# Efficient Synthesis of (3*E*)-3-[Amino(aryl)methylidene]chromane-2,4-diones (=(3*E*)-3-[Amino(aryl)methylene]-2*H*-1-benzopyran-2,4(3*H*)-diones) *via* a Three-Component Reaction

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Dedicated to Prof. *Junes Ipaktschi* on the occasion of his 70th birthday

The *Michael*-type addition of a 4-hydroxycoumarin (=4-hydroxy-2*H*-1-benzopyran-2-one) **1** to a $\beta$-nitrostyrene (=(2-nitroethenyl)benzene) **2** in the presence of $AcONH_4$ leads to substituted (3*E*)-3-[amino(aryl)methylidene]chroman-2,4-diones (=(3*E*)-3-[amino(aryl)methylene]-2*H*-1-benzopyran-2,4(3*H*)-diones) **4** (*Table 1*). High yields, short reaction time, and easy workup are advantages of this novel one-pot three-component reaction.

**Introduction.** – The 3-substituted 4-hydroxycoumarins (=4-hydroxy-2*H*-1-benzopyran-2-ones) are interesting heterocyclic compounds because of their biological activity and therapeutic use [1]. These compounds, which are widely distributed in nature, have antibacterial, anti-HIV [2], antiviral [3], anticoagulant [4], and antioxidant [5] activities, and they have also been used as anticancer agents [6]. Warfarin and phenprocoumon are examples of compounds which contain a 3-substituted 4-hydroxy coumarin moiety (*Fig. 1*). Warfarin is a synthetic compound which can be used as a rodenticide and anticoagulant, while phenprocoumon exhibits antiviral and anti-HIV activities [7].

The (3*E*)-3-[amino(aryl)methylidene]chromane-2,4-diones (=(3*E*)-3-[amino(aryl)methylene]-2*H*-1-benzopyran-2,4(3*H*)-diones) have shown cytotoxic effects on the

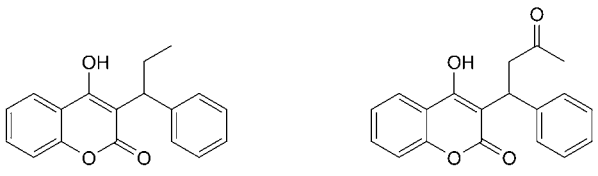


Fig. 1. *Warfarin and Phenprocoumon, containing a 3-substituted 4-hydroxycoumarin moiety*

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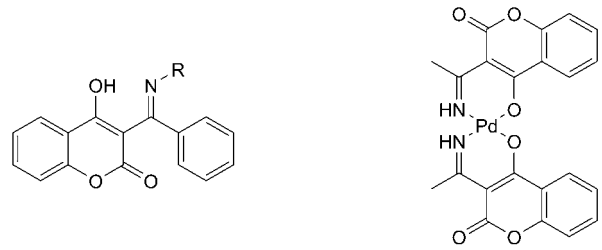
two leukemia cell lines HL-60 and NALM-6 [8], and some compounds **A** with a 4-hydroxycoumarin skeleton have a great potential for complexation with different metals, and the products have different biological activities (see, *e.g.*, **B** in *Fig. 2*) [9]. Therefore, the development of new procedures for the synthesis of this skeleton is of great interest.



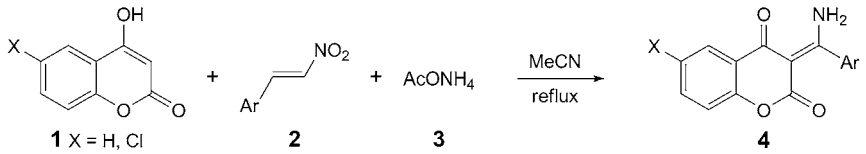

**A** R = Me, $HOCH_2CH_2$, or Bn **B**

Fig. 2. *Known (3*E*)-3-[amino(aryl)methylidene]chromane-2,4-diones* **A** *and a palladium complex* **B**

[Amino(aryl)methylidene]chromanediones have usually been synthesized *via* multistep reactions starting with acetylation of 4-hydroxycoumarins [9][10]. In the second step, the 3-acetyl-4-hydroxycoumarins are treated with a variety of amines leading to substituted (3*E*)-3-[amino(aryl)methylidene]chromane-2,4-diones. Harsh conditions of this process such as high temperature, low yields, multistep reactions, and tedious workup make this method less attractive. Therefore, it is advantageous to carry out this synthesis under shorter and more efficient conditions. In continuation of our research to find new tandem multicomponent reactions [11], we became interested in the synthesis of (3*E*)-3-[amino(aryl)methylidene]chromane-2,4-diones **4**. Herein, we present a new one-pot approach to **4** *via* a three-component reaction of a 4-hydroxycoumarin **1**, a *β*-nitrostyrene (=(2-nitroethenyl)benzene) **2**, and $AcONH_4$ (**3**), which markedly reduces the reaction time.

