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Reaction of 3-formylchromones with aromatic amino carboxylic acids

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Abstract—2-Alkoxy-3-(arylaminomethylene)chroman-4-ones and 3-(aryliminomethyl)chromones were prepared by acid catalyzed reaction of 3-formylchromones with aromatic amino carboxylic acids in alcoholic reaction media. The results of the kinetic study have confirmed that 3-(aryliminomethyl)chromones are formed from 2-alkoxy-3-(arylaminomethylene)chroman-4-ones. The dependence of the reaction rate on reactant structure, the reaction media and the concentration of catalyst has been studied. In contrast to the alcoholic media reaction, the same reaction in dry aprotic reaction media yielded only 2-hydroxy-3-(arylaminomethylene)chroman-4-ones. No 3-(aryliminomethyl)chromones were isolated in that case.

1. Introduction

The synthetic significance of 4-oxo-4*H*-[1]-benzopyran-3-carboxaldehydes (4-oxochromene-3-carboxaldehydes, 3-formylchromones) **1** comes from their usefulness as reactive agents and valuable precursors for many different heterocycles. They contain three electron deficient sites (C-2, C-4, CHO) suitable for nucleophilic attack and as a consequence of competition between these centers, various types of compounds can form upon the reaction of **1** with strong nucleophiles.[1]

Reaction between equimolar quantities of 3-formylchromone **1** and a primary aromatic amine in benzene leads to a mixture of the 3-(aryliminomethyl)chromone and 2-arylamino-3-(arylaminomethylene)chroman-4-one, making the isolation of pure compounds difficult.[2,3] The reason for this rather unusual ring addition of a second aromatic amine molecule to the imine is the formation of the stable ketoamine hydrogen bond.[4] Alcohols, thiols and amines are sufficiently nucleophilic to add to 3-(aryliminomethyl)chromones.[3,5,6] A much improved yield of 3-(aryliminomethyl)chromones can be obtained from the condensation of reactants in the presence of 4-toluenesulfonic acid.[3,7] Pure 3-(aryliminomethyl)chromones can be prepared from 2-alkoxy-3-(arylaminomethylene)chroman-4-ones via elimination of a molecule of alcohol by heating the compounds to their melting point under vacuum.[6] Primary aromatic amines having a nucleophilic functionality at their *ortho* position react with 3-formylchromones giving fused seven-membered heterocycles,[8–10] 3-(aryliminomethyl)chromones[8–10] or dihydrotetraaza[1]-anulenes.[11,12]

There are two possible pathways for the formation of 3-(aryliminomethyl)chromones. The first is a straightforward 1,2-addition of the amine to the aldehyde function of **1**, while the second is a 1,4-addition of the amine with concomitant opening of the pyrone ring and subsequent recyclization of the intermediate. In spite of a thorough investigation of the reaction of 3-formylchromones **1** with primary aromatic amines, the exact mechanism of the formation of products is not clear.[1]

In a preliminary communication we described the acid catalyzed synthesis of 3-(aryliminomethyl)chromones in ethanol.[13] We now report an investigation, including the reaction kinetics, of reaction between 6-substituted 3-formylchromones and aromatic amino carboxylic acids. The aim of this study was to contribute to the clarification of preparation of imines, enamines and their mutual transformation in the reaction of weak *N*-nucleophiles with aldehydes **1**. Some of the prepared compounds have been

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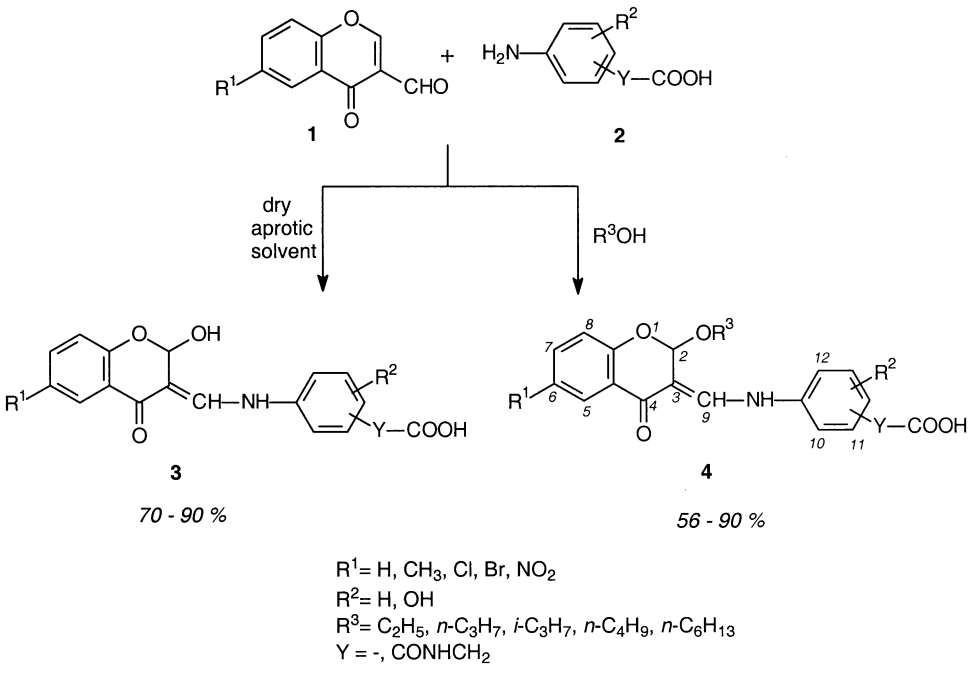


R^1= H, CH_3, Cl, Br, NO_2
R^2= H, OH
R^3= C_2H_5, *n*-C_3H_7, *i*-C_3H_7, *n*-C_4H_9, *n*-C_6H_{13}
Y = -, $CONHCH_2$

Scheme 1.

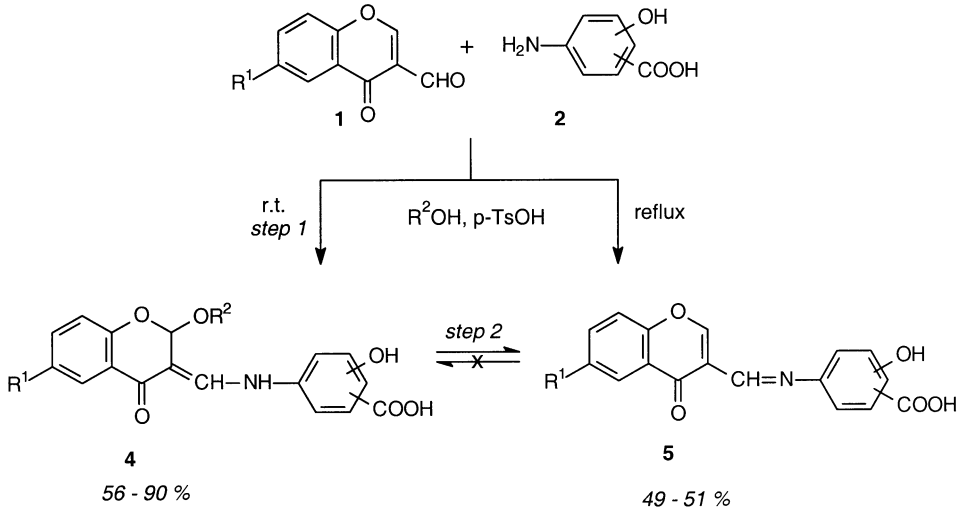
active against mycobacterial strains,[13] in photosynthesis[14] and have a hereditary bleaching effect (similar to antibiotics) on the plastid system of *Euglena gracilis*.[15]

2. Results and discussion

2.1. Synthetic study

2.1.1. Reactions in dry aprotic solvents. Reaction of 6-substituted 3-formylchromones **1** with all of the aromatic amino carboxylic acids **2** in benzene or toluene yielded only 3-(arylaminomethylene)-2-hydroxychroman-4-ones **3** at room temperature or under reflux (Scheme 1). Changing the solvent, reaction temperature or amount of catalyst did not affect the yield of enamines **3**. This is surprising, as we expected the formation of 3-(aryliminomethyl)chromones when the reactions were carried out under reflux. In comparison with reported procedures[2,3,7] for synthesis of imines we prolonged the reaction time from 30 min to 1–3 h, but no effect on the reaction was observed.

Enamines **3** can be produced either by fast 1,4-addition of reaction water to the temporarily formed imine, or as intermediates which arise due to pyrone ring opening, caused by 1,4-addition of aromatic amino carboxylic acid to the 3-formylchromone **1**, and recyclisation. The driving force for both processes is the stabilisation of the enamines **3** by a hydrogen bond between the pyranone carbonyl oxygen and the hydrogen of the NH group.[16]



Scheme 2.

