Solvent-less synthesis of imines of 3-formylchromones catalyzed by Boric acid

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Abstract: In our effort to develop hybrid molecules, we conceived the synthesis of imines from 3-formylchromone and 2-aminobenzothiazole in presence of boric acid as a green catalyst.

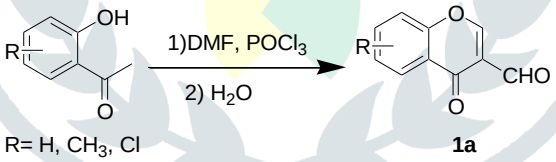
Index terms: 3-formylchromone, 2-aminobenzothiazole, imines, boric acid

Introduction

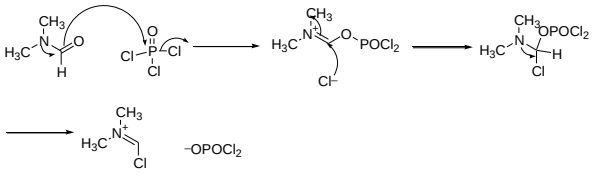
Imines[1] are biologically active and are known to possess antibacterial,[2] anti mouse hepatitis virus (MHV),[3] inhibition of herpes simplex virus type 1 (HSV-1) and adenovirus type 5 (Ad 5),[4] anti cancer[5] and anti-mosquito larvae.[6] Imines are known to possess antimicrobial,[7] antifungal,[8] antitumor,[9] and herbicidal properties.[10] 3-Formylchromone[11] derivatives have been extensively used as versatile building blocks for the synthesis of variety of heterocyclic systems.[12] In our effort to develop hybrid molecules, we conceived the synthesis of imines from 3-formylchromone[13] and 2-aminobenzothiazole[14] in presence of boric acid[15] as a green catalyst in extension of our work with alum.[16]

Results and discussion

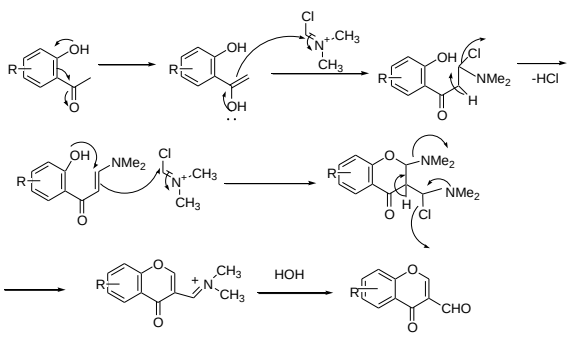
3-Formylchromones[17] **1a** can be synthesized by Vilsmeier reaction. The desired compounds carrying various substituents were prepared by the similar method in one step.