**Results.** – *β*-Nitrostyrene (**2a**) and its derivatives are important synthetic intermediates and starting materials for the synthesis of a variety of useful building blocks [12]. In addition, due to the strong electron-withdrawing nature of the $NO_2$ group, they play a key role in the *Michael* addition reaction which, in this case, leads to the desired products in high yields [13]. Thus the reaction between *β*-nitrostyrenes **2** (prepared by condensation of benzaldehydes and $MeNO_2$ under basic conditions) and 4-hydroxycoumarins **1** in the presence of $AcONH_4$ (**3**) under reflux conditions in MeCN afforded (3*E*)-3-[amino(aryl)methylene]chromane-2,4-diones **4a**–**4j** in good to excellent yields (*Table 1*). In all cases, the reactions were completed within 2 h. It is noticeable that a Cl substituent at the benzene moiety of the 4-hydroxycoumarin decreased the reactivity and yield of the reaction. The structures of the products **4a**–**4j** were assigned by IR, $^1$H- and $^{13}$C-NMR, and high-resolution MS data [14]. In $^1$H-NMR spectra of the product, the distinguished signals are related to the two H-atoms of the $NH_2$ group which resonate at $\delta$(H) 11.75–11.98 (intramolecular H-bonding of one

Table 1. *Synthesis of (3*E*)-3-[Amino(aryl)methylidene)chromane-2,4-diones* **4a**–**4j** via *the Three-Component Reaction*




**1** X = H, Cl **2** **3** **4**

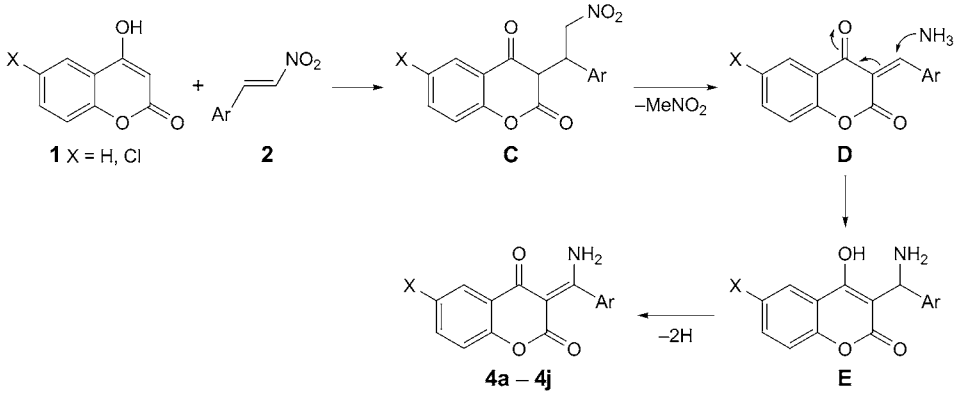
| Product | X | Ar | Yield [%][a]) | Product | X | Ar | Yield [%][a]) |
|---|---|---|---|---|---|---|---|
| **4a** | H | Ph | 98 | **4f** | H | 3-$NO_2$–$C_6H_4$ | 93 |
| **4b** | H | 4-Br–$C_6H_4$ | 88 | **4g** | Cl | Ph | 75 |
| **4c** | H | 4-Cl–$C_6H_4$ | 98 | **4h** | Cl | 4-Br–$C_6H_4$ | 60 |
| **4d** | H | 4-MeO–$C_6H_4$ | 86 | **4i** | Cl | 4-Cl–$C_6H_4$ | 64 |
| **4e** | H | 4-Me–$C_6H_4$ | 93 | **4j** | Cl | 4-Me–$C_6H_4$ | 69 |

[a]) Yields of isolated chromane-2,4-diones.

