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Reactivity of 3-formyl- and 3-cyanothiochromones toward some *N*- and *C*-nucleophiles. Novel synthesis of 3-substituted 2-aminothiochromones

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3-Di(indol-3-yl)methylthiochromones
Nucleophilic addition
Regioselectivity

ABSTRACT

The reactions of 3-formylthiochromone with *o*-phenylenediamines, *o*-aminobenzenethiol, and indoles proceeded at the aldehyde group to give 3-(benzimidazol-2-yl)thiochromone, 3-(benzothiazol-2-yl) thiochromone, and 3-di(indol-3-yl)methylthiochromones, respectively. 3-Formyl- and 3-cyanothiochromones react with primary aromatic amines and phenylhydrazine to give the corresponding anils and phenylhydrazones of 3-formyl- and 2-amino-3-formylthiochromones. The reaction of 3-cyanochromones with *o*-phenylenediamines gave 2-amino-3-[(2-aminophenyl)iminomethyl]-4*H*-chromen-4-ones.

1. Introduction

Derivatives of 4*H*-1-benzopyran-4-one, also known as 4*H*-chromen-4-ones or chromones, belong to an important class of natural oxygen-containing heterocycles that are widely distributed among many plants.[1] Many natural and synthetic chromone derivatives exhibit various types of biological activity[2] and find use as valuable synthetic intermediates in the preparation of pharmacologically relevant products and new heterocyclic systems.[3] In recent years, 3-formyl- and 3-acylchromones have attracted considerable attention as highly reactive compounds, which can serve as the starting materials in syntheses of a whole series of heterocycles with useful properties due to three strong electrophilic centers (carbon atoms C-2 and C-4 of the chromone system and the RCO group).[4] These compounds possess a highly polarized C2–C3 π-bond and their reactions with dinucleophiles start predominantly from the attack of the unsubstituted C-2 atom (1,4-addition) and are accompanied by pyrone ring-opening to form the β-dicarbonyl intermediate capable of undergoing intramolecular heterocyclizations.[4,5] Along with this route, the initial attack can occur at the 3-RCO group as well (1,2-addition), which does not exclude the variant of recyclization due to the internal nucleophilic substitution.[5]

While 3-formylchromones **1** have been extensively investigated regarding their chemical properties,[4] little attention has been paid toward the reactivity of 3-formylthiochromones **2**, probably owing to the lack of general methods for the preparation of these compounds. Only a handful of papers describing some reactions of 3-formylthiochromone **2** with a number of *N*-nucleophiles[6] and such *C*-nucleophiles as indolinium or benzothiazolinium salts,[7] the Wittig–Horner reagent of diethyl α-(benzylthio)benzylphosphonate,[8] and malonic acid (with 3-formylthioflavone)[9] are present in the literature. All these reactions proceed by nucleophilic 1,2-addition to give 3-substituted thiochromones without opening of the thiopyrone ring.

The first synthesis of thiochromone **2** from 3-(hydroxymethylene) thiochroman-4-one **3** and *N*-chlorosuccinimide was reported by Chen and Reynolds in 1979.[10] However, on repeating their procedure, Giles and Marson[11] were unable to obtain **2**; instead, they found that this reaction afforded the chlorinated ketones: 3-chlorothiochroman-4-one, 3-chlorothiochromone, and 2,3-dichlorothiochrome. The reaction of thiochroman-4-one **4** with the Vilsmeier–Haack reagent

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affords 4-chloro-2*H*-thiochromene-3-carbaldehyde **5**, however, with excess of reagent at 100 °C for 4 days, thiochromone **2** was obtained in 29% yield together with aldehyde **5** as a major product (40% yield).[11] An alternative synthesis of 3-formylthiochromone **2** relies on the Sarett oxidation of 3-(hydroxymethyl)thiochromone **6**, which in turn was obtained by hydrolysis of 3-(bromomethyl)thiochromone.[9] Very recently,[12] we reported the preparation of **2** in good yield (67%) via a chlorination–dehydrochlorination sequence by treating of 3-formyl-4*H*-thiochroman-4-one **3** with sulfuryl chloride (Fig. 1). This simple and convenient method allowed us to investigate some chemical properties of the thiochromone system in more detail.