No products were obtained as a result of the rearrangement of the benzopyrone ring. We have never managed to isolate the mixture of imine and 2-arylamino-3-(arylaminomethylene)chroman-4-one from the reaction between the aldehyde **1** and aromatic amino carboxylic acid **2** (1:1 molar ratio) in dry aprotic solvents. This difference between reactivity of anilines[2,3] and aromatic amino carboxylic acids can be explained by lower nucleophility and basicity of arylamino acids in comparison with aniline derivatives. In the case of anilines having a nucleophilic functionality at their *ortho* position, fused seven-membered heterocycles were prepared.[8–10] Formation of this type of compounds was not proved in the case of 3-aminosalicylic acid.

2.1.2. Reactions in protic solvents. Protic solvents led to different reaction products than those found in dry aprotic ones. 2-Alkoxy-3-(arylaminomethylene)chroman-4-ones **4** were synthesized by reaction of 3-formylchromones **1** with all five aromatic amino carboxylic acids in the presence of 4-toluenesulfonic acid as catalyst in an alcoholic reaction medium at room temperature (Scheme 2).

4-Aminobenzoic and 4-aminohippuric acids yielded the 2-alkoxyderivatives **4a–e** also when the reaction was carried out under reflux. Aminosalicylic acids reacted differently. 3-(Aryliminomethyl) chromones **5** were isolated from reactions performed at higher temperature (reflux) for 3 h (Scheme 2). The imines are sparingly soluble in solvents, and precipitate from the reaction mixture. Prolonged heating of the reaction mixture for more than 20 h led to polymerization of the imine. The prepared 3-(aryliminomethyl)chromones **5** did not give 2-alkoxy-3-(arylaminomethylene)chroman-4-ones **4** after 3 days standing at room temperature or after 6 h reflux in alcohol.

^{1}H NMR spectra of enamines **4** display two singlets for the proton at position 2 of the chromanone ring. We recently reported that PM3 semiempirical computations indicate the presence of several isomers for 2-substituted 3-(acylaminomethylene)chroman-4-ones (Fig. 1).[17] For all computed compounds the **A** isomers were predicted to be more stable than the **B** isomers, although the computed energy differences between isomers **A**, **B** were only 4.184–12.552 kJ mol^{-1}.[17] The computed energy differences between ketoamine **A** and hydroxyimine **C** tautomers (R=acyl, phenyl) were higher (46.024–58.576 kJ mol^{-1}).[16] It was found for derivatives of 4-aminobenzoic acid that the isomer ratio depends on the method of preparation of 2-alkoxy-3-(4-carboxyphenyl)aminomethylenechroman-4-one. For instance, spectra of enamine **4b** prepared at room temperature reveal an isomer ratio of 89:11, while for the same compound synthesized under reflux, the ratio is 66:34. This finding may indicate that heating the reaction mixture causes isomerization of enamines to the isomer with geometry favourable for elimination of the molecule of alcohol. This assumption is supported by observed the course of reaction of 6-bromo-3-formylchromone with 4-aminosalicylic acid in ethanol under reflux. At first, yellow 6-bromo-3-(4-carboxy-3-hydroxyphenyl)aminomethylene-2-ethoxychroman-4-one **4i** precipitated from reaction mixture. The ^{1}H NMR spectra of the isolated enamine **4i** revealed a slightly different isomer ratio to the enamine prepared at room temperature. After prolonged heating the precipitate slowly changed colour from yellow to red–brown. The latter was identified after isolation as 6-bromo-3-[(4-carboxy-3-hydroxyphenyl)-iminomethyl]chromone **5b**.

These synthetic results contradict the previously proposed mechanism for the conversion of 2-substituted-3-(arylaminomethylene)chroman-4-ones from 3-(aryliminomethyl)chromones[3,6] and are supported by kinetic study of the above process.

2.2. Kinetics

We performed a kinetic study on the reaction of 3-formylchromones **1** with 3- and 4-aminosalicylic acids. The conversion of reactants into products **4**, **5** proceeded through steps which may be competitive, parallel or consecutive. The kinetic study clarified how the reaction proceeds. We have studied the dependence of reaction rate on: (i) the structure of starting compounds, (ii) the type of reaction medium and (iii) the concentration of catalyst. The mechanistic pathway of the studied reaction is depicted in Scheme 2. UV–VIS absorption spectra were used for monitoring the kinetics of the above process. All of the components of the reaction mixture had different absorption bands and intensities. Both products **4**, **5** have the absorption maximum bathochromicaly shifted in comparison with starting compounds and catalyst. The intensity of the absorption band of **4** is approximately 10 times larger than that of **5**.

The results show clearly that enamines **4** are formed via the reaction of 6-substituted 3-formylchromones **1** with aminosalicylic acids in alcoholic reaction media (Scheme 2, step 1) and are consecutively transformed into chromones **5** (Scheme 2, step 2) under the same conditions (at 40.5°C). The reaction rate was monitored using the absorption band at 380 nm due to 6-substituted 2-alkoxy-3-(arylaminomethylene)chroman-4-ones **4**. At first, the absorbance of **4** increases, reaches a maximum and then decreases again. Decrease in absorbance of **4** is accompanied by a proportional increase in the absorbance of **5**.

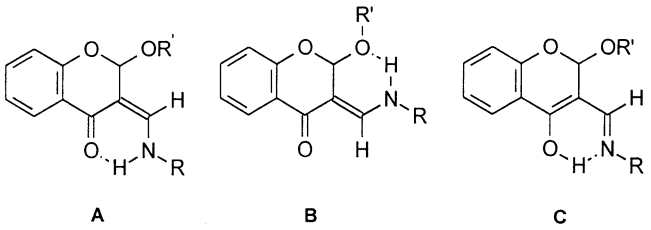


Figure 1.

Table 1. Effect of the structure of reactants on the rate in ethanol at $c_{cat}=1\times10^{-4}$ mol dm^{-3}

R[1]	k (dm^3 mol^{-1} s^{-1})	k (dm^3 mol^{-1} s^{-1})
	4-Aminosalicylic acid	3-Aminosalicylic acid
Cl	$2.86\times10^{-5}\pm1\times10^{-6}$	$4.30\times10^{-4}\pm1\times10^{-5}$
NO_2	$7.99\times10^{-5}\pm6\times10^{-6}$	$1.16\times10^{-3}\pm2\times10^{-5}$
H	$8.15\times10^{-5}\pm5\times10^{-7}$	$2.10\times10^{-3}\pm2\times10^{-5}$

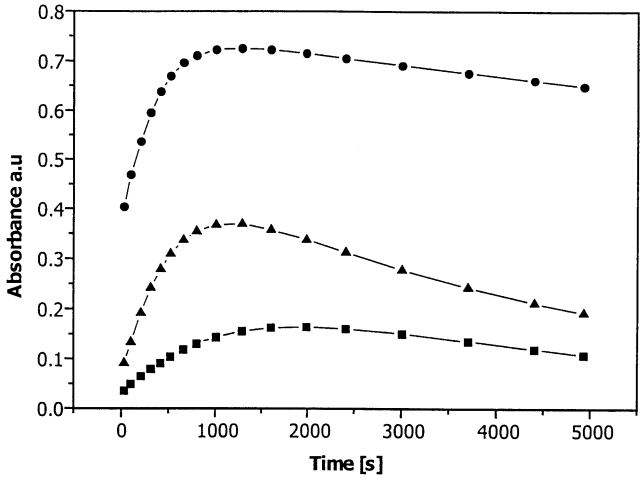


Figure 2. Change of the absorbance at $\lambda=380$ nm due to conversion of enamines **4** to imines **5** in ethanol at $c_{cat}=10^{-4}$ mol dm^{-3}; 3-formylchromone (▲), 6-chloro-3-formylchromone (■), 6-nitro-3-formylchromone (●).