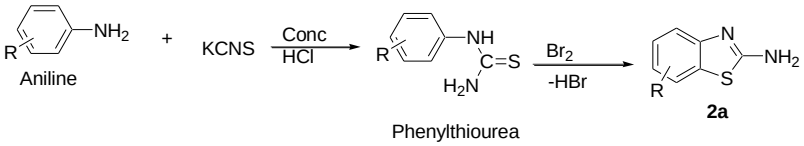
Mechanism



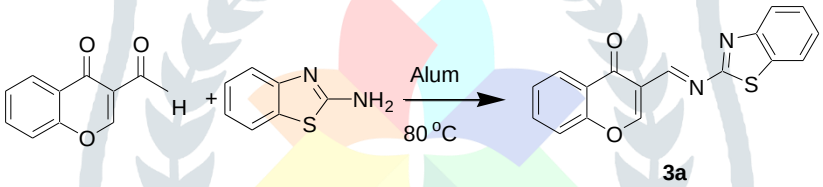
Vilsmeier reagent



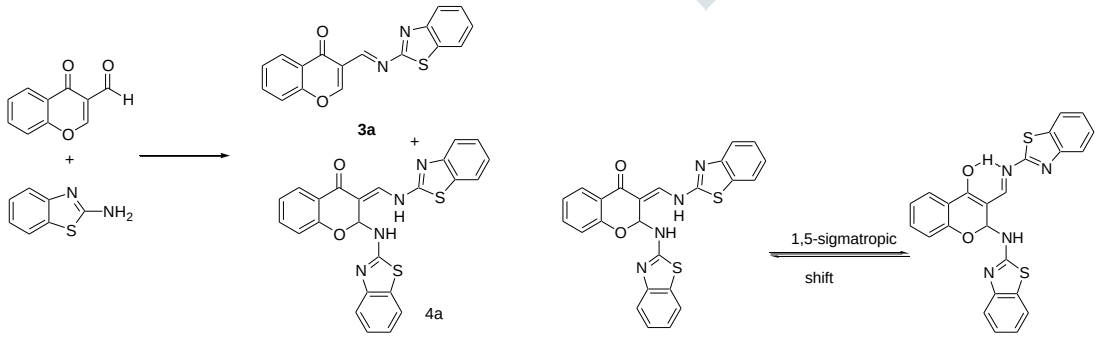
2-Aminobenzothiazoles were prepared first from substituted anilines following the Jacobsen protocol. Refluxing aniline with KCNS in acidic conditions gave *N*-phenylthiourea which on cyclization with bromine in chloroform resulted in formation of 2-aminobenzothiazole.



3- Formylchromone readily reacts with primary aromatic amines in presence of boric acid. The condensation reaction between the equimolar quantities of the two resulted in the formation of imine**.** 2-Aminobenzothiazoles were used as aromatic amines. When a mixture of 3-formylchromone (1 mmol) and 2-aminobenzothiazole (1 mmol) was heated in presence of pulverized boric acid (0.154 g) without any solvent in a round bottom flask at 80ºC for about 40 minutes, the formation of a newer spot was noticed on TLC and the new product was isolated in 90% yield by recrystallization from DMSO/ ethanol mixture. This compound **3a** was found to be 2-(4-oxo-4*H*-chromen-3-yl)methyleneaminobenzathiazole as revealed by the comparison of its spectral and physical data with the authentic sample.[17] ^{1}H NMR spectrum showed multiplet at δ 8.1 - 7.4 for eight aromatic protons, two singlets at δ 8.2 and δ 7.7 corresponding to C-H. ^{13}C NMR spectrum showed signals at δ 187, 164, 158, 156, 155, 153, 135, 133, 131, 127, 126, 125, 124, 123, 122, 118 and 106. The IR spectrum showed peak at 1640 cm^{-1} corresponding to C=O group.



However, in absence of catalyst both anil (**3a**) and 1,4-adduct (**4a**) were formed. The formation of 1,4-adduct makes the isolation of the pure compound difficult. The 1,4-adduct undergoes 1,5- sigmatropic rearrangement and the rearranged adduct is stabilized by hydrogen bonding. 1,4-Adduct can also be obtained by reacting aldehyde and aniline in presence of alum; the ratio of aldehyde and aniline being 1:2. The stable hydrogen bond so formed and is the driving force and therefore leads to the ring-addition of the anils to amines.



When a mixture of 3-formylchromone (1 mmol), 2-aminobenzothiazole (2 mmol) and pulverized boric acid (0.154g) was heated, under solvent free conditions in a round bottom flask at 80^{O}C for about 40 minutes, the formation of a newer compound in addition to imine was noticed on TLC and was isolated in 35% yield by column chromatography. The 1,4-Adduct so formed was then further recrystallized from ethanol**.** This

compound **4a** was found to be 2-(benzothiazol-2-yl-amino)-3-(benzothiazol-2-yl-aminomethylene)chroman-4-one as revealed by its spectral and physical data. ^{1}H NMR spectrum showed peaks at δ 8.5 - 7.4 as multiplet for twelve aromatic protons, singlets at δ 6.2 and δ 5.9 for two C-H, broad singlet at δ 11.8 for two N-H. The IR spectrum showed peaks at 3100 cm^{-1} (N-H), 1620 cm^{-1} (C=O).