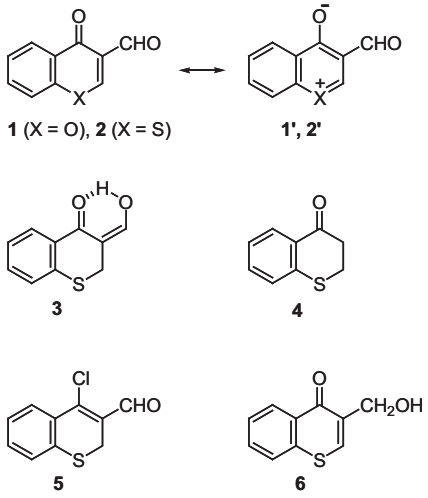
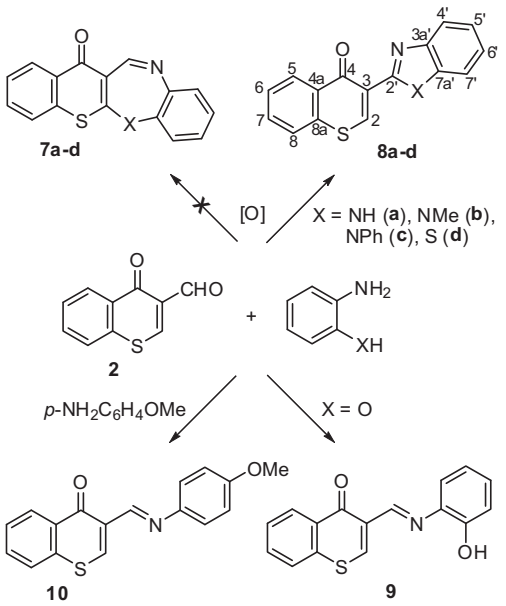


Figure 1.

2. Results and discussion

Continuing our studies on the synthetic potential of 3-substituted chromones,[13] we were interested in the reactivity of 3-formylthiochromone **2**. As mentioned above, some reactions of **2** with *N*-nucleophiles, such as hydroxylamine, hydrazine, ethylenediamine, and primary aromatic amines, have already been studied before.[6] Condensation of **2** with *o*-phenylenediamines and *o*-aminobenzenethiol was reported to afford 1-benzothiopyrano[2,3-*b*]-1,5-benzodiazepines **7a**–**c** and 1-benzothiopyrano[2,3-*b*]-1,5-benzothiazepine **7d** in low yields (13–33%). However, the seven-membered ring formation was not firmly established and in light of the known behavior 3-formylchromones **1** in reactions with *o*-phenylenediamine, which afforded 3-(benzimidazol-2-yl)chromones,[14,15] it was anticipated that the cyclization stage would proceed via a 1,2-addition process (five-membered ring formation, compounds **8a**–**d**) rather than the alternative intramolecular 1,4-nucleophilic addition (compounds **7a**–**d**). We therefore repeated the reactions of thiochromone **2** with *o*-phenylenediamines and *o*-aminobenzenethiol following the literature method (ethanol, reflux). Close scrutiny of the ^{1}H spectral data provided in Ref. 6 revealed that the seven-membered structure **7** was assigned erroneously; the structural assignment of the reaction products as the benzimidazole **8a** and benzthiazole **8d** was made on the basis of ^{1}H and ^{13}C NMR spectral analysis and comparison of the spectroscopic data with the data reported for related systems.[14,16] In particular, the benzimidazole protons of **8a** (δ 7.18–7.24 m, H-5′, H-6′; 7.62–7.72 m, H-4′, H-7′; 12.74 s, NH) compare well with those of 3-(benzimidazol-2-yl)chromone (δ 7.18–7.23 m, H-5′, H-6′; 7.63–7.70 m, H-4′, H-7′; 12.64 s, NH) the structure of which was confirmed by X-ray diffraction analysis.[14] In addition, all the signals in the ^{1}H and ^{13}C NMR spectra of **8a** were assigned on the basis of 2D ^{1}H–^{13}C HSQC and HMBC experiments. Consequently, structure **7** should be revised to **8** (Scheme 1).

