Table 1) and 0.27 g chloroaldehyde **6** (1 mmol), the nitrile (1.2 mmol) was added with stirring. The resulting mixture was refluxed and stirred for 20–30 min and evaporated to dryness. The residue was subjected to appropriate purification.

Methyl 4-chloro-3-(2,2-dicyanovinyl)-6-fluoro-2H-chromene-2-carboxylate (**7**, $C_{15}H_8ClFN_2O_3$)
Obtained from chloroaldehyde **6** in 0.3 g (96%) yield after column chromatography (CH_2Cl_2 as the eluent) as a yellow solid. M.p.: 173–175 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.30 (s, 1H, C*H*C(CN)$_2$), 7.53 (dd, $^3J_{HF}$ = 8.0 Hz, $^4J_{HH}$ = 3 Hz, 1H), 7.46 (td, $^3J_{HF}$ = 8.0 Hz, $^4J_{HH}$ = 3 Hz, $^3J_{HH}$ = 8 Hz, 1H), 7.24 (dd, $^4J_{HF}$ = 4.0 Hz, $^3J_{HH}$ = 8 Hz, 1H), 6.40 (s, 1H), 3.66 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.6, 155.4, 153.4, 153.6, 134.4, 127.6, 127.9, 115.8, 115.4, 113.6 (2C), 112.5, 105.3, 81.5, 52.5 ppm; MS: calcd. for $C_{15}H_8ClFN_2O_3$ 318.69, found 318.69.

Methyl 3-[(Z)-2-(1H-benzimidazol-2-yl)-2-cyanovinyl]-4-chloro-6-fluoro-2H-chromene-2-carboxylate (**9a**, $C_{21}H_{13}ClFN_3O_3$)
Obtained from chloroaldehyde **6** in 0.38 g (95%) yield after column chromatography (CH_2Cl_2 as the eluent) as an orange solid. M.p.: 201–204 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.21 (br s, 1H, N*H*), 8.28 (s, 1H, C*H*C(CN)), 7.65 (dd, $^3J_{HH}$ = 6.4 Hz, $^4J_{HH}$ = 2.8 Hz, 2H), 7.49 (dd, $^3J_{HF}$ = 8.0 Hz, $^4J_{HH}$ = 3 Hz, 1H), 7.37 (td, $^3J_{HF}$ = 8.0 Hz, $^4J_{HH}$ = 3 Hz, $^3J_{HH}$ = 8 Hz, 1H), 7.33 (dd, $^3J_{HH}$ = 6.4 Hz, $^4J_{HH}$ = 2.8 Hz, 2H), 7.21 (dd, $^4J_{HF}$ = 4.0 Hz, $^3J_{HH}$ = 8 Hz, 1H), 6.59 (s, 1H), 3.67 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.8, 155.3, 153.4, 141.6, 146.3, 138.9 (2C), 134.2, 127.9, 127.4, 123.0 (2C), 116.4, 115.7, 115.8, 115.3 (2C), 112.3, 111.6, 82.4, 52.6 ppm; MS: calcd. for $C_{21}H_{13}ClFN_3O_3$ 409.80, found 409.81.

Methyl 4-chloro-3-[(Z)-2-cyano-2-(5,6-dimethyl-1H-benzimidazol-2-yl)vinyl]-6-fluoro-2H-chromene-2-carboxylate (**9b**, $C_{23}H_{17}ClFN_3O_3$)
Obtained from chloroaldehyde **6** in 0.4 g (91%) yield after recrystallization from *i*-PrOH as an orange solid. M.p.: 229–230 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.28 (br s, 1H, N*H*), 8.27 (s, 1H, C*H*C(CN)), 7.52 (s, 1H), 7.50 (dd, $^3J_{HF}$ = 8.0 Hz, $^4J_{HH}$ = 3 Hz, 1H), 7.41 (td, $^3J_{HF}$ = 8.0 Hz, $^4J_{HH}$ = 3 Hz, $^3J_{HH}$ = 8 Hz, 1H), 7.37 (s, 1H), 7.25 (dd, $^4J_{HF}$ = 4.0 Hz, $^3J_{HH}$ = 8 Hz, 1H), 6.61 (s, 1H), 3.71 (s, 3H), 2.38 (s, 3H), 2.36 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.6, 155.1, 153.2, 141.5, 146.4, 135.6 (2C), 134.1, 130.2 (2C), 127.9, 127.4, 118.4, 115.7, 115.8, 115.2 (2C), 112.2, 111.7, 82.3, 52.4, 21.0 (2C) ppm; MS: calcd. for $C_{23}H_{17}ClFN_3O_3$ 437.85, found 437.85.