Table 2. Effect of the solvent on the rate of formation of enamines **4** derived from unsubstituted aldehyde at $c_{cat=}1\times10^{-4}$ mol dm^{-3}

Solvent	k (dm^3 mol^{-1} s^{-1})	k (dm^3 mol^{-1} s^{-1})
	4-Aminosalicylic acid	3-Aminosalicylic acid
Methanol	$4.16\times10^{-6}\pm1\times10^{-7}$	$1.90\times10^{-4}\pm5\times10^{-6}$
Ethanol	$8.15\times10^{-5}\pm5\times10^{-7}$	$2.10\times10^{-3}\pm1\times10^{-4}$
2-Propanol	–	$5.63\times10^{-4}\pm8\times10^{-6}$
n-Propanol	$7.41\times10^{-5}\pm3\times10^{-6}$	$5.44\times10^{-4}\pm3\times10^{-5}$
n-Butanol	$6.40\times10^{-5}\pm2\times10^{-6}$	$8.92\times10^{-4}\pm5\times10^{-6}$
t-Butanol	–	$3.28\times10^{-3}\pm3\times10^{-5}$

Table 3. Effect of the concentration of 4-toluenesulfonic acid on the rate of conversion of enamine **4** (derived from 3-formylchromone) to imine **5** in 2-propanol

Concentration of catalyst (mol dm^{-3})	k (dm^3 mol^{-1} s^{-1})	k (dm^3 mol^{-1} s^{-1})
	4-Aminosalicylic acid	3-Aminosalicylic acid
1×10^{-5}	$2.00\times10^{-4}\pm3\times10^{-5}$	$8.55\times10^{-4}\pm5\times10^{-6}$
1×10^{-4}	$3.16\times10^{-4}\pm1\times10^{-5}$	$5.78\times10^{-4}\pm5\times10^{-5}$
1×10^{-3}	$1.53\times10^{-3}\pm3\times10^{-5}$	Very fast[a]
1×10^{-2}	$8.63\times10^{-3}\pm6\times10^{-4}$	Very fast[a]

[a] It was impossible to prepare enamines **4** at a catalyst concentration $>1\times10^{-4}$ mol dm^{-3} because imine **5** was formed immediately.

2.2.1. Effect of structure of reactants. It was found that the rate of reaction of 3-formylchromone **1** with 4-aminosalicylic acid is, approximately, 14.6 times slower than with 3-aminosalicylic acid (Table 1). Lower basicity of the nitrogen of the 4-aminoderivative is the reason for the decrease in the reaction rate. Similarly, the substituent at position C-6 of the benzopyrane ring affects the reaction rate. The substituent at position C-6 leads to a change of fragment charge on the aldehydic carbon and modifies both the reactivity, and the reaction rate. The reaction rate decreases in the following order of substituents $H>NO_2>Cl$ (Fig. 2).

2.2.2. Effect of reaction media. The study of reaction kinetics was performed in six different alcohols: methanol, ethanol, 1-propanol, 2-propanol, 2,2-dimethylpropanol, and 1-butanol (Table 2). It was found that ethanol and 1-butanol are suitable solvents for preparation of enamine derivatives **4** derived from 3-aminosalicylic acid. The kinetic measurements show that the rate of formation of imine derivative **5** is lower than that for formation of the enamine. Consequently, it is possible to isolate 2-alkoxy-3-(3-carboxy-2-hydroxyphenylaminomethylene)chroman-4-ones from the reaction mixture in high yields.

The findings for 4-aminosalicylic acid are different. The rate of formation of enamine **4** is comparable to the rate of formation of imine **5**. Therefore, the isolated yield of

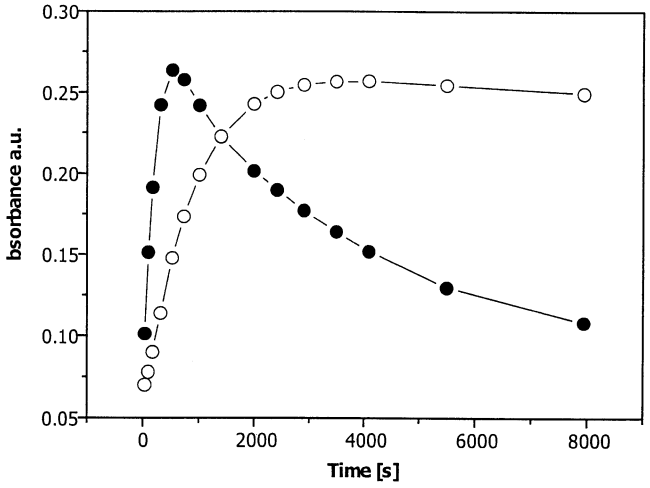


Figure 3. Time change of absorbance at $\lambda=380$ nm due to formation of imine **5** in reaction of 3-aminosalicylic acid with 3-formylchromone at $c_{cat}=10^{-4}$ mol dm^{-3}; 2-propanol (●), methanol (○).

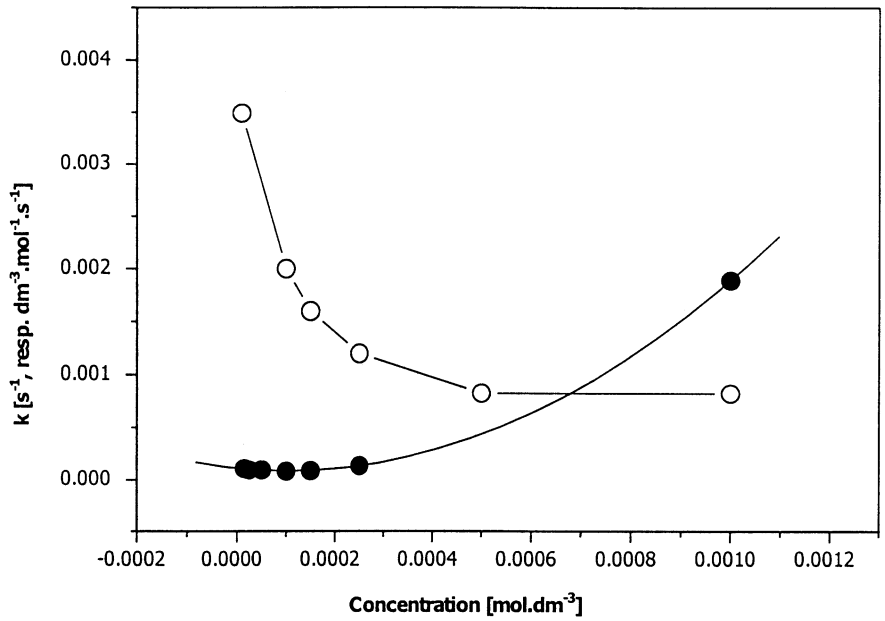


Figure 4. Effect of the catalyst concentration on the rate of reaction of 3-formylchromone in ethanol; 3-aminosalicylic acid (○), 4-aminosalicylic acid (●).

Table 4. Effect of the concentration of 4-toluenesulfonic acid on the rate of reaction of 3-formylchromone with aminosalicylic acids in ethanol

Concentration of catalyst (mol dm^{-3})	k (dm^3 mol^{-1} s^{-1})	k (dm^3 mol^{-1} s^{-1})
	4-Aminosalicylic acid	3-Aminosalicylic acid
1×10^{-5}	–	$3.55\times10^{-3}\pm2\times10^{-4}$
2.5×10^{-5}	$9.28\times10^{-5}\pm5\times10^{-6}$	–
5×10^{-5}	$9.40\times10^{-5}\pm3\times10^{-7}$	$3.99\times10^{-3}\pm7\times10^{-5}$
1×10^{-4}	$8.15\times10^{-5}\pm5\times10^{-7}$	$2.10\times10^{-3}\pm1\times10^{-4}$
1.5×10^{-4}	$8.56\times10^{-5}\pm1\times10^{-6}$	$1.60\times10^{-3}\pm3\times10^{-5}$
2.5×10^{-4}	$1.07\times10^{-5}\pm5\times10^{-6}$	$1.21\times10^{-3}\pm7\times10^{-4}$
5×10^{-4}	–	$8.26\times10^{-4}\pm5\times10^{-5}$
1×10^{-3}	$1.89\times10^{-3}\pm2\times10^{-5}$	$8.25\times10^{-4}\pm7\times10^{-5}$
1×10^{-2}	–	$3.38\times10^{-4}\pm2\times10^{-5}$

2-alkoxy-3-(4-carboxy-3-hydroxyphenylaminomethylene)-chroman-4-ones **4** from the reaction mixture is substantially lower than that in case of 3-aminosalicylic acid.

When the reaction of 3-aminosalicylic acid was carried out in 2-propanol or methanol, the rate of formation of imine **5** (for 2-propanol $k=5.78\times10^{-4}$, Table 3) is higher than that of enamine ($k=5.63\times10^{-4}$ Table 2). The enamine being formed reacts immediately to yield an imine (Fig. 3).

2.2.3. Effect of catalyst concentration. Concentration of 4-toluenesulfonic acid influences the reaction rate as well as the ratio of enamine **4** and imine **5** in the reaction mixture. The effect on the course of the reaction depends on the structure of reactants. Rate of formation of enamines **4** derived from 3-aminosalicylic acid decreases with an

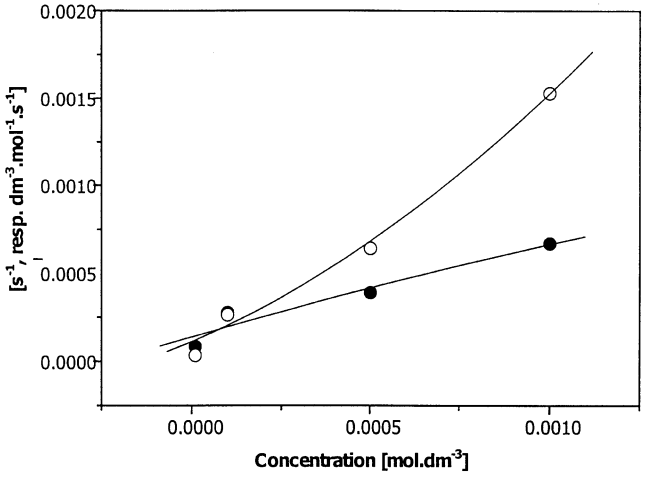


Figure 5. Effect of the catalyst concentration on the rate of conversion of enamine **4** to imine **5** in ethanol; reaction of 3-formylchromone, 3-aminosalicylic acid (●), 4-aminosalicylic acid (○).