General procedure

I. Synthesis of 3-formylchromone

The Vilsmeir reagent was prepared by the drop wise addition of freshly distilled phosphorous oxychloride to dry DMF (dimethylformamide) with stirring and cooling in ice. The reagent was allowed to stand at room temperature and was then added to a stirred solution of the substituted *o*-hydroxyacetophenone in dry DMF. The reaction mixture was kept at room temperature for 13 hour. The mixture was then poured into ice cold water. The solution was made basic by the addition of Na_2CO_3 solution and exhaustively extracted with ethyl acetate; combined extracts were washed successively with dil. HCl, H_2O and saturated brine, and finally dried over Na_2SO_4. The different compounds were obtained in varied yields. The compound **1a** was isolated in 75% yield and was found to be 3-formylchromone as revealed by the comparison of its spectral and physical data with that of the authentic sample.[19]

II. Synthesis of 2-aminobenzothiazoles

2-Aminobenzothiazoles can be synthesized in two steps:

Step I. Proceedure for the synthesis of phenylthioureas

Substituted aniline (0.1 mmol) was dissolved in a mixture of concentrated hydrochloric acid (9 ml) and water (25 ml) by heating. After cooling the reaction mixture to room temperature, potassium thiocyanate (0.1 mmol) was added and the resultant was refluxed for four hours. It was allowed to cool down to room temperature and the product precipitated upon cooling was filtered, washed with water and was crystallized from alcohol (86 %).

Step II. Proceedure for the synthesis of 2-aminobenzothiazoles

To a solution of substituted thiourea (0.1 mmol) (obtained in step I) in chloroform (100 ml) was added a solution of bromine (0.1 mmol) in chloroform (50 mL) drop wise, over a period of two hour with good stirring at 0 - 5 ºC. After the complete addition, the temperature of the reaction was allowed to come to room temperature. After stirring the reaction mixture at room temperature for 1 hour, it was heated to reflux till the evolution of HBr gas ceased (3 - 4 hour). The solvent was removed and the solid obtained was dissolved in cold water (100 mL) followed by its neutralization with aq. NH_4OH solution. The solid obtained was recrystallized from ethanol (85 %).

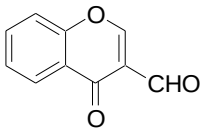
Synthesis of imines of 3-formylchromones and 2-aminobenzothiazoles

A mixture of 3-formylchromone (1 mmol), 2-aminobenzothiazole (1 mmol) and pulverized boric acid (0.154 g) was heated, without any solvent in a round bottom flask at 80ºC for about 40 minutes, the formation of a newer compound was noticed as revealed by TLC. The reaction mixture was diluted with ethyl acetate 20 mL) and filtered. The filterate was washed with brine (2 × 10 mL), dried over anhydrous Na_2SO_4, ethyl acetate was distilled off under reduced pressure and the residue was recrystallised from DMSO/ ethanol mixture in 85 - 90% yield **[3a - 3f].**

Synthesis of 1,4-adducts

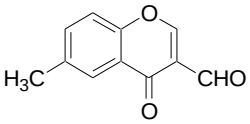
A mixture of 3-formylchromone (1 mmol), 2-aminobenzothiazole (2 mmol) and pulverized boric acid (0.154 g) was heated, without any solvent in a round bottom flask at 80ºC for about 40 minutes, the completion of the reaction was noticed as revealed by TLC. The reaction mixture was diluted with ethyl acetate (20 mL) and filtered. The filterate was washed with brine (2 × 10 mL), dried over anhydrous Na_2SO_4, ethyl acetate was distilled off under reduced pressure. The residue was then subjected to column chromatography over silica gel (60-120 mesh) and the compounds were eluted with graded solvent systems of ethyl acetate – *n*-hexane. The 1,4-adduct was then recrystallised from ethanol in 30 - 35% yield **[4a – 4d]**.