Methyl 4-chloro-3-[(Z)-2-cyano-2-(1-methyl-1H-benzimidazol-2-yl)vinyl]-6-fluoro-2H-chromene-2-carboxylate (**9c**, $C_{22}H_{15}ClFN_3O_3$)
Obtained from chloroaldehyde **6** in 0.38 g (90%) yield after column chromatography (CH_2Cl_2 as the eluent) as an orange solid. M.p.: 168–170 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.19 (s, 1H, C*H*C(CN)), 7.66 (dd, $^3J_{HH}$ = 6.4 Hz, $^4J_{HH}$ = 2.8 Hz, 2H), 7.40 (dd, $^3J_{HF}$ = 8.0 Hz, $^4J_{HH}$ = 3 Hz, 1H), 7.32 (td, $^3J_{HF}$ = 8.0 Hz, $^4J_{HH}$ = 3 Hz, $^3J_{HH}$ = 8 Hz, 1H), 7.27 (dd, $^3J_{HH}$ = 6.4 Hz, $^4J_{HH}$ = 2.8 Hz, 2H), 7.15 (dd, $^4J_{HF}$ = 4.0 Hz, $^3J_{HH}$ = 8 Hz, 1H), 6.55 (s, 1H), 4.04 (s, 3H), 3.74 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.8, 155.1, 153.2, 141.5, 146.1, 138.9, 134.4, 134.0, 127.9, 127.4, 123.0 (2C), 118.6, 115.7, 115.8, 115.2 (2C), 112.2, 111.7, 82.2, 52.4, 35.9 ppm; MS: calcd. for $C_{22}H_{15}ClFN_3O_3$ 423.83, found 423.83.

Methyl 4-chloro-3-[(Z)-2-cyano-2-[1-(difluoromethyl)-1H-benzimidazol-2-yl]vinyl]-6-fluoro-2H-chromene-2-carboxylate (**9d**, $C_{22}H_{13}ClF_3N_3O_3$)
Obtained from chloroaldehyde **6** in 0.44 g (96%) yield after column chromatography (CH_2Cl_2 as the eluent) as an orange solid. M.p.: 144–146 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.37 (t, $^2J_{HF}$ = 57.6 Hz, 1H, C*H*F$_2$), 7.99 (s, 1H, C*H*C(CN)), 7.91 (d, $^2J_{HH}$ = 8 Hz, 1H), 7.86 (d, $^2J_{HH}$ = 8 Hz, 1H), 7.56 (dd, $^3J_{HF}$ = 8.0 Hz, $^4J_{HH}$ = 3 Hz, 1H), 7.53 (d, $^2J_{HH}$ = 8 Hz, 1H), 7.50 (d, $^2J_{HH}$ = 8 Hz, 1H), 7.44 (td, $^3J_{HF}$ = 8.0 Hz, $^4J_{HH}$ = 3 Hz, $^3J_{HH}$ = 8 Hz, 1H), 7.29 (dd, $^4J_{HF}$ = 4.0 Hz, $^3J_{HH}$ = 8 Hz, 1H), 6.57 (s, 1H), 3.74 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.8, 155.1, 153.2, 141.6, 146.0, 138.9, 138.6, 134.2, 134.0, 127.9, 127.4, 122.8 (2C), 118.8, 115.6, 115.8, 115.4 (2C), 112.3, 111.6, 82.1, 52.3 ppm; MS: calcd. for $C_{22}H_{13}ClF_3N_3O_3$ 459.81, found 459.81.

Methyl 3-[(Z)-2-(1-benzyl-1H-imidazol-2-yl)-2-cyanovinyl]-4-chloro-6-fluoro-2H-chromene-2-carboxylate (**9e**, $C_{24}H_{17}ClFN_3O_3$)
Obtained from chloroaldehyde **6** in 0.37 g (84%) yield after column chromatography (CH_2Cl_2 as the eluent) as a yellow solid. M.p.: 78–80 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.59 (s, 1H), 7.53 (s, 1H), 7.38 (m, 3H), 7.31 (m, 2H), 7.20 (s, 1H, C*H*C(CN)), 7.15 (dd, $^3J_{HF}$ = 8.0 Hz, $^4J_{HH}$ = 3 Hz, 1H), 7.10 (td, $^3J_{HF}$ =

8.0 Hz, $^4J_{HH}$ = 3 Hz, $^3J_{HH}$ = 8 Hz, 1H), 7.08 (dd, $^4J_{HF}$ = 4.0 Hz, $^3J_{HH}$ = 8 Hz, 1H), 6.36 (s, 1H), 5.52 (s, 2H, CH_2), 3.57 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.4, 157.8, 156.5, 149.7, 140.6, 138.2, 137.2, 129.8, 129.2, 129.1, 128.1, 126.7, 126.1, 123.8, 121.5, 121.4, 120.2, 118.7, 116.3, 112.8, 105.1, 82.9, 53.2, 52.2 ppm; MS: calcd. for $C_{24}H_{17}ClFN_3O_3$ 449.86, found 449.86.