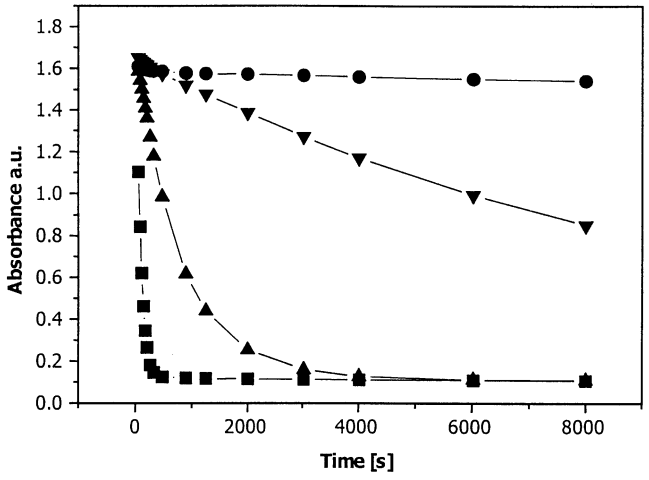


Figure 6. Absorbance at $\lambda=380$ nm probing the conversion of enamine **4o** to imine as a function of time, illustrating the dependence of reaction rate on the catalyst concentration in ethanol; $c_{cat}=10^{-5}$ mol dm^{-3} (●), 10^{-4} mol dm^{-3} (▼), 10^{-3} mol dm^{-3} (▲), 10^{-2} mol dm^{-3}(■).

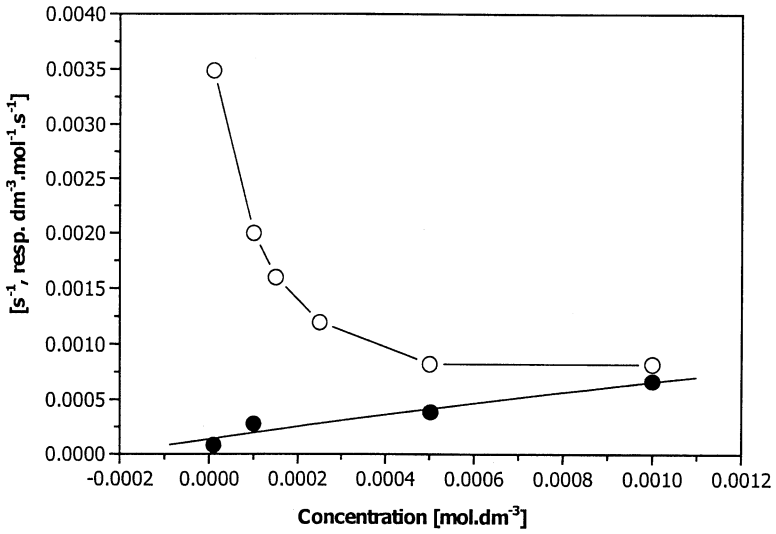


Figure 7. Effect of the catalyst concentration on the rate of reaction of 3-aminosalicylic acid with 3-formylchromone in ethanol; formation of enamine **4o** (○), conversion of enamine to imine (●).

increase in catalyst concentration. The reverse is true for 4-aminosalicylic acid derivatives (Fig. 4).

The rate constant of the conversion of enamine to imine (**4→5**) increases proportionally with catalyst concentration (Tables 3 and 4; Figs. 5 and 6).

The ratio of derivatives **4** and **5** in the reaction mixture can be controlled by changing the catalyst concentration. In the case of 3-aminosalicylic acid, particularly at low catalyst concentration, enamine **4** accumulates in the reaction mixture because the conversion rate **4→5** is slow (Fig. 7).

The reverse is true for 4-aminosalicylic acid reactions. The rate of conversion of enamine to imine (**4→5**) is higher than that for the formation of enamine **4** at low catalyst concentrations. The enamine reacts immediately, yielding the imine under these conditions. Therefore, it is possible to isolate enamine **4** from the reaction mixture only if the reaction rate of transformation **4→5** is lower than that of formation of the enamine **4** (Fig. 8).

3. Conclusions

6-Substituted 3-formylchromones **1** with aromatic amino carboxylic acids **2** yield enamines **3**, **4** or imines **5** in depending on the reaction conditions. The results can be summarized as follows:

1. 3-(Arylaminomethylene)-2-hydroxychroman-4-ones **3** are formed in the reaction of aldehydes **1** with aromatic amino acids **2** in the presence of 4-toluenesulfonic acid as catalyst in dry aprotic reaction media at room temperature or under reflux.
2. 4-Aminobenzoic and 4-aminohippuric acids react with **1** in alcohols at room temperature or under reflux, respectively, giving 2-alkoxy-3-(arylaminomethylene)chroman-4-ones **4a**–**e**.

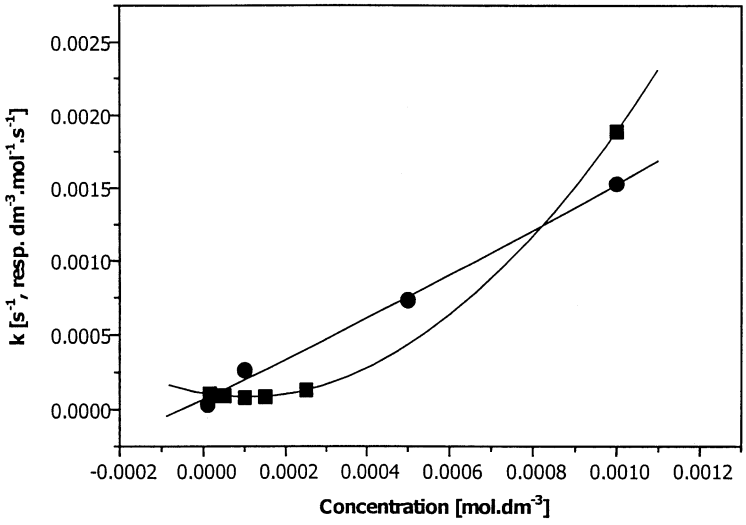


Figure 8. Effect of the catalyst concentration on the rate of reaction of 4-aminosalicylic acid with 3-formylchromone in ethanol; formation of enamine **4f** (■), conversion of enamine to imine **5a** (●).

3. Aminosalicylic acids with 6-substituted 3-formylchromones **1** in the presence of catalyst in alcohol yield enamines **4** at room temperature and imines **5** under reflux. Imines **5** are formed from enamines **4** by elimination of a molecule of the appropriate alcohol. The reverse reaction does not occur.
4. Ethanol and 1-butanol are suitable reaction media for preparation of chroman-4-ones **4**, derived from aminosalicylic acids, in the presence of 4-toluenesulfonic acid as catalyst at temperatures lower than 40°C.
5. The rate of formation of enamines **4f–r** and imines **5** is proportional to the concentration of 4-toluenesulfonic acid. Only imines **5** were isolated from reaction mixture when a large excess (100 fold) of catalyst was used.

4. Experimental

Melting points (uncorrected) were measured on a Kofler hot stage. The NMR spectra were recorded in DMSO-d_6 on Tesla BS-487 (^{1}H at 80 MHz) or Varian VXR-300 (^{1}H at 300 MHz) spectrometers. IR spectra were taken in paraffin oil on a Specord 75 IR (Zeiss, Jena) spectrometer, and main IR absorptions are given in cm^{-1}. Elemental analyses were performed on a Carlo Erba Strumentacione 1106 apparatus.

4.1. Starting materials

Commercial chemicals (solvents, 4-aminosalicylic acid, 4-aminobenzoic acid, 4-aminohippuric acid and 4-toluenesulfonic acid) were used after purification and drying (if their purity was <99%). 3-Aminosalicylic acid,[18] 5-aminosalicylic acid[19] and 3-formylchromones[20] were prepared according to literature procedures.

4.1.1. 3-(Arylaminomethylene)-2-hydroxychroman-4-ones 3a–e. *Method A*. An aromatic amino carboxylic acid **2** (1.148 mmol) was added to a stirred solution of 6-substituted 3-formylchromone **1** (1.148 mmol) and 4-toluene sulfonic acid (0.029 mmol) in dry benzene or toluene (6 mL), and the solution was stirred at room temperature for 12 h. The yellow precipitate was filtered off, washed with water and dried.