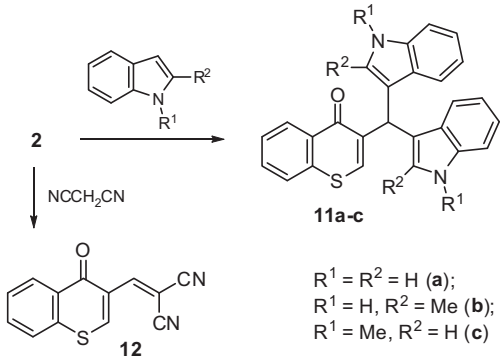


Scheme 1.

On the other hand, we found that reaction of **2** with *o*-aminophenol gave only the known imine **9**.[6] A similar reaction with *p*-anisidine in ethanol also proceeded at the formyl group to afford compound **10** in 77% yield without the formation of any side products arising from Michael-type addition onto the C-2 atom of the thiopyrone moiety. It should be noted that, in contrast to the arylimines derived from **1**,[17] products **9** and **10** are rather stable compounds, which do not react with amines, alcohols, and water under usual reaction conditions.

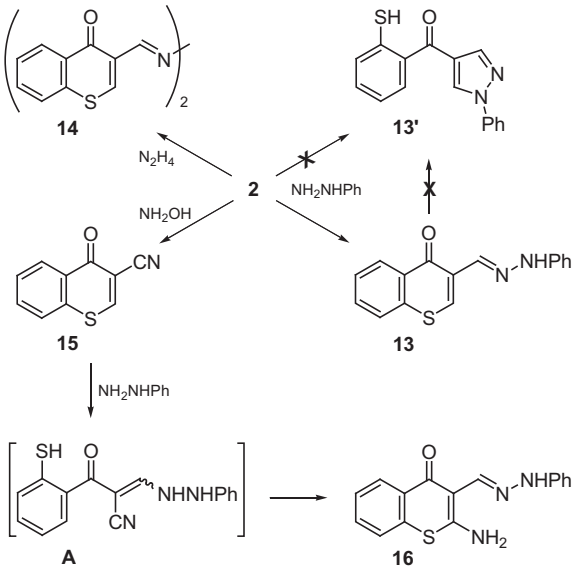
Recently,[18] we have reported that the reaction of 3-formylchromones **1** with indoles could proceed either as double addition at the CHO group (1,2-addition) or as 1,4-addition at C-2 with concomitant opening of the pyrone ring and subsequent intramolecular cyclization due to the phenolic hydroxy and aldehyde groups. The analogous reaction of 3-formylthiochromone **2** with indole and its methylated derivatives occurred exclusively via 1,2-addition. As in the case of aromatic aldehydes,[19] this reaction does not stop after mono-addition but affords bis-adducts **11a**–**c** in variable yields 22–73%. The ^{1}H and ^{13}C NMR spectra of **11a**–**c** in DMSO-d_6 are characterized by twice the number of the indole protons and carbons suggesting their equivalence. Owing to a deshielding effect of the carbonyl oxygen, the H-5 proton in these compounds is shifted downfield to 8.3–8.4 ppm; the signal at ca. δ 6.3 ppm is due to the resonance of the CH proton. (Thiochromon-3-yl)bis(indol-3-yl) methanes **11a**–**c** represent a new class of tris(heteroaryl)methanes, in which two different heterocycles with remarkably important biological and pharmaceutical activities are linked at the same carbon atom. The reaction of **2** with malononitrile (reflux, water) afforded the expected dicyanomethylidene derivative **12** in 68% yield. It is obvious from these results and from the literature data[6–9] that the reactions of **2** with primary amines, indoles, and methylene active compounds proceed exclusively by nucleophilic 1,2-addition of the nucleophile to the formyl group rather than conjugate addition and thiopyrone ring-opening (Scheme 2).