Physical and spectral data



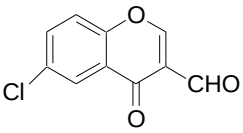
1a. 4-Oxo-4*H*-chromene-3-carbaldehyde

White solid, M.pt. 151 - 153 ºC. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ: 10.1 (1H, s), 7.8 (1H, s), 8.0 - 7.6 (4H, m). **IR** (KBr) ν_{max}/cm^{-1}: 3315, 2890, 1685, 1650. *Anal Calcd.* for $C_{10}H_6O_3$: C, 68.97, H, 3.47. Found: C, 69.33, H, 3.82.



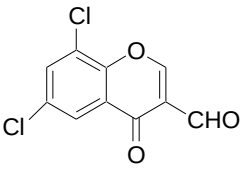
1b. 6-Methyl-4-oxo-4*H*-chromene-3-carbaldehyde

White solid, M.pt. 174 - 175 ºC. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ: 9.8 (1H, s), 7.8 (1H, s), 8.0 – 7.7 (3H, m), 2.1 (3H, s). **IR** (KBr) ν_{max}/cm^{-1}: 3310, 2890, 1695, 1655. *Anal Calcd.* for $C_{11}H_8O_3$: C, 70.21, H, 4.29. Found: C, 70.52, H, 4.62.



1c. 6-Chloro-4-oxo-4*H*-chromene-3-carbaldehyde

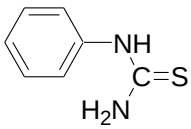
White solid, M.pt. 166 - 168 ºC. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ: 10.2 (1H, s), 8.0 (1H, s), 8.1 – 7.7 (3H, s). **IR** (KBr) ν_{max}/cm^{-1}: 3315, 2892, 1695, 1660. *Anal Calcd.* for $C_{10}H_5ClO_3$: C, 57.58, H, 2.42. Found: C, 57.92, H, 2.76.



1d. 6,8-Dichloro-4-oxo-4*H*-chromene-3-carbaldehyde

White solid, M.pt. 171 - 173 ºC. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ: 10.3 (1H, s), 8.1 (1H, s) 8.0 - 7.7 (2H, s). **IR** (KBr) ν_{max}/cm^{-1}: 3310, 2895, 1695, 1655. *Anal Calcd.* for $C_{10}H_4Cl_2O_3$: C, 49.42, H, 2.10. Found: C, 57.78, H, 2.53.

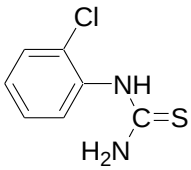
1. Phenylthiourea



Dirty white solid, M.pt. 145 - 150 ºC. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ: 7.1 - 6.9 (5H, m), 4.2 (1H, br s). **IR** (KBr) ν_{max}/cm^{-1}: 3310, 2890, 1420.

Anal Calcd. for $C_7H_8N_2S$: C, 55.23, H, 5.30, N, 18.40. Found: C, 55.58, H, 5.63, N, 18.84.

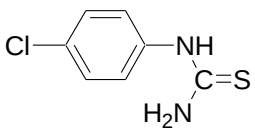
2. *o*-Chloro phenylthiourea



White solid, M.pt. 174 - 176 ºC.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.1 - 6.9 (4H, m), 4.2 (1H, br s). **IR** (KBr) ν_{max}/cm^{-1}: 3312, 2895, 1425. *Anal Calcd.* for $C_7H_7ClN_2S$: C, 45.04, H, 3.78, N, 15.01. Found: C, 45.42, H, 4.12, N, 15.38.

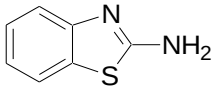
3. *p*-Chloro phenylthiourea



White solid, M.pt. 166 - 168 ºC. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ: 7.4 - 7.1 (4H, m), 4.2 (1H, br s). **IR** (KBr) ν_{max}/cm^{-1}: 3315, 2890, 1430.