Method B. An aromatic amino carboxylic acid **2** (1.148 mmol) was added to a boiling stirred solution of 6-substituted 3-formylchromone **1** (1.148 mmol) and 4-toluene sulfonic acid (0.029 mmol) in dry benzene or toluene (6 mL), and the solution was refluxed for 3 h. The yellow precipitate was filtered off, washed with water and dried.

4.1.2. 3-(4-Carboxyphenyl)aminomethylene-2-hydroxychroman-4-one (3a). Method A, work-up as described above gave 76% of **3a** as yellow needles: mp 217–220°C; ^{1}H NMR (80 MHz): δ 6.15 (s, 0.6H, 2-H), 6.42 (s, 0.4H, 2-H), 6.98–7.99 (m, 8H, Arom-H), 8.27 (d, 1H, 9-H, ^3J=10.2 Hz), 11.94 (d, 1H, NH, ^3J=10.2 Hz); IR: $\tilde{\nu}$ 1380 (C–N), 1600 (C=C), 1650 (C=$O_{chromanone}$), 1692 (C=O_{COOH}). Anal. Calcd for $C_{17}H_{13}NO_5$ (311.29): C, 65.59; H, 4.29; N, 4.50. Found: C, 65.53; H 4.03; N, 4.45%.

4.1.3. 3-(4-Carboxyphenyl)aminomethylene-2-hydroxy-6-methylchroman-4-one (3b). Method A, work-up as described above gave 78% of **3b** as yellow needles: mp 339–342°C; ^{1}H NMR (300 MHz): δ 2.31 (s, 3H, CH_3), 5.86 (bs, 1H, OH), 6.15 (s, 1H, 2-H), 6.90–7.68 (m, 3H, 5-H, 7-H, 8-H), 7.38 (d, 2H, 10-H, $^3J_{10,11}$=8.4 Hz), 7.94 (d, 2H, 11-H, $^3J_{10,11}$=8.4 Hz), 8.06 (d, 1H, 9-H, ^3J=12.3 Hz), 11.84 (d, 1H, NH, ^3J=12.3 Hz); IR: $\tilde{\nu}$ 1384 (C–N), 1602 (C=C), 1652 (C=$O_{chromanone}$), 1690 (C=O_{COOH}). Anal. Calcd for $C_{18}H_{15}NO_5$ (352.32): C, 66.46; H, 4.65; N, 4.30. Found: C, 66.38; H, 4.60; N, 4.34%.

4.1.4. 3-[4-(*N*-Carboxymethylcarbamoyl)phenylaminomethylene]-2-hydroxy-6-methylchroman-4-one (3c). Method A, work-up as described above gave 70% of **3c** as yellow needles: mp 235–239°C; ^{1}H NMR (80 MHz): δ 2.30 (s, 3H, CH_3), 3.75 (d, 2H, CH_2, ^3J=14.4 Hz), 6.17 (s, 1H, 2-H), 6.55–8.01 (m, 9H, Arom-H, NH, OH), 8.08 (d, 1H, 9-H, ^3J=13.3 Hz), 11.27 (d, 1H, NH–C=, ^3J=13.3 Hz); IR: $\tilde{\nu}$ 1376 (C–N), 1602 (C=C), 1648 (C=O_{amide}), 1656 (C=$O_{chromanone}$), 1690 (C=O_{COOH}). Anal. Calcd for $C_{20}H_{18}N_2O_6$ (382.37): C, 62.82; H, 4.74; N, 7.33. Found: C, 62.54, H, 4.71, N, 7.15%.

4.1.5. 3-(4-Carboxy-3-hydroxyphenyl)aminomethylene-2-hydroxychroman-4-one (3d). Method A, work-up as described above gave 90% of **3d**, method B, work-up as described above gave 92% of **3d** as yellow needles: mp 231–234°C; ^{1}H NMR (80 MHz): δ 6.17 (s, 1H, 2-H), 7.07–7.94 (m, 7H, Arom-H), 8.06 (d, 1H, 9-H, ^3J=12.2 Hz), 11.66 (d, 1H, NH, ^3J=12.2 Hz); IR: $\tilde{\nu}$ 1380 (C–N), 1608 (C=C), 1652 (C=$O_{chromanone}$), 1682 (C=O_{COOH}). Anal. Calcd for $C_{17}H_{13}NO_6$ (326.29): C, 62.39; H, 4.01; N, 4.28. Found: C, 62.04; H, 3.98; N, 4.29%.

4.1.6. 3-(3-Carboxy-2-hydroxyphenyl)aminomethylene-6-chloro-2-hydroxychroman-4-one (3e). Method B, work-up as described above gave 90% of **3e** as yellow needles: mp >360°C; ^{1}H NMR (80 MHz): δ insoluble in DMSO-d_6; IR: $\tilde{\nu}$ 1378 (C–N), 1600 (C=C), 1652 (C=$O_{chromanone}$), 1680 (C=O_{COOH}). Anal. Calcd for $C_{17}H_{12}NClO_6$ (361.74): C, 56.45; H, 3.34; N, 3.87; Cl, 9.80. Found: C, 56.30; H, 3.25; N, 3.85; Cl, 9.75%.

4.1.7. 2-Alkoxy-3-(arylaminomethylene)chroman-4-ones 4a–t. *Method A*. A solution of aromatic amino carboxylic acid **2** (1.148 mmol) in 6 mL of the appropriate alcohol was added dropwise to a stirred solution of 6-substituted 3-formylchromone **1** (1.148 mmol) and 4-toluenesulfonic acid (0.029 mmol) in 6 mL alcohol, and the solution was stirred at room temperature for 12 h. The yellow precipitate was filtered off, washed with alcohol and recrystallized from the appropriate alcohol.

Method B. Hot solutions of 6-aminobenzoic acid or 4-aminohippuric acid (1.148 mmol), respectively, in 6 mL of ethanol were added dropwise to a stirred and boiling solution of 6-substituted 3-formylchromone **1** (1.148 mmol) and 4-toluenesulfonic acid (0.029 mmol) in 6 mL of ethanol, and the solution was refluxed for 3 h. The yellow precipitate was filtered off, washed with alcohol and recrystallized from the appropriate alcohol.

4.1.8. 3-(4-Carboxyphenyl)aminomethylene-2-ethoxychroman-4-one (4a). Method A, work-up as described above gave 92% of **4a**, method B, work-up as described above gave 60% of **4a** as yellow needles: mp 289–291°C; ^{1}H NMR (80 MHz): δ 1.10, 1.12 (2t, 3H, CH_3, ^3J=7.1 Hz), 3.43, 3.89 (2q, 2H, CH_2, ^3J=7.1 Hz), 5.99 (s, 0.7H, 2-H), 6.36 (s, 0.3H, 2-H), 7.05–8.04 (m, 8H, Arom-H), 8.19 (d, 1H, 9-H, ^3J=12.7 Hz), 10.83 (bs, 1H, COOH), 11.88 (d, 1H, NH, ^3J=12.7 Hz); IR: $\tilde{\nu}$ 1380 (C–N), 1602 (C=C), 1653 (C=$O_{chromanone}$), 1673 (C=O_{COOH}). Anal. Calcd for $C_{19}H_{17}NO_5$ (340.56): C, 67.01; H, 5.38; N, 4.11. Found: C, 67.07; H, 5.15; N, 4.22%.

4.1.9. 3-(4-Carboxyphenyl)aminomethylene-6-chloro-2-ethoxychroman-4-one (4b). Method A, work-up as described above gave 90% of **4b** as yellow needles: mp 318–320°C; ^{1}H NMR (300 MHz): δ 1.06, 1.09 (2t, 3H, CH_3, ^3J=7.0 Hz), 3.69, 3.75 (2q, 2H, CH_2, ^3J=7.0 Hz), 6.00 (s, 0.89H, 2-H), 6.55 (s, 0.11H, 2-H), 7.16 (d, 1H, 8-H, $^3J_{7,8}$=5.6 Hz), 7.50 (d, 2H, 10-H, $^3J_{10,11}$=8.7 Hz), 7.59 (dd, 1H, 7-H, $^4J_{5,7}$=2.5 Hz, $^3J_{7,8}$=5.6 Hz), 7.77 (d, 1H, $^4J_{5,7}$=2.5 Hz), 7.95 (d, 2H, 11-H, $^3J_{10,11}$=8.7 Hz), 8.15 (d, 0.11H, 9-H, ^3J=12.4 Hz), 8.24 (d, 0.89H, 9-H, ^3J=12.5 Hz), 11.78 (d, 0.89H, NH, ^3J=12.5 Hz), 11.87 (d, 0.11H, NH, ^3J=12.4 Hz), 12.7 (bs, 1H, COOH); IR: $\tilde{\nu}$ 1380 (C–N), 1600 (C=C), 1644 (C=$O_{chromanone}$), 1692 (C=O_{COOH}). Anal. Calcd for $C_{19}H_{16}NClO_5$ (373.80): C, 61.05; H, 4.31; Cl, 9.48; N, 3.75. Found: C, 60.85; H, 4.25; N, 3.74; Cl, 9.45%.