Methyl 4-chloro-3-[(Z)-2-cyano-2-(4-methyl-1,3-thiazol-2-yl)vinyl]-6-fluoro-2H-chromene-2-carboxylate (**9f**, $C_{18}H_{12}ClFN_2O_3S$)

Obtained from chloroaldehyde **6** in 0.37 g (97%) yield after column chromatography (CH_2Cl_2 as the eluent) as a yellow solid. M.p.: 165–167 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.14 (s, 1H, C*H*C(CN)), 7.56 (s, 1H), 7.43 (dd, $^3J_{HF}$ = 8.0 Hz, $^4J_{HH}$ = 3 Hz, 1H), 7.33 (td, $^3J_{HF}$ = 8.0 Hz, $^4J_{HH}$ = 3 Hz, $^3J_{HH}$ = 8 Hz, 1H), 7.18 (dd, $^4J_{HF}$ = 4.0 Hz, $^3J_{HH}$ = 8 Hz, 1H), 6.47 (s, 1H), 3.65 (s, 3H), 2.43 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.4, 161.0, 158.9, 156.5, 155.1, 149.9, 135.5, 133.8, 123.6, 121.6, 120.7, 118.9, 116.2, 113.0, 108.3, 82.2, 53.6, 17.3 ppm; MS: calcd. for $C_{18}H_{12}ClFN_2O_3S$ 390.82, found 390.82.

Methyl 4-chloro-3-[(E)-2-cyano-2-(pyridin-2-yl)vinyl]-6-fluoro-2H-chromene-2-carboxylate (**9g**, $C_{19}H_{12}ClFN_2O_3$)

Obtained from chloroaldehyde **6** in 0.34 g (91%) yield after column chromatography (CH_2Cl_2 as the eluent) as a yellow solid. M.p.: 135–137 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.71 (d, $^2J_{HH}$ = 4 Hz, 1H), 8.52 (s, 1H, C*H*C(CN)), 8.00 (t, $^2J_{HH}$ = 8 Hz, 1H), 7.79 (d, $^2J_{HH}$ = 4 Hz, 1H), 7.51 (dd, $^3J_{HF}$ = 8.0 Hz, $^4J_{HH}$ = 3 Hz, 1H), 7.44 (dd, $^2J_{HH}$ = 7.6 Hz, 1H), 7.33 (td, $^3J_{HF}$ = 8.0 Hz, $^4J_{HH}$ = 3 Hz, $^3J_{HH}$ = 8 Hz, 1H), 7.19 (dd, $^4J_{HF}$ = 4.0 Hz, $^3J_{HH}$ = 8 Hz, 1H), 6.52 (s, 1H), 3.64 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.4, 155.8, 155.2, 153.4, 148.8, 145.9, 137.4, 134.2, 127.9, 127.4, 122.6, 120.6, 118.8, 115.7, 115.8, 115.1, 112.4, 82.2, 52.3 ppm; MS: calcd. for $C_{19}H_{12}ClFN_2O_3$ 370.76, found 370.76.

Methyl 4-chloro-3-[(Z)-2-cyano-2-(4,6-dimethylpyrimidin-2-yl)vinyl]-6-fluoro-2H-chromene-2-carboxylate (**9h**, $C_{20}H_{15}ClFN_3O_3$)

Obtained from chloroaldehyde **6** in 0.36 g (90%) yield after column chromatography (CH_2Cl_2 as the eluent) as a yellow solid. M.p.: 195–197 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.75 (s, 1H, C*H*C(CN)), 7.45 (dd, $^3J_{HF}$ = 8.0 Hz, $^4J_{HH}$ = 3 Hz, 1H), 7.36 (td, $^3J_{HF}$ = 8.0 Hz, $^4J_{HH}$ = 3 Hz, $^3J_{HH}$ = 8 Hz, 1H), 7.31 (s, 1H), 7.20 (dd, $^4J_{HF}$ = 4.0 Hz, $^3J_{HH}$ = 8 Hz, 1H), 6.58 (s, 1H), 3.65 (s, 3H), 2.35 (s, 6H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.6, 164.9, 164.8, 163.4, 155.1, 153.2, 146.2, 134.2, 127.9, 127.4, 118.6, 115.8, 115.5, 111.6, 112.5, 112.2, 82.2, 52.2, 25.5 (2C) ppm; MS: calcd. for $C_{20}H_{15}ClFN_3O_3$ 399.81, found 399.81.