NH) and $\delta$(H) 10.00–10.30 (free NH), respectively. These peaks disappeared on addition of $D_2O$ [9][10b].

Although the mechanistic details of the reaction are not known, a plausible rationalization for product formation is displayed in *Scheme 1*. It is conceivable that the reaction can start with deprotonation of the 4-hydroxycoumarin **1** and *Michael* addition of the potential carbanion to the $\beta$-nitrostyrene **2** under formation of **C**. Elimination of $MeNO_2$ results in enone **D**. Addition of $NH_3$ to intermediate **D** leads to **E** followed by dehydrogenation which leads to products **4a**–**4j**.

Scheme 1. *Plausible Mechanism for the Formation of Compounds* **4a**–**4j**. For X and Ar, see *Table 1*.

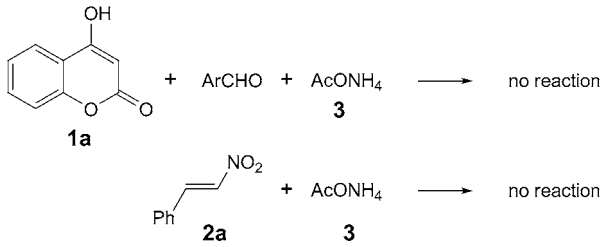



**1** X = H, Cl **2** **C** **D** **E** **4a** – **4j**

To gain more insight into the reaction mechanism, we tried to show the importance of the $\beta$-nitrostyrene on the outcome of this reaction. Therefore, the reaction of $\beta$-nitrostyrene adduct with $AcONH_4$ was studied; but it did not proceed (*Scheme 2*). In another attempt, the three-component reaction of benzaldehyde, 4-hydroxycoumarin (**1**), and $AcONH_4$ (**3**) was selected as the model reaction. Also in this case, we did not

obtain the desired product, (aminomethylidene)chromane-2,4-dione. Although the aldehydes are used to synthesize the imine functional group, using them instead of $\beta$-nitrostyrene in the described reaction did not form the anticipated products. It shows the importance of $\beta$-nitrostyrene to form the desired products **4** in this reaction.

*Scheme 2*




To obtain more information about the structure of the products, we performed an X-ray crystal-structure determination with single crystals of compound **4a**, which confirmed the presence of the [amino(aryl)methylidene]chromanedione structure (see *Fig. 3*).

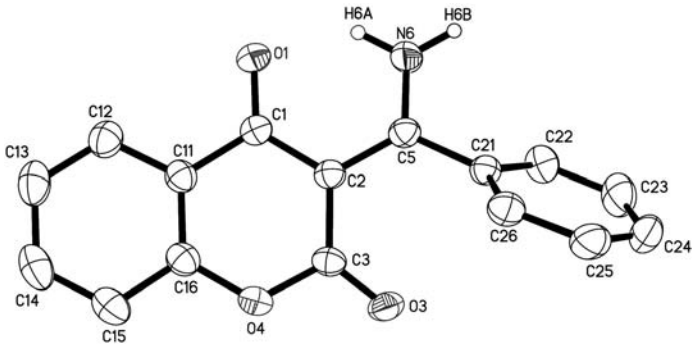



Fig. 3. *ORTEP Structure of compound* **4a**. Arbitrary atom numbering.

The bond lengths for the C=O of the ketone and lactone moiety of **4a** are 1.2435 and 1.2117 Å, respectively; these bond lengths are similar to the reported bond lengths 1.230 and 1.190 Å for $C(sp^2)$–(C=O)–$C(sp^2)$ and $C(sp^2)$–(C=O)–O–$C(sp^2)$, respectively [14]. While the reported bond length for $C(sp^2)$–$NH_2$ is 1.336 Å [14], the bond length for the C–N of **4a** is 1.307 Å. Thus in all cases, the bond lengths feature anomalies. It seems that the reason for this is the conjugation between the C=O of both the ketone and lactone moiety. The crystal structure is stabilized by intramolecular and intermolecular H-bonding of the type N–H$\cdots$O=C. The different H-bonds in the crystal structure of **4a** are shown in *Fig. 4*.