Anal Calcd. for $C_7H_7ClN_2S$: C, 45.04, H, 3.78, N, 15.01. Found: C, 45.37, H, 4.12, N, 15.38.

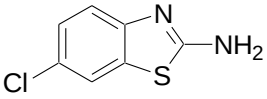
2a. 2-Aminobenzothiazole



Dirty white solid, M.pt. 128 ºC. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ: 8.0 - 7.8 (4H, m), 4.2 (2H, br s). **IR** (KBr) ν_{max}/cm^{-1}: 3315, 2985, 1580.

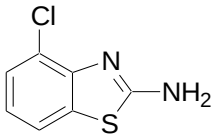
Anal Calcd. for $C_7H_6N_2S$: C, 55.97, H, 4.03, N, 18.65. Found: C, 56.31, H, 4.35, N, 18.99.

2b. 2-Amino-6-chlorobenzothiazole



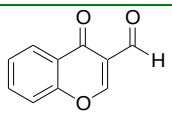
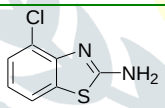
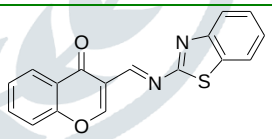
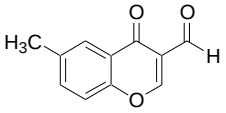
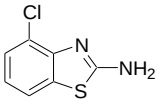
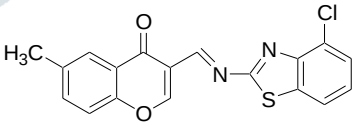
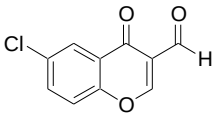
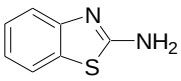
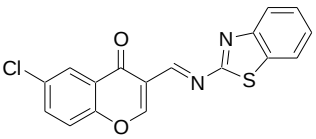
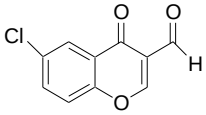
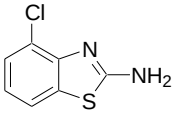
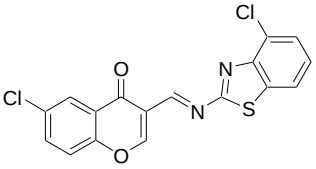
White solid, M.pt. 199 - 201 ºC.**^{1}H NMR** ($CDCl_3$, 400 MHz) δ: 8.2 - 7.9 (3H, m), 4.2 (2H, br s). **IR** (KBr) ν_{max}/cm^{-1}: 3310, 2980, 1575. ESI-MS: m/z =185 (100) $(M+H)^+$, 187 (30) $(M+H)^+$. *Anal Calcd.* for $C_7H_5ClN_2S$: C, 45.33, H, 2.73, N, 15.17. Found: C, 45.69, H, 3.07, N, 15.31.