4.1.10. 3-(4-Carboxyphenyl)aminomethylene-2-ethoxy-6-nitrochroman-4-one (4c). Method A, work-up as described above gave 87% of **4c** as yellow needles: mp 298–305°C (decomp.); ^{1}H NMR (300 MHz): δ 1.05, 1.09 (2t, 3H, CH_3, ^3J=7.4 Hz), 3.76, 3.77 (2q, 2H, CH_2, ^3J=7.4 Hz), 6.14 (s, 0.84H, 2-H), 6.64 (s, 0.16H, 2-H), 7.33 (d, 1H, 8-H, $^3J_{7,8}$=6.7 Hz), 7.52 (d, 2H, 10-H, $^3J_{10,11}$=8.8 Hz), 7.95 (d, 2H, 11-H, $^3J_{10,11}$=8.8 Hz), 8.22 (d, 0.16H, 9-H, ^3J=11.6 Hz), 8.30 (d, 0.84H, 9-H, ^3J=12.6 Hz), 8.36 (dd, 1H, 7-H, $^4J_{5,7}$=2.7 Hz, $^3J_{7,8}$=6.3 Hz), 8.58 (d, 1H, 5-H, $^4J_{5,7}$=2.7 Hz), 10.25 (d, 0.16H, NH, ^3J=11.6 Hz), 11.80 (d, 0.84H, NH, ^3J=12.6 Hz), 12.90 (bs, 1H, COOH); IR: $\tilde{\nu}$ 1352, 1516 (NO_2), 1592 (C=C), 1660 (C=$O_{chromanone}$), 1692 (C=O_{COOH}). Anal. Calcd for $C_{19}H_{16}N_2O_7$ (384.35): C, 59.38; H, 4.20; N, 7.29. Found: C, 58.95; H, 4.23; N, 7.31%.

4.1.11. 3-(4-Carboxyphenyl)aminomethylene-2-ethoxy-6-methylchroman-4-one (4d). Method A, work-up as described above gave 85% of **4d** as yellow needles: mp 309–311°C (decomp.); ^{1}H NMR (300 MHz): δ 1.05, 1.07 (2t, 3H, CH_3, ^3J=6.9 Hz), 2.31 (s, 3H, CH_3), 3.67, 3.71 (2q, 2H, CH_2, ^3J=6.9 Hz), 5.92 (s, 0.84H, 2-H), 6.44 (s, 0.16H, 2-H), 6.97 (d, 1H, 8-H, $^3J_{7,8}$=5.8 Hz), 7.35 (dd, 1H, 7-H, $^4J_{5,7}$=2.3 Hz, $^3J_{7,8}$=5.8 Hz), 7.45 (d, 2H, 10-H, $^3J_{10,11}$=8.7 Hz), 7.62 (d, 1H, 5-H, $^4J_{5,7}$=2.3 Hz), 7.94 (d, 2H, 11-H, $^3J_{10,11}$=8.7 Hz), 8.06 (d, 0.16H, 9-H, ^3J=12.4 Hz), 8.16 (d, 0.84H, 9-H, ^3J=12.4 Hz), 9.91 (d, 0.16H, NH, ^3J=12.4 Hz), 11.79 (d, 0.84H, NH, ^3J=12.4 Hz), 12.62 (bs, 1H, COOH); IR: $\tilde{\nu}$ 1380 (C–N), 1600 (C=C), 1656 (C=$O_{chromanone}$), 1692 (C=O_{COOH}). Anal. Calcd for $C_{20}H_{19}NO_5$ (353.37): C, 67.98; H, 5.42; N, 3.96. Found: C, 67.67; H, 5.34; N, 3.84%.

4.1.12. 3-[4-(*N*-Carboxymethylcarbamoyl)phenylaminomethylene]-2-ethoxychroman-4-one (4e). Method A, work-up as described above gave 81% of **4e** as yellow needles: mp 228–230°C; ^{1}H NMR (80 MHz): δ 1.10 (t, 3H, CH_3, ^3J=7.1 Hz), 3.60–3.98 (m, 4H, 2xCH_2), 5.97 (s, 0.83H, 2-H), 6.49 (s, 0.17H, 2-H), 7.03-7.99 (m, 8H, Arom-H), 8.19 (d, 1H, 9-H, ^3J=12.4 Hz), 8.80 (t, 1H, NH), 11.86 (d, 1H, NH, ^3J=12.4 Hz), 12.59 (bs, 1H, COOH); IR: $\tilde{\nu}$ 1380 (C–N), 1596 (C=C), 1648 (C=O_{amide}), 1657 (C=$O_{chromanone}$), 1690 (C=O_{COOH}). Anal. Calcd for $C_{21}H_{20}N_2O_6$ (396.40): C, 66.63; H, 5.09; N, 7.07. Found: C, 66.51; H, 5.05; N, 6.98%.

4.1.13. 3-(4-Carboxy-3-hydroxyphenyl)aminomethylene-2-ethoxychroman-4-one (4f). Method A, work-up as described above gave 73% of **4f** as yellow needles: mp 215–219°C (decomp.); ^{1}H NMR (80 MHz): δ 1.07, 1.10 (2t, 3H, CH_3, ^3J=7.1 Hz), 3.46, 3.73 (2q, 2H, CH_2, ^3J=7.1 Hz), 5.96 (s, 0.57H, 2-H), 6.87 (s, 0.43H, 2-H), 6.98–7.91 (m, 7H, Arom-H), 8.16 (d, 1H, 9-H, ^3J=12.2 Hz), 11.67 (d, 1H, NH, ^3J=12.2 Hz); IR: $\tilde{\nu}$ 1370 (C–N), 1595 (C=C), 1650 (C=$O_{chromanone}$), 1670 (C=O_{COOH}). Anal. Calcd for $C_{19}H_{17}NO_6$ (355.35): C, 64.22; H, 4.82; N, 3.94. Found: C, 64.08; H, 4.81; N, 3.37%.

4.1.14. 3-(4-Carboxy-3-hydroxyphenyl)aminomethylene-6-chloro-2-ethoxychroman-4-one (4g). Method A, work-up as described above gave 84% of **4g** as yellow needles: mp 205–207°C (decomp.); ^{1}H NMR (80 MHz): δ 1.10 (t, 3H, CH_3, ^3J=7.1 Hz), 3.76 (q, 2H, CH_2, ^3J=7.1 Hz), 5.99 (s, 1H, 2-H), 6.88–7.84 (m, 6H, Arom-H), 8.19 (d, 1H, 9-H, ^3J=12.4 Hz), 11.64 (d, 1H, NH, ^3J=12.4 Hz); IR: $\tilde{\nu}$ 1388 (C–N), 1604 (C=C), 1656 (C=$O_{chromanone}$), 1688 (C=O_{COOH}). Anal. Calcd for $C_{19}H_{16}NClO_6$ (389.06): C, 58.65; H, 4.14; N, 3.60; Cl 9.11. Found: C, 58.16; H, 4.07; N, 3.59; Cl, 9.10%.

4.1.15. 3-(4-Carboxy-3-hydroxyphenyl)aminomethylene-2-ethoxy-6-nitrochroman-4-one (4h). Method A, work-up as described above gave 79% of **4h** as yellow needles: mp 207–209°C (decomp.); ^{1}H NMR (80 MHz): δ 1.03–1.25 (2t, 3H, CH_3, ^3J=7.1 Hz), 3.59–3.91 (2q, 2H, CH_2, ^3J=7.1 Hz), 5.61 (s, 0.28H, 2-H), 6.13 (s, 0.72H, 2-H), 6.89–7.84, 8.41–8.61 (m, 6H, Arom-H), 8.26 (d, 1H, 9-H, ^3J=13.0 Hz), 11.66 (d, 1H, NH, ^3J=13.0 Hz); IR: $\tilde{\nu}$ 1360, 1524 (NO_2), 1600 (C=C), 1644 (C=$O_{chromanone}$), 1685 (C=O_{COOH}). Anal. Calcd for $C_{19}H_{16}N_2O_8$ (400.34): C, 57.00; H, 4.03; N, 7.00. Found: C, 56.87; H, 4.05; N, 6.95%.