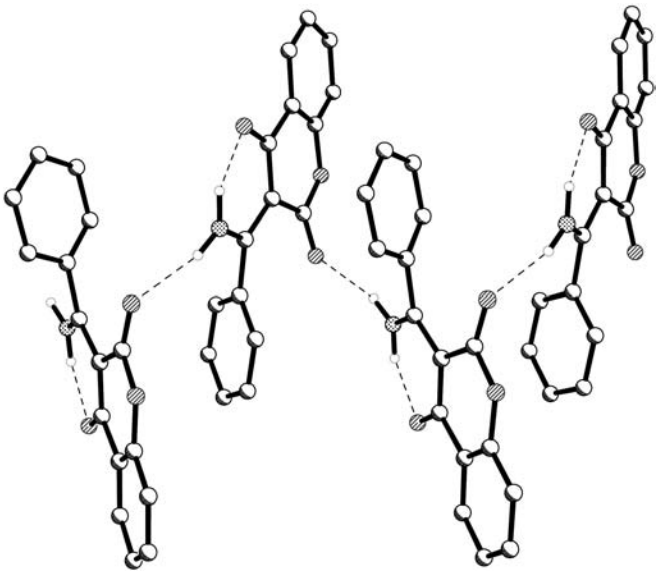


Fig. 4. *Intramolecular and intermolecular H-bonding in compound* **4a**. The H-atoms are omitted for the sake of clarity, except for those of the $NH_2$ groups.

In conclusion, we reported an easy and efficient method for the synthesis of substituted [amino(aryl)methylidene]chromane-2,4-diones in good to excellent yields. Simple reaction conditions, inexpensive starting materials, simple workup, and short reaction times are the advantages of the presented method. Further studies on the applications of these compounds as ligands to prepare complexes with different metal ions and also to study the biological activities of these compounds are under study.

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## Experimental Part

1. *General.* Commercially available materials were used without further purification. TLC: silica gel *60 $F_{254}$* (*Merck*). M.p.: *Electrothermal-9100* apparatus; uncorrected. IR Spectra: *ABB-FTLA 2000* FT-IR spectrometer; $\tilde{\nu}$ in $cm^{-1}$. $^1H$- and $^{13}C$-NMR Spectra: *Bruker* spectrometers; 500 or 300 ($^1H$), and 125 or 75 MHz ($^{13}C$); in ($D_6$)DMSO; $\delta$ in ppm rel. to $Me_4Si$ as internal standard, *J* in Hz. HR-ESI-MS: *Mass-ESI-POS* (*Apex Qe-FT-ICR* instrument) spectrometer; in *m*/*z*.

2. *Synthesis of* **4a**–**4j**: *General Procedure.* A mixture of a 4-hydroxycoumarin **1** (162 mg, 1 mmol), a $\beta$-nitrostyrene **2** (1 mmol), and $AcONH_4$ (**3**; 450 mg,10 mmol) in MeCN (10 ml) was stirred under reflux. After completion of the reaction (TLC (petroleum ether/AcOEt 1:1) monitoring), the mixture was cooled to r.t., the solvent evaporated, and the resulting solid washed with $H_2O$ and extracted with AcOEt. The org. phase was dried ($MgSO_4$). In some cases, further purification was done by recrystallization from petroleum ether/$CH_2Cl_2$.

*(*3E*)-3-[Amino(phenyl)methylene]-2*H*-1-benzopyran-2,4(3*H*)-dione* (**4a**): Yield 255 mg (98%). Colorless crystal. M.p. 218–219°. IR (KBr): 3252, 1683, 1607. $^1H$-NMR (500 MHz): 7.24 (*d*, *J* = 8.2, 1 arom. H); 7.29 (*t*, *J* = 7.5, 1 arom. H); 7.42 (*t*, *J* = 7.0, 2 arom. H); 7.46 (*t*, *J* = 7.0, 2 arom. H); 7.47–7.53 (*m*,

1 arom. H); 7.63 (*t*, *J* = 7.7, 1 arom. H); 7.94 (*d*, *J* = 7.7, 1 arom. H); 10.09 (*s*, NH); 12.00 (*s*, NH···O). $^{13}$C-NMR (125 MHz): 94.0; 116.4; 120.5; 123.6; 125.7; 127.2; 127.9; 130.0; 134.1; 136.5; 153.6; 161.3; 175.6; 179.6. HR-ESI-MS: 266.08135 ($[M+H]^+$, $C_{16}H_{12}NO_3^+$; calc. 266.08142).