Methyl 3-[(Z)-2-(6-bromo-3,4-dihydro-4-oxoquinazolin-2-yl)-2-cyanovinyl]-4-chloro-6-fluoro-2H-chromene-2-carboxylate (**9i**, $C_{22}H_{12}BrClFN_3O_4$)

Obtained from chloroaldehyde **6** in 0.48 g (93%) yield after recrystallization from *i*-PrOH as an orange solid. M.p.: >250 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.19 (br s, 1H), 8.27 (s, 1H, C*H*C(CN)), 8.21 (s, 1H), 8.10 (d, $^2J_{HH}$ = 8.8 Hz, 1H), 7.68 (d, $^2J_{HH}$ = 8.4 Hz, 1H), 7.47 (dd, $^3J_{HF}$ = 8.0 Hz, $^4J_{HH}$ = 3 Hz, 1H), 7.38 (td, $^3J_{HF}$ = 8.0 Hz, $^4J_{HH}$ = 3 Hz, $^3J_{HH}$ = 8 Hz, 1H), 7.21 (dd, $^4J_{HF}$ = 4.0 Hz, $^3J_{HH}$ = 8 Hz, 1H), 6.47 (s, 1H), 3.65 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.8, 160.6, 156.8, 155.2, 153.2, 151.4, 146.1, 136.4, 134.2, 132.5, 127.9, 127.4, 124.6, 123.2, 121.8, 116.8, 115.8, 115.4, 112.5, 112.2, 82.1, 52.4 ppm; MS: calcd. for $C_{22}H_{12}BrClFN_3O_4$ 516.70, found 516.70.

Methyl 8-cyano-2-fluoro-6H-chromeno[3′,4′:5,6]-pyrido[1,2-a]benzimidazole-6-carboxylate (**10**, $C_{21}H_{12}FN_3O_3$)

A solution of 0.4 g **9a** (1 mmol) in 5 cm^3 dry DMF was refluxed for 2 h with stirring and evaporated to dryness. The residue was recrystallized from *i*-PrOH to give 0.3 g (82%) of **10** as a yellow solid. M.p.: >250 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.54 (s, 1H), 8.35 (d, $^2J_{HH}$ = 8 Hz, 1H), 8.29 (dd, $^3J_{HF}$ = 8.0 Hz, $^4J_{HH}$ = 3 Hz, 1H), 7.91 (d, $^2J_{HH}$ = 8 Hz, 1H), 7.60 (t, $^2J_{HH}$ = 8.4 Hz, 1H), 7.49 (t, $^2J_{HH}$ = 8.4 Hz, 1H), 7.47 (td, $^3J_{HF}$ = 8.0 Hz, $^4J_{HH}$ = 3 Hz, $^3J_{HH}$ = 8 Hz, 1H), 7.32 (dd, $^4J_{HF}$ = 4.0 Hz, $^3J_{HH}$ = 8 Hz, 1H), 6.28 (s, 1H), 3.60 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.9, 162.9, 155.7, 153.0, 141.8, 139.6, 138.5, 135.2, 132.2, 123.8, 123.0, 123.1, 117.2, 116.1, 115.7, 115.2, 115.3, 116.7, 106.4, 87.2, 52.4 ppm; MS: calcd. for $C_{21}H_{12}FN_3O_3$ 373.34, found 373.34.

Dimethyl 8-fluoro-4H-thieno[3,2-c]chromene-2,4-dicarboxylate (**11**, $C_{15}H_{11}FO_5S$)

Methyl mercaptoacetate (0.13 g, 1.2 mmol) was added to a solution of 0.27 g **6** (1 mmol) and 0.12 g potassium bicarbonate (1.2 mmol) in 10 cm^3 MeOH. The reaction mixture was refluxed for 3 h and evaporated to dryness. Then, 10 cm^3 H_2O were added to the residue, and the mixture was stirred for 15 min. The precipitate was filtered off, washed with H_2O (2 × 5 cm^3), and dried to give 0.3 g (93%) of **11** as a white solid. M.p.: 172–174 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.67 (s, 1H), 7.25 (dd, $^3J_{HF}$ = 8.0 Hz, $^4J_{HH}$ = 3 Hz, 1H), 7.11 (td, $^3J_{HF}$ = 8.0 Hz, $^4J_{HH}$ = 3 Hz, $^3J_{HH}$ = 8 Hz, 1H), 7.04 (dd,

$^4J_{HF} = 4.0$ Hz, $^3J_{HH} = 8$ Hz, 1H), 6.17 (s, 1H), 3.87 (s, 3H), 3.68 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 169.8, 160.6, 155.4, 152.8, 142.1, 138.7, 134.2, 132.9, 123.8, 116.8, 116.4, 116.3, 88.7, 52.4, 51.6$ ppm; MS: calcd. for $C_{15}H_{11}FO_5S$ 322.33, found 322.33.

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