4.1.16. 6-Bromo-3-(4-carboxy-3-hydroxyphenyl)aminomethylene-2-ethoxychroman-4-one (4i). Method A, work-up as described above gave 86% of **4i** as yellow needles: mp 206–210°C (decomp.); ^{1}H NMR (80 MHz): δ 1.01 (t, 3H, CH_3, ^3J=7.1 Hz), 3.73 (q, 2H, CH_2, ^3J=7.1 Hz), 5.99 (s, 1H, 2-H), 6.78–7.89 (m, 6H, Arom-H), 8.19 (d, 1H, 9-H, ^3J=13.5 Hz), 11.62 (d, 1H, NH, ^3J=13.5 Hz); IR: $\tilde{\nu}$ 1380 (C–N), 1602 (C=C), 1644 (C=$O_{chromanone}$), 1680 (C=O_{COOH}). Anal. Calcd for $C_{19}H_{16}NBrO_6$ (434.24): C, 52.55; H, 3.71; N, 3.23; Cl, 18.40. Found: C, 52.04; H, 3.64; N, 2.95; Cl, 18.10%.

4.1.17. 3-(4-Carboxy-3-hydroxyphenyl)aminomethylene-2-ethoxy-6-methylchroman-4-one (4j). Method A, work-up

as described above gave 73% of **4j** as yellow needles: Mp 194–197°C (decomp.); ^{1}H NMR (80 MHz): δ 1.08, 1.10 (2t, 3H, CH_3, ^3J=7.1 Hz), 2.32 (s, 3H, CH_3), 3.37, 3.44 (2q, 2H, CH_2, ^3J=7.1 Hz), 5.92 (s, 0.46H, 2-H), 6.42 (s, 0.54H, 2-H), 6.45–7.92 (m, 6H, Arom-H), 8.12 (d, 1H, 9-H, ^3J=12.2 Hz), 11.67 (d, 1H, NH, ^3J=12.2 Hz); IR: $\tilde{\nu}$ 1380 (C–N), 1612 (C═C), 1644 (C═$O_{chromanone}$), 1689 (C═O_{COOH}). Anal. Calcd for $C_{20}H_{19}NO_6$ (369.37): C, 65.03; H, 5.18; N, 3.79. Found: C, 64.78; H, 5.18; N, 3.83%.

4.1.18. 2-(*n*-Butyloxy)-3-(4-carboxy-3-hydroxyphenyl)-aminomethylene-6-chlorochroman-4-one (4k). Method A, work-up as described above gave 86% of **4k** as yellow needles: mp 210–211°C (decomp.); ^{1}H NMR (80 MHz): δ 0.83 (t, 3H, CH_3, ^3J=5.8 Hz), 1.07–1.54 (m, 4H, CH_2CH_2), 3.68 (t, 2H, CH_2, ^3J=6.3 Hz), 5.97 (s, 0.89H, 2-H), 6.51 (s, 0.11H, 2-H), 6.88–7.19 (m, 3H, Arom-H), 7.51–7.84 (m, 3H, Arom-H), 8.20 (d, 1H, 9-H, ^3J=12.4 Hz), 11.17 (d, 1H, NH, ^3J=12.4 Hz); IR: $\tilde{\nu}$ 1380 (C–N), 1602 (C═C), 1644 (C═$O_{chromanone}$), 1688 (C═O_{COOH}). Anal. Calcd for $C_{21}H_{20}NClO_6$ (417.85): C, 60.42; H, 4.83; N, 3.36; Cl, 8.48. Found: C, 59.85; H, 4.81; N, 3.16; Cl, 8.45%.

4.1.19. 3-(4-Carboxy-3-hydroxyphenyl)aminomethylene-6-chloro-2-*n*-hexyloxychroman-4-one (4l). Method A, work-up as described above gave 56% of **4l** as yellow needles: mp 139–140°C (decomp.); ^{1}H NMR (80 MHz): δ 0.86 (t, 3H, CH_3, ^3J=5.8 Hz), 1.17–1.46 (m, 8H $(CH_2)_4$), 3.39 (t, 2H, CH_2, ^3J=6.1 Hz), 5.56 (s, 0.5H, 2-H), 6.19 (s, 0.5H, 2-H), 7.02–7.91 (m, 7H, arom-H, OH), 8.23 (d, 1H, 9-H, ^3J=12.0 Hz), 11.61 (d, 1H, NH, ^3J=12.0 Hz); IR: $\tilde{\nu}$ 1380 (C–N), 1600 (C═C), 1644 (C═$O_{chromanone}$), 1686 (C═O_{COOH}). Anal. Calcd for $C_{23}H_{24}NClO_6$ (445.90): C, 61.95; H, 5.43; N, 3.14; Cl, 7.95. Found: C, 61.72; H, 5.35; N, 3.19; Cl, 7.79%.

4.1.20. 3-(4-Carboxy-3-hydroxyphenyl)aminomethylene-6-chloro-2-*n*-propyloxychroman-4-one (4m). Method A, work-up as described above gave 62% of **4m** as yellow needles: mp 206–208°C (decomp.); ^{1}H NMR (80 MHz): δ 0.76, 0.85 (2t, 3H, CH_3, ^3J=6.8 Hz), 0.96–1.52 (m, 2H, CH_2), 3.51, 3.63 (2t, 2H, CH_2, ^3J=7.6H z), 5.59 (s, 0.37H, 2-H), 5.98 (s, 0.63H, 2-H), 6.84–7.82 (m, 6H, Arom-H), 8.28 (d, 1H, 9-H, ^3J=8.0 Hz), 11.62 (d, 1H, NH, ^3J=8.0 Hz); IR: $\tilde{\nu}$ 1380 (C–N), 1604 (C═C), 1644 (C═$O_{chromanone}$), 1685 (C═O_{COOH}). Anal. Calcd for $C_{20}H_{18}NClO_6$ (403.82): C, 59.49; H, 4.49; N, 3.47; Cl, 8.78. Found: C, 59.15; H, 4.39; N, 3.45; Cl, 8.75%.

4.1.21. 3-(4-Carboxy-3-hydroxyphenyl)aminomethylene-6-nitro-2-*i*-propyloxychroman-4-one (4n). Method A, work-up as described above gave 58% of **4n** as yellow needles: mp 216–219°C (decomp.); ^{1}H NMR (300 MHz): δ 1.07, 1.21 (2d, 6H, $2CH_3$, ^3J=6.3 Hz), 4.09–4.20 (m, 1H, CH), 6.23 (s, 1H, 2-H), 6.89 (dd, 1H, 10-H, $^3J_{10,11}$=8.4 Hz, $^4J_{10,12}$=1.8 Hz), 7.00 (d, 1H, 12-H, $^4J_{10,12}$=1.8 Hz), 7.33 (d, 1H, 8-H, $^3J_{7,8}$=9.1 Hz), 7.79 (d, 1H, 11-H, $^3J_{10,11}$=8.4 Hz), 8.26 (d, 1H, 9-H, ^3J=12.8 Hz), 8.38 (dd, 1H, 7-H, $^3J_{7,8}$=9.1 Hz, $^4J_{5,7}$=2.6 Hz), 8.59 (d, 1H, 5-H, $^4J_{5,7}$=2.6 Hz), 11.65 (d, 1H, NH, ^3J=12.8 Hz); IR: $\tilde{\nu}$ 1348, 1520 (NO_2), 1600 (C═C), 1640 (C═$O_{chromanone}$), 1670 (C═O_{COOH}). Anal. Calcd for $C_{20}H_{18}N_2O_8$ (414.37): C, 57.79; H, 4.38; N, 6.76. Found: C, 57.65; H, 4.36; N, 6.70%.

4.1.22. 3-(3-Carboxy-2-hydroxyphenyl)aminomethylene-2-ethoxychroman-4-one (4o). Method A, work-up as described above gave 57% of **4o** as yellow needles: mp 145–146°C; ^{1}H NMR (80 MHz): δ 1.06 (t, 3H, CH_3, ^3J=7.2 Hz), 3.42 (q, 2H, CH_2, ^3J=7.2 Hz), 5.95 (s, 0.5H, 2-H), 6.17 (s, 0.5H, 2-H), 6.89–7.82 (m, 7H, Arom-H), 8.03 (d, 1H, 9-H, ^3J=12.1 Hz), 12.07 (d, 1H, NH, ^3J=12.1 Hz); IR: $\tilde{\nu}$ 1372 (C–N), 1612 (C═C), 1644 (C═$O_{chromanone}$), 1670 (C═O_{COOH}). Anal. Calcd for $C_{19}H_{17}NO_6$ (355.35): C, 64.22; H, 4.82; N, 3.94. Found: C, 63.78; H, 4.57; N 3.93%.