*(3*E*)-3-[Amino(4-bromophenyl)methylene]-2*H*-1-benzopyran-2,4(3*H*)-dione* (**4b**): Yield 283 mg (88%). Yellow solid. M.p. 227–230°. IR (KBr): 3238, 1682, 1602. $^1$H-NMR (300 MHz): 7.25 (*d*, *J* = 8.1, 1 arom. H); 7.29 (*t*, *J* = 8.1, 1 arom. H); 7.38 (*d*, *J* = 8.5, 2 arom. H); 7.60–7.64 (*m*, 1 arom. H); 7.65 (*d*, *J* = 8.5, 2 arom. H); 7.93 (*dd*, *J* = 8.5, 1.4, 1 arom. H); 10.14 (*s*, NH); 11.94 (*s*, NH···O). $^{13}$C-NMR (75 MHz): 95.2; 116.5; 120.4; 123.4; 123.7; 125.8; 129.4; 130.9; 134.3; 135.8; 153.6; 161.5; 174.4; 179.7. HR-ESI-MS: 343.99195 ($[M+H]^+$, $C_{16}H_{11}BrNO_3^+$; calc. 343.99203).

*(3*E*)-3-[Amino(4-chlorophenyl)methylene]-2*H*-1-benzopyran-2,4(3*H*)-dione* (**4c**): Yield 310 mg (98%). Yellow solid. M.p. 218–220°. IR (KBr): 3254, 1682, 1611. $^1$H-NMR (300 MHz): 7.27 (*m*, 2 arom. H); 7.45 (*d*, *J* = 8.4, 2 arom. H); 7.53 (*d*, *J* = 8.4, 2 arom. H); 7.64 (*t*, *J* = 7.6, 1 arom. H); 7.93 (*d*, *J* = 7.6, 1 arom. H); 10.14 (*s*, NH); 11.95 (*s*, NH···O). $^{13}$C-NMR (75 MHz): 95.2; 116.5; 120.5; 123.7; 125.8; 128.1; 129.3; 134.3; 134.7; 135.4; 153.6; 161.5; 174.4; 179.7. HR-ESI-MS: 300.04240 ($[M+H]^+$, $C_{16}H_{11}ClNO_3^+$; calc. 300.04247).

*(3*E*)-3-[Amino(4-methoxyphenyl)methylene]-2*H*-1-benzopyran-2,4(3*H*)-dione* (**4d**): Yield 225 mg (86%). Yellow solid. M.p. 218–219°. IR (KBr): 3277, 1692, 1614. $^1$H-NMR (300 MHz): 3.82 (*s*, MeO); 7.0 (*d*, *J* = 8.6, 2 arom. H); 7.24 (*d*, *J* = 8.5, 1 arom. H); 7.27 (*t*, *J* = 7.5, 1 arom. H); 7.41 (*d*, *J* = 8.7, 2 arom. H); 7.62 (*td*, *J* = 7.5, 1.1, 1 arom. H); 7.93 (*d*, *J* = 7.7, 1 arom. H); 9.98 (br. *s*, NH); 11.87 (br. *s*, NH···O). $^{13}$C-NMR (75 MHz): 55.3; 94.9; 113.4; 116.4; 120.6; 123.5; 125.7; 128.3; 129.6; 134.0; 153.6; 161.2; 161.5; 175.1; 179.4. HR-ESI-MS: 296.09200 ($[M+H]^+$, $C_{17}H_{14}NO_4^+$; calc. 296.09209).

*(3*E*)-3-[Amino(4-methylphenyl)methylene]-2*H*-1-benzopyran-2,4(3*H*)-dione* (**4e**): Yield 255 mg (93%). Yellow solid. M.p. 208–210°. IR (KBr): 3257, 1697, 1611. $^1$H-NMR (300 MHz): 2.48 (*s*, Me); 7.21–7.33 (*m*, 6 arom. H); 7.62 (*dt*, *J* = 7.2, 1.2, 1 arom. H); 7.93 (*d*, *J* = 7.7, 1 arom. H); 10.02 (br. *s*, NH); 11.94 (br. *s*, NH···O). $^{13}$C-NMR (75 MHz): 21.0; 95.1; 116.4; 120.5; 123.6; 125.7; 127.4; 128.5; 133.6; 134.1; 140.0; 153.6; 161.4; 175.7; 179.6. HR-ESI-MS: 280.09703 ($[M+H]^+$, $C_{17}H_{13}NO_3^+$; calc. 280.09710).