After a detailed study of the chemical behavior of **2** with different mono- and dinucleophiles, we have found that this compound is much less reactive than 3-formylchromone **1** and mainly behaves as an aromatic aldehyde. All attempts to obtain five- and



Scheme 2.

six-membered heterocycles from **2** and dinucleophiles, such as hydroxylamine, hydrazines, and amidines under the same conditions that had previously been used for the corresponding reactions of 3-formylchromone **1**,[4,5,13] failed. In all cases, the reactions proceeded without cleavage of the thiopyrone ring and only 1,2-addition at the aldehyde group took place, leading to 3-substituted thiochromones. Thus, we were unable to recyclise phenylhydrazone **13**, prepared from **2** and phenylhydrazine base (reflux, benzene, 4 h), into the corresponding pyrazole **13′** under a variety of conditions. Also, it is known that the reactions of **2** with hydrazine and hydroxylamine result in the formation of azine **14**[6] and 3-cyanothiochromone **15**[9] as the sole products, whereas 3-formylchromone **1** easily reacts with these reagents affording a number of rearranged products[4,5,13] (Scheme 3).



Scheme 3.

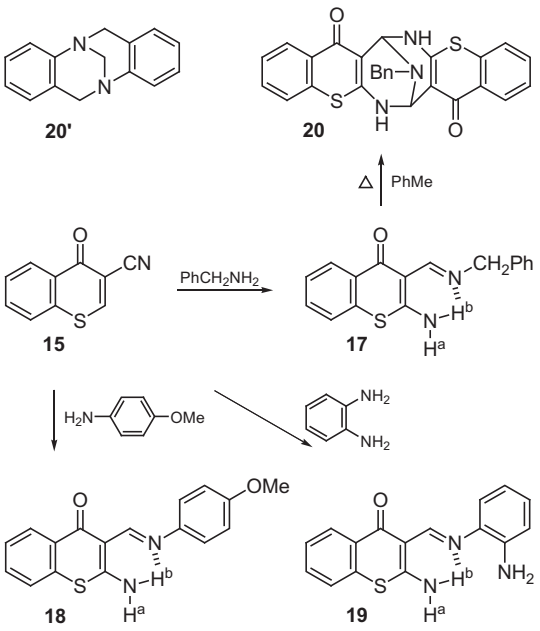
The observed striking differences in reactivity between **1** and **2** appears to be connected with the difficulty met by the nucleophile in cleaving the thiopyrone S–C bond arising from the less electronegative character of the sulfur atom, which strongly reduces the electrophilicity of the 2-position, and the greater aromaticity of the thiochromone system as compared with chromones (structures **1′** and **2′**, Fig. 1). In fact, there is some double-bond character to S1–C2 (1.712 Å) and C3–C4 (1.457 Å) in 3-formylthiochromone **2**,[20] indicating a significant contribution of the resonance form **2′** involving the delocalization of the lone pair on sulfur into the carbonyl (for thiophene S1–C2 (1.712 Å)).[21] This delocalization is also reflected in the IR spectra of thiochromone derivatives, which have a carbonyl band at 1610–1630 cm^{-1}, that is, considerably lower than those of chromones (1650–1670 cm^{-1}).

The reaction of **2** with hydroxylamine represents a simple and convenient method for the preparation of the hitherto unexplored 3-cyanothiochromone **15**, which we decided to use in the reactions with *N*-nucleophiles in order to determine whether the cyano group in **15** influence the S–C bond cleavage. It is well-known that introduction of the electron-withdrawing CN group at the 3-position of the chromone system significantly changes the reactivity of the pyrone ring with respect to nucleophiles, and provides broad synthetic potential for 3-cyanochromone.[22] Among the diverse transformations of this compound, one of the most important is its conversion, under basic conditions, into 2-amino-3-formylchromone. The reaction includes the nucleophilic 1,4-addition with concomitant opening of the pyrone ring and subsequent intramolecular cyclization at the cyano group. Unfortunately, all our attempts to prepare 2-amino-3-formylthiochromone from **15** under a variety of conditions were fruitless.