4.1.23. 3-(3-Carboxy-2-hydroxyphenyl)aminomethylene-6-chloro-2-ethoxychroman-4-one (4p). Method A, work-up as described above gave 73%of **4p** as yellow needles: mp 203–207°C; ^{1}H NMR (80 MHz): δ 1.07 (t, 3H, CH_3, ^3J=7.1 Hz), 2.52 (q, 2H, CH_2, ^3J=7.1 Hz), 5.96 (s, 0.37H, 2-H), 6.20 (s, 0.63H, 2-H), 7.01–7.81 (m, 6H, Arom-H), 8.15 (d, 1H, 9-H, ^3J=12.0 Hz), 12.06 (d, 1H, NH, ^3J=12.0 Hz); IR: $\tilde{\nu}$ 1380 (C–N), 1604 (C═C), 1644 (C═$O_{chromanone}$), 1672 (C═O_{COOH}). Anal. Calcd for $C_{19}H_{16}NClO_6$ (389.06): C, 58.65; H, 4.14; N, 3.60; Cl, 9.11. Found: C, 58.24; H, 4.36; N, 3.43; Cl 8.90%.

4.1.24. 3-(3-Carboxy-2-hydroxyphenyl)aminomethylene-2-ethoxy-6-nitrochroman-4-one (4q). Method A, work-up as described above gave 68% of **4q** as yellow needles: mp 172–175°C (decomp.); ^{1}H NMR (80 MHz): δ 1.06, 1.09 (2t, 3H, CH_3, ^3J=7.5 Hz), 3.46, 3.72 (2q, 2H, CH_2, ^3J=7.5 Hz), 5.97 (s, 0.71H, 2-H), 6.94 (s, 0.29H, 2-H), 7.00–7.88 (m, 7H, Arom-H, OH), 8.04 (d, 1H, 9-H, ^3J=12.4 Hz), 8.96 (s, 0.43H, COOH), 8.94 (s, 0.57H, COOH), 11.90 (d, 1H, NH, ^3J=12.4 Hz); IR: $\tilde{\nu}$ 1356, 1552 (NO_2), 1376 (C–N), 1608 (C═C), 1640 (C═$O_{chromanone}$), 1670 (C═O_{COOH}). Anal. Calcd for $C_{19}H_{16}N_2O_8$ (400.34): C, 57.00; H, 4.03; N, 7.00. Found: C, 56.91; H, 3.99; N, 6.95%.

4.1.25. 3-(3-Carboxy-2-hydroxyphenyl)aminomethylene-2-*i*-propyloxychroman-4-one (4r). Method A, work-up as described above gave 60% of **4r** as yellow needles: mp 139–143°C; ^{1}H NMR (80 MHz): δ 0.76–0.86 (m, 6H, 2×CH_3), 3.60–3.75 (m, 1H, CH), 5.94 (s, 0.5H, 2-H), 6.17 (s, 0.5H, 2-H), 7.01–8.08 (m, 7H, Arom-H), 8.14 (d, 1H, 9-H, ^2J=12.1 Hz), 12.06 (d, 1H, NH, ^2J=12.1 Hz); IR: $\tilde{\nu}$ 1380 (C–N), 1608 (C═C), 1640 (C═$O_{chromanone}$), 1672 (C═O_{COOH}). Anal. Calcd for $C_{20}H_{19}NO_6$ (369.37): C, 65.03; H, 5.18; N, 3.79. Found: C, 64.78; H, 5.15; N, 3.71%.

4.1.26. 3-(3-Carboxy-4-hydroxyphenyl)aminomethylene-2-ethoxychroman-4-one (4s). Method A, work-up as described above gave 62% of **4s** as yellow needles: mp 285–287°C (decomp.); ^{1}H NMR (80 MHz): δ 1.06, 1.09 (2t, 3H, CH_3, ^3J=7.1 Hz), 3.45, 3.72 (2q, 2H, CH_2, ^3J=7.1 Hz), 5.97 (s, 0.71H, 2-H), 6.94 (s, 0.29H, 2-H), 7.00–7.87 (m, 8H, Arom-H, OH), 8.04 (d, 1H, 9-H, ^3J=12.7 Hz), 8.69 (s, 0.43H, COOH), 8.93 (s, 0.57H, COOH), 11.90 (d, 1H, NH, ^3J=12.7 Hz); IR: $\tilde{\nu}$ 1380 (C–N), 1612 (C═C), 1640 (C═$O_{chromanone}$), 1672 (C═O_{COOH}). Anal. Calcd for $C_{19}H_{17}NO_6$ (355.35): C, 64.22; H, 4.82; N, 3.94. Found: C, 63.87; H, 4.76; N, 3.90%.

4.1.27. 3-(3-Carboxy-4-hydroxyphenyl)aminomethylene-2-ethoxy-6-methylchroman-4-one (4t). Method A, work-up as described above gave 65% of **4t**: mp 275–277°C (decomp.); ^{1}H NMR (80 MHz): δ 1.01, 1.08 (2t, 3H, CH_3, ^3J=7.2 Hz), 2.31 (s, 3H, CH_3), 3.46, 3.69 (2q, 2H, CH_2, ^3J=7.2 Hz), 5.92 (s, 0.5H, 2-H), 6.16 (s, 0.5H, 2-H), 6.84–7.94 (m, 7H, Arom-H, OH), 8.05 (d, 1H, 9-H, ^3J=12.2 Hz), 11.84 (d, 1H, NH, ^3J=12.2 Hz); IR: $\tilde{\nu}$ 1380 (C–N), 1602 (C=C), 1650 (C=$O_{chromanone}$), 1685 (C=O_{COOH}). Anal. Calcd for $C_{20}H_{19}NO_6$ (369.37): C, 65.03; H, 5.18; N, 3.79. Found: C, 64.75; H, 5.12; N, 3.63%.

4.1.28. Synthesis of 3-(aryliminomethyl)chromones 5. Hot solutions of 4-aminosalicylic acid or 3-aminosalicylic acid (1.148 mmol) in 6 mL of ethanol were added dropwise to a stirred and boiling solution of 6-substituted 3-formylchromone **1** (1.148 mmol) and 4-toluenesulfonic acid (0.029 mmol) in 6 mL of ethanol, and refluxed for 3 h. The precipitate was filtered off, washed with diethyl ether and dried.

4.1.29. 3-[(4-Carboxy-3-hydroxyphenyl)iminomethyl]-chromone (5a). Work-up as described above gave 51% of **5a** as light ochre powder: mp 249–250°C; ^{1}H NMR (80 MHz): δ 7.01 (s, 1H, Arom-H), 7.10 (s, 1H, OH), 7.37–7.60 (m, 4H, Arom-H), 8.11 (s, 0.5H, 9-H), 8.21 (s, 0.5H, 9-H), 8.80 (s, 1H, 2-H), 8.86 (d, 1H, 8-H, ^3J=1.2 Hz), 9.25 (d, 1H, 5-H, ^4J=2.2 Hz), 10.40 (s, 1H, COOH); IR: $\tilde{\nu}$ 1602 (C=N), 1653 (C=$O_{chromone}$), 1673 (C=O_{COOH}). Anal. Calcd for $C_{17}H_{11}NO_5$ (309.28): C, 66.02; H, 3.58; N, 4.52. Found: C, 65.57; H, 3.56; N, 4.21%.

4.1.30. 6-Bromo-3-[(4-carboxy-3-hydroxyphenyl)imino-methyl]chromone (5b). Work-up as described above gave 49% of **5b** as red–brown powder: mp 226–230°C; ^{1}H NMR (80 MHz): δ 7.08–7.16 (m, 5H, Arom-H, OH), 8.11 (s, 1H, 9-H), 8.65 (s, 1H, 8-H), 9.10 (s, 2H, 2-H, 5-H), 10.44 (s, 1H, COOH); IR: $\tilde{\nu}$ 1596 (C=N), 1652 (C=$O_{chromone}$), 1670 (C=O_{COOH}). Anal. Calcd for $C_{17}H_{10}NBrO_5$ (388.17): C, 52.60; H, 2.59; N, 3.60; Br, 20.58. Found: C, 52.15; H, 2.44; N, 3.32; Br 20.60%.

Kinetics. An alcoholic solution (2 mL, c=4×10^{-4} mol dm^{-3}) of 6-substituted 3-formylchromone **1** was mixed with 2 mL of alcoholic solution of 4-toluenesulfonic acid (c=4×10^{-4} mol dm^{-3}). The resultant solution and 2 mL of alcoholic solution of aminosalicylic acid **2** (c=2×10^{-4} mol dm^{-3}) were separately heated to 40.5°C and then mixed. All measurements were performed in a 1-cm thick absorption cell at 40.5°C. The kinetics of reactions was monitored via UV–VIS spectrophotometry using a Hewlett-Packard 'Diode Array 8254' spectrometer. The rate constants were calculated using the Hewlett-Packard programme-assisted method of initial rate, followed by fitting of the experimental data to a parabolic curve. Kinetic experiments were measured until the limiting equilibrium concetration was reached.

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