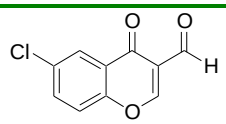
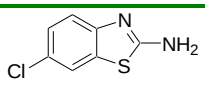
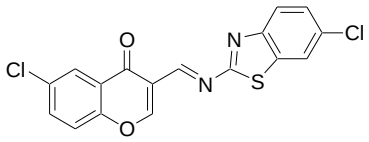
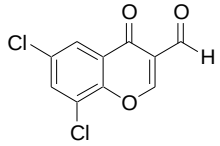
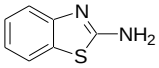
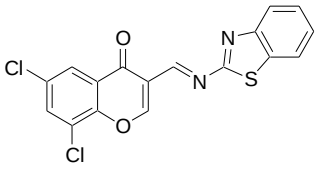
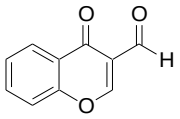
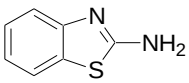
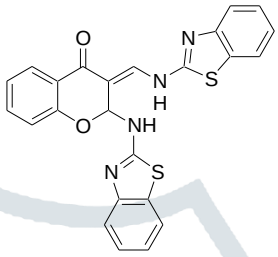
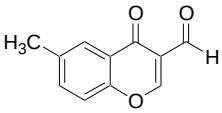
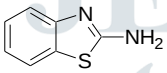
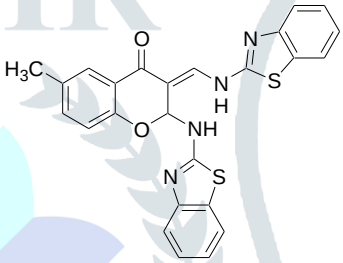
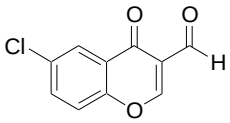
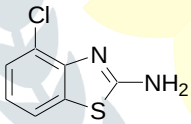
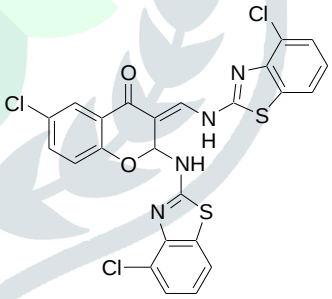
2c. 2-Amino-4-chlorobenzothiazole



White solid, M.pt. 203 - 305 ºC. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ: 8.1 - 7.8 (3H, m), 4.2 (2H, br s). **IR** (KBr) ν_{max}/cm^{-1}: 3310, 2980, 1580. *Anal Calcd.* for $C_7H_5ClN_2S$: C, 45.33, H, 2.73, N, 15.17. Found: C, 45.69, H, 3.06, N, 15.52.

Table 1: Synthesis of imines of 3-formylchromones

S.No	3-formyl chromone	2-amino benzothiazole	Product	Time (min.)	Yield % [a]
1			 3a	60	90
2			 3b	60	88
3			 3c	80	87
4			 3d	80	86

5			 3e	80	85
6			 3f	90	85
7			 4a	80	35
8			 4b	80	35
9			 4c	90	30

[a] Isolated yields.

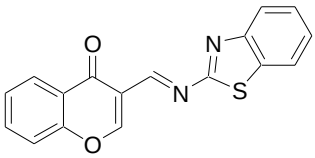
Experimental

All experiments were performed in an oven dried glass apparatus. Melting points were measured in open capillaries on Buchi melting point apparatus and are uncorrected. Elemental analysis was performed on Leco CHNS-932. IR spectra on KBr were recorded on Perkin-Elmer FTIR spectrophotometer. NMR (^{1}H broadband decoupled and ^{13}CNMR) spectra were recorded on Brucker Ac-200 (400 MHz and 100 MHz respectively) spectrometer. ^{1}H NMR and ^{13}C NMR of the compounds 3b, 3c, 3e, 3f were not measured due to low solubility in organic solvents. ESI-MS spectra were recorded on Micro-Mass VG- 7070 H mass spectrometer. The recrystallization of imines was carried from DMSO/ethanol mixture. The column

chromatography was performed over silica gel (60-120 mesh) with graded solvent systems of ethyl acetate – *n*-hexane. The solvents were dried before use as per the established procedures.

The physical and spectral data of products

3a. 2-(4-Oxo-4*H*-chromen-3-yl)methyleneaminobenzathiazole

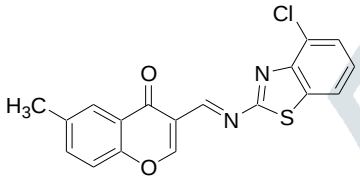


Obs. M.pt. 195 – 197 °C; Lit. M.pt. 196 - 198 °C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.2 (1H, s), 8.1 - 7.4 (8H, m), 7.7 (1H, s). **^{13}C NMR** (DMSO-d_6, 100 MHz) δ: 187, 164, 158, 156, 155, 153, 135, 133, 131, 127, 126, 125, 124, 123, 122, 118, 106. **IR** (KBr) ν_{max}/cm^{-1}: 1680, 1640. **ESI-MS** m/z = 307 $(M+H)^+$.