Very recently,[23] we have shown that the initial Michael addition of phenylhydrazine to 3-cyanochromone, depending on the reaction conditions, leads to three different types of products, 5-amino-4-salicyloyl-1-phenylpyrazole, 2-aminochromone-3-carbaldehyde phenylhydrazone, and 1-phenylchromeno[4,3-*c*]pyrazol-4(1*H*)-one, and the 1,2-addition at the CN group was not observed at all. As the unsubstituted C-2 atom of 3-cyanochromones is more susceptible to nucleophilic attack than the cyano group, we thought that this Michael-type addition could possibly be extended to the thiochromone series. Indeed, we found that the reaction of **15** with phenylhydrazine, carried out in refluxing benzene in the presence of a catalytic amount of triethylamine, gave a new product in 67% yield. This compound was characterized as the phenylhydrazone of 2-amino-3-formylthiochromone **16**, which represents a new derivative of the 2-aminothiochromone family. Previously, 3-substituted 2-aminothiochromones were obtained via a C-acylation reaction of active methylene compounds with thiosalicylic acid derivatives followed by an in situ cyclization reaction[24] and from 2-methylthio-3-cyanothiochromones under the action of amines.[25] In our case, a Michael addition takes place leading to cleavage of the S–C bond (this is a rare case of the S–C bond cleavage in the thiochromone series; other examples see Ref. 8,26). It is noteworthy that due to the chemical equivalency of the 3-CHO group and C-2 (masked aldehydic group) the formation of hydrazone **13** from **2** can be explained by both 1,2- and 1,4-addition, whereas the structure of hydrazone **16** indicates unambiguously the primary attack at C-2 (intermediate **A**) followed by recyclization with the participation of the cyano group (Scheme 3).

In accordance with this, when 3-cyanothiochromone **15** was treated with benzylamine and *p*-anisidine at reflux in toluene in the presence of a catalytic amount of triethylamine for 1 and 12 h, respectively, 2-amino-3-(benzyliminomethyl)- and 2-amino-3-(anisyliminomethyl)thiochromones **17** and **18** were formed as the sole products. In the light of this finding we envisaged that the reaction of **15** with *o*-phenylenediamine would produce the corresponding anil. Indeed, we found that **15** smoothly reacted with 2 equiv of *o*-phenylenediamine under the same conditions to produce the expected 2-amino-3-[(2-aminophenyl)iminomethyl]thiochromone **19** in 64% yield (Scheme 4). This behavior of 3-cyanothiochromone **15** closely resembles that already reported[27] for 3-cyanochromone and clearly indicates that the C-2 atom of **15** is susceptible to nucleophilic attack and makes it an attractive building block for the synthesis of 2-aminothiochromone derivatives. The latter have attracted considerable interest because of their biological significance.[24]

Interestingly, when **17** was treated with benzylamine and triethylamine in refluxing toluene for 12 h, 2,6,9-triazabicyclo[3.3.1]nonane **20** incorporating an annelated thiochromone system was isolated in 28% yield. To the best of our knowledge, the only example of 2,6,9-triazabicyclo[3.3.1]nonanes with fused heterocyclic ring system are derivatives, which were obtained by



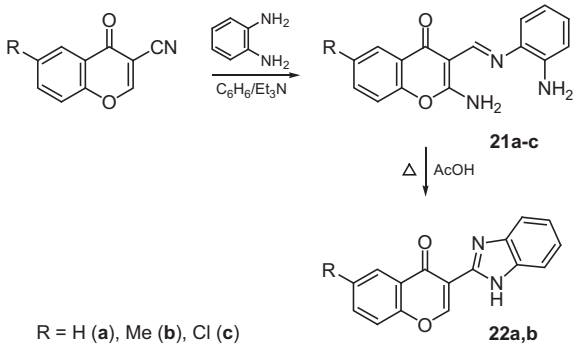
Scheme 4.

reaction of 5-amino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carbaldehyde with aliphatic primary amines.[28] The main interest of these compounds lies in their structural similarity to Tröger's bases **20′**, which provide relatively rigid chiral frameworks for the construction of chelating and biomimetic systems.[29] A suitable mechanism for the formation of tetrahydro[1,5]diazocines has been reported.[28,30]

It can be concluded from these data that the electron-withdrawing cyano group enhances the electrophilicity of the C-2 atom of **15** and thus favors both 1,4-addition and cyclization of an open intermediate to the final product. This is a novel approach to the synthesis of 3-substituted 2-aminothiochromones, which has advantages with regard to ease of operation and the ready availability of starting materials. However, in contrast to the results found in the 3-cyanochromone series,[13] the expected products were not formed in the reaction of **15** with hydroxylamine. Presumably, the amino group of hydroxylamine was not nucleophilic enough to add to the C-2 position, which was rendered somewhat less electrophilic by the adjacent lone pair on sulfur.