*(3*E*)-3-[Amino(3-nitrophenyl)methylene]-2*H*-1-benzopyran-2,4(3*H*)-dione* (**4f**): Yield 315 mg (93%). Yellow solid. M.p. 245–249°. IR (KBr): 3368, 1689, 1617. $^1$H-NMR (500 MHz): 7.25 (*d*, *J* = 8.1, 1 arom. H); 7.29 (*t*, *J* = 7.5, 1 arom. H); 7.64 (*dt*, *J* = 7.6, 1.0, 1 arom. H); 7.75 (*t*, *J* = 8.0, 1 arom. H); 7.91 (*d*, *J* = 7.5, 1 arom. H); 7.93 (*d*, *J* = 7.5, 1 arom. H); 8.31 (*s*, 1 arom. H); 8.35 (*d*, *J* = 8.0, 1 arom. H); 10.28 (*s*, NH); 11.98 (*s*, NH···O). $^{13}$C-NMR (125 MHz): 95.4; 116.5; 120.4; 122.2; 123.8; 124.3; 125.8; 129.6; 134.0; 134.4; 138.1; 147.3; 153.6; 161.7; 172.9; 179.7. HR-ESI-MS: 311.06655 ($[M+H]^+$, $C_{16}H_{11}N_2O_5^+$; calc. 311.06665).

*(3*E*)-3-[Amino(phenyl)methylene]-6-chloro-2*H*-1-benzopyran-2,4(3*H*)-dione* (**4g**): Yield 220 mg (75%). Yellow solid. M.p. 230–235°. IR (KBr): 3427, 1700, 1609. $^1$H-NMR (300 MHz): 7.29 (*d*, *J* = 8.7, 1 arom. H); 7.41–7.54 (*m*, 5 arom. H); 7.65 (*dd*, *J* = 8.7, 2.6, 1 arom. H); 7.83 (*d*, *J* = 2.6, 1 arom. H); 10.23 (*s*, NH); 11.88 (*s*, NH···O). $^{13}$C-NMR (75 MHz): 95.0; 118.8; 121.9; 124.8; 127.3; 127.8; 128.0; 130.2; 133.7; 136.3; 152.2; 161.0; 175.8; 178.2. HR-ESI-MS: 300.04240 ($[M+H]^+$, $C_{16}H_{11}ClNO_3^+$; calc. 300.04247).

*(3*E*)-3-[Amino(4-bromophenyl)methylene]-6-chloro-2*H*-1-benzopyran-2,4(3*H*)-dione* (**4h**): Yield 223 mg (60%). Yellow solid. M.p. 287–300°. IR (KBr): 3253, 1699, 1612. $^1$H-NMR (300 MHz): 7.30 (*d*, *J* = 8.7, 1 arom. H); 7.39 (*d*, *J* = 8.4, 2 arom. H); 7.65 (*d*, *J* = 8.7, 1 arom. H); 7.66 (*d*, *J* = 8.7, 2 arom. H); 7.82 (*d*, *J* = 2.5, 1 arom. H); 10.24 (*s*, NH); 11.83 (*s*, NH···O). $^{13}$C-NMR (75 MHz): 95.1; 118.8; 121.8; 123.6; 124.8; 127.9; 129.5; 131.0; 133.8; 135.5; 152.2; 161.1; 174.5; 178.2. HR-ESI-MS: 377.95300 ($[M+H]^+$, $C_{16}H_{10}BrClNO_3^+$; calc. 377.95308).

*(3*E*)-3-[Amino(4-chlorophenyl)methylene]-6-chloro-2*H*-1-benzopyran-2,4(3*H*)-dione* (**4i**): Yield 244 mg (64%). Yellow solid. M.p. 284–287°. IR (KBr): 3249, 1702, 1613, 1595. $^1$H-NMR (300 MHz): 7.30 (*d*, *J* = 8.7, 1 arom. H); 7.46 (*d*, *J* = 8.5, 2 arom. H); 7.53 (*d*, *J* = 8.5, 2 arom. H); 7.66 (*dd*, *J* = 8.7, 2.6, 1 arom. H); 7.82 (*d*, *J* = 2.6, 1 arom. H); 10.29 (br. *s*, NH); 11.75 (br. *s*, NH···O). $^{13}$C-NMR (75 MHz): 95.1; 118.8; 121.8; 124.8; 127.9; 128.1; 129.3; 133.8; 134.8; 135.1; 152.2; 161.1; 174.5; 178.2. HR-ESI-MS: 344.00355 ($[M+H]^+$, $C_{16}H_{10}Cl_2NO_3^+$; calc. 334.00356).