Anal Calcd. for $C_{17}H_{10}N_2O_2S$: C, 66.65, H, 3.29, N, 9.14, S, 10.47. Found: C, 66.96, H, 3.62, N, 9.52, S, 10.83.

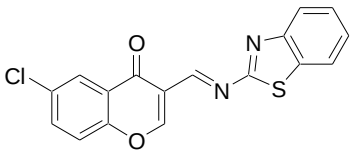
3b. 4-Chloro-2-(6-methyl-4-oxo-4*H*-chromen-3-yl)methyleneaminobenzathiazole



Obs. M.pt. 214 - 216 °C; Lit. M.pt. 216 - 218 °C.

IR (KBr) ν_{max}/cm^{-1}: 1675, 1630. *Anal Calcd.* for $C_{18}H_{11}ClN_2O_2S$: C, 60.93, H, 3.12, N, 7.90, S, 9.04. Found: C, 61.25, H, 3.46, N, 8.32, S, 9.36.

3c. 2-(6-Chloro-4-oxo-4*H*-chromen-3-yl)methyleneaminobenzathiazole



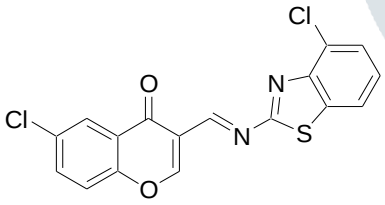
Obs. M.pt. 196 - 198 °C, Lit. M.pt. 195 - 197 °C.

IR (KBr) ν_{max}/cm^{-1}: 1620, 1550.

ESI-MS m/z = 363(100) $(M+Na)^+$, 365 (30), $(M+Na)^+$.

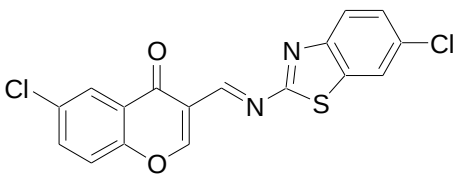
Anal Calcd. for $C_{17}H_9ClN_2O_2S$: C, 59.92, H, 2.66, N, 8.22, S, 9.41. Found: C, 60.37, H, 2.98, N, 8.59, S, 9.74.

3d. 4-Chloro-2-(6-chloro-4-oxo-4*H*-chromen-3-yl)methyleneaminobenzathiazole Obs. M.pt. 243 – 245 °C; Lit. M.pt. 246 - 248 °C.



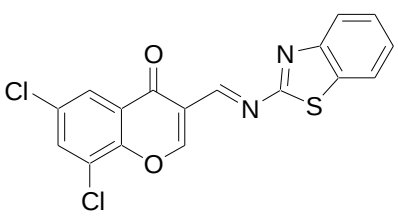
^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.7 (1H, s), 8.5 - 7.6 (6H, m), 7.8 (1H, s). **IR** (KBr) ν_{max}/cm^{-1}: 1645, 1620. *Anal Calcd.* for $C_{17}H_8Cl_2N_2O_2S$: C, 54.42, H, 2.15, N, 7.46, S, 8.54. Found: C, 54.77, H, 2.48, N, 7.81, S, 8.90.

3e. 6-Chloro-2-(6-chloro-4-oxo-4*H*-chromen-3-yl)methyleneaminobenzathiazole Obs. M.pt. 298 – 300 °C; Lit. M.pt. 305 - 307 °C.



IR (KBr) ν_{max}/cm^{-1}: 1640, 1625. *Anal Calcd.* for $C_{17}H_8Cl_2N_2O_2S$: C, 54.42, H, 2.15, N, 7.46, S, 8.54. Found: C, 54.78, H, 2.51, N, 7.78, S, 8.89.

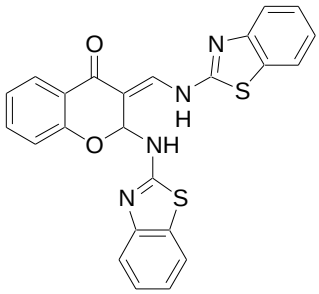
3f. 2-(6,8-Dichloro-4-oxo-4*H*-chromen-3-yl)methyleneaminobenzathiazole



Obs. M.pt. 212 – 214 °C; Lit. M.pt. 214 - 216 °C.

IR (KBr) ν_{max}/cm^{-1}: 1645, 1630. *Anal Calcd.* $C_{17}H_8Cl_2N_2O_2S$: C, 54.42, H, 2.15, N, 7.46, S, 8.54. Found: C, 54.77, H, 2.48, N, 7.78, S, 8.89.

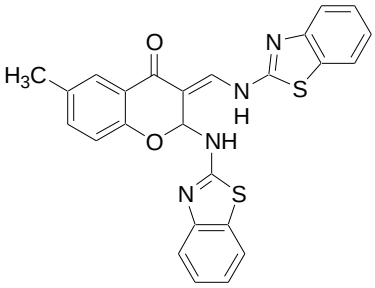
4a. 2-(Benzothiazol-2-yl-amino)-3-(benzothiazol-2-yl) aminomethylenechroman-4-one



Yield 30%. Obs. M.pt. 176 – 178 ^{o}C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ: 11.8 (2H, br s), 8.3 - 7.4 (12H, m), 6.2 (1H, s), 5.9 (1H, s). **IR** (KBr) ν_{max}/cm^{-1}: 3310, 1645, 1630. **ESI-MS** m/z = 457 $(M+H)^{+}$. *Anal Calcd.*: $C_{24}H_{16}N_4O_2S_2$: C, 63.54, H, 3.24, N, 11.84, S, 13.54. Found: C, 63.90, H, 3.57, N, 12.21, S, 13.89.

4b. 2-(Benzothiazol-2-yl-amino)-3-(benzothiazol-2-yl)aminomethylene- 6-methyl-chroman-4-one



Yield 35%.

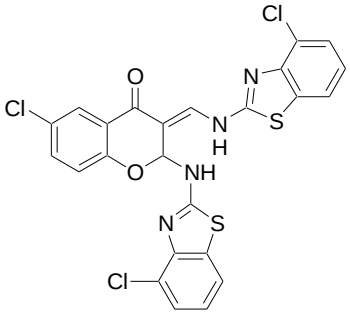
Obs. M.pt. 182 – 184 ^{o}C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ: 11.7 (2H, br s), 8.4 - 7.3 (11H, m), 6.1 (1H, s), 5.9 (1H, s), 2.3 (3H, s).

IR (KBr) ν_{max}/cm^{-1}: 3315, 2890, 1625.

Anal Calcd. for $C_{25}H_{18}N_4O_2S_2$: C, 63.81, H, 3.85, N, 11.91, S, 13.63. Found: C, 64.18, H, 4.19, N, 12.32, S, 13.96.

4c. 6-Chloro-2-(4-chlorobenzothiazol-2-yl-amino)-3-(4-chlorobenzothiazol-2-yl) aminomethylenechroman-4-one



Yield 30%. Obs. M.pt. 203 – 205 ^{o}C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ: 11.8 (2H, br s), 8.6 - 7.8 (9H, m), 6.3 (1H, s), 5.9 (1H, s). **IR** (KBr) ν_{max}/cm^{-1}: 3310, 2985, 1620. *Anal Calcd.* for $C_{24}H_{13}Cl_3N_4O_2S_2$: C, 51.49, H, 2.34, N, 10.01, S, 11.45. Found: C, 51.82, H, 2.68, N, 10.35, S, 11.79.

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