*(3*E*)-3-(Amino(4-methylphenyl)methylene)-6-chloro-2*H*-1-benzopyran-2,4(3*H*)-dione* (**4j**): Yield 217 mg (69%). Yellow solid. M.p. 247–250°. IR (KBr): 3224, 1694, 1601. $^1$H-NMR (300 MHz): 2.38 (*s*, Me); 7.25 (*d*, *J* = 8.1, 1 arom. H); 7.30 (*d*, *J* = 8.4, 1 arom. H); 7.33 (*d*, *J* = 8.1, 2 arom. H); 7.66 (*dd*, *J* = 8.4,

2.7, 1 arom. H); 7.84 (*d*, *J* = 2.6, 1 arom. H); 10.16 (*s*, NH); 11.82 (*s*, NH ··· O). $^{13}$C-NMR (75 MHz): 21.0; 94.9; 118.8; 121.9; 124.7; 127.5; 127.8; 128.5; 133.3; 133.7; 140.2; 152.2; 161.0; 175.8; 178.1. HR-ESI-MS: 314.05810 ($[M+H]^+$, $C_{17}H_{13}ClNO_3^+$; calc. 314.05818).

3. *X-Ray Structure Determination of* **4a** (*Table 2*). *Bruker-APEX* diffractometer; $\omega$-scans with CCD area detector, covering a whole sphere in reciprocal space. Intensities were corrected for *Lorentz* and polarization effects, an empirical absorption correction was applied with SADABS [15] based on the *Laue* symmetry of the reciprocal space, $T_{min} = 0.96$, $T_{max} = 1.00$. The structure was solved by direct methods and refined against $F^2$ with a full-matrix least-squares algorithm and the SHELXTL (Version 2008/4) software package [16]; 189 parameters were refined, and H-atoms were treated by means of appropriate riding models. CCDC-787516 contains the supplementary crystallographic data for this article. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre via* www.ccdc.cam.ac.uk/data_request/cif.

Table 2. *Crystallographic Data of Compound* **4a**

| | | | |
|---|---|---|---|
| Crystallized from | petroleum ether (40–60°)/$CH_2Cl_2$ 3 : 1 | $\theta_{range}$ [°] | 2.3–28.3 |
| | | $\mu$ [mm$^{-1}$] | 0.10 |
| Empirical formula | $C_{16}H_{11}NO_3$ | Data collection method | 0.3° $\omega$-scans |
| $M_r$ [g mol$^{-1}$] | 265.26 | No. of measured reflections | 25238 |
| Crystal color, habit | colorless, plate | No. of independent reflections | 3167 ($R_{int} = 0.0488$) |
| Crystal dimension [mm] | 0.42 × 0.17 × 0.05 | No. of observed reflections | 2627 |
| Temp. [K] | 200(2) | Criterion of observed reflections | $I > 2\sigma(I)$ |
| Crystal system | orthorhombic | $R_{int}$ | 0.0488 |
| Space group | *Pbca* | $\theta_{max}$ [°] | 28 |
| $Z$ | 8 | Refinement | full-matrix least-squares on $F^2$ |
| Unit cell parameters: | | $R_1$ ($F$) | 0.052 |
| $a$ [Å] | 12.8481(9) | $wR$ ($F^2$) | 0.124 |
| $b$ [Å] | 8.3308(6) | $h_{min}$, $h_{max}$ | −16/17 |
| $c$ [Å] | 23.7480(16) | $k_{min}$, $k_{max}$ | −11/11 |
| $V$ [Å$^3$] | 2541.9(3) | $k_{min}$, $l_{max}$ | −31/31 |
| $D_x$ [Mg m$^{-3}$] | 1.39 | Goodness-of-fit on $F^2$ | 1.08 |
| $T$ [K] | 200(2) | Final $R$ indices ($I > 2\sigma(I)$) | $R^1 = 0.052$, $\omega R^2 = 0.124$ |
| Radiation type | Mo$K_\alpha$ | Residual electron density [eA$^{-3}$] | −0.22 to 0.37 |
| Wavelength [Å] | 0.71073 | | |

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