The ^{1}H NMR spectra of thiochromone derivatives **17**–**19** in DMSO-d_6 consisted of a characteristic singlet due to the CH=N proton at δ 9.0–9.2 ppm and two singlets due to the resonances of the non-equivalent NH_2 protons at δ 9.1–9.3 (H^a) and 11.5–11.8 ppm (H^b). Addition of CD_3CO_2D resulted in the disappearance of the two latter signals. It is reasonable to assume that the non-equivalence of the NH_2 protons is connected with an intramolecular hydrogen bond involving H^b and the imine nitrogen atom. This explains the formation of *E*-anils **17**–**19**, exclusively. The most interesting feature of the ^{1}H NMR spectrum of the pseudo-Tröger's base **20** is the anisochrony of the N–CH_2 protons reflecting its chiral nature (AB-system with $^2J_{AB}$=13.0 Hz at 3.64 ppm); the CH protons appear as singlet at δ 5.35 ppm while the NH protons resonate at 9.5 ppm (slightly broad).

Recently,[27] we reported on the reaction of unsubstituted 3-cyanochromone with *o*-phenylenediamine at reflux in ethanol (benzene can also be used) and on the basis of ^{1}H and ^{13}C NMR spectroscopy using 2D HSQC, HMBC, and NOESY experiments found that in contrast to the literature data,[31,32] the product was 2-amino-3-[(2-aminophenyl)iminomethyl]chromone **21a**. Now we have extended this reaction to 6-substituted 3-cyanochromones and obtained compounds **21a**–**c**, which were converted into the known benzimidazoles **22a**,**b**[14,15c,32] at reflux in acetic acid for 3 h (Scheme 5). A possible mechanism for the transformation of **21** into **22**, which includes several addition–elimination sequences, has been suggested by us in preceding communication.[27] Compounds **21a** and **22a** were used for comparison of their spectral data with those of derivatives **8a** and **19**.



Scheme 5.

3. Conclusion

In conclusion, we have shown that 3-formylthiochromone reacts with primary aromatic amines, phenylhydrazine, and indoles at the aldehyde group to give the corresponding addition products in good yields. At the same time, the reactions of 3-cyanothiochromone with primary amines and phenylhydrazine proceed as 1,4-nucleophilic addition with subsequent opening of the thiopyrone ring and cyclization with the participation of the cyano group into imines and phenylhydrazone of 2-amino-3-formylthiochromone. Thus, a hitherto unknown reactivity pattern of the thiochromone system was observed.

4. Experimental

4.1. General

^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker DRX-400 spectrometer in DMSO-d_6 and $CDCl_3$ with TMS as an internal standard. IR spectra were recorded on a Perkin–Elmer Spectrum BX-II instrument (KBr) and Bruker Alpha instrument (ATR, ZnSe). Elemental analyses were performed at the Microanalysis Services of the Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences. All solvents used were dried and distilled per standard procedures. The starting 3-formyl-4*H*-thiochroman-4-one **3** was prepared according to described procedure.[12]

*4.1.1. 4-Oxo-4H-thiochromene-3-carbaldehyde (**2**).* Freshly distilled SO_2Cl_2 (1.5 g, 11.4 mmol) was added carefully to a well stirred solution of 3-formylthiochroman-4-one **3** (2.0 g, 10.4 mmol) in $CHCl_3$ (100 mL). After stirring at rt for 20 h, the formed orange solution was evaporated under reduced pressure. The resulting brown semisolid was purified by filtration through a pad of silica gel (10 cm, the elution solvent–$CHCl_3$) to give a product as a yellow powder. Yield 1.3 g (67%), mp 157–158 °C (lit.[11b] mp 162–163 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60–7.75 (m, 3H, H-6, H-7, H-8), 8.63 (m, 1H, H-5), 8.79 (s, 1H, H-2), 10.40 (s, 1H, CHO).

4.2. Compounds 8–10

*4.2.1. 3-(1H-Benzimidazol-2-yl)-4H-thiochromen-4-one (**8a**).* This compound was prepared from thiochromone **2** and

o-phenylenediamine according to the procedure described previously.[6a] Yield 140 mg (34%), mp 246–248 °C (lit.[6a] mp 247–248 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.18–7.24 (m, 2H, H-5′, H-6′), 7.62–7.72 (m, 2H, H-4′, H-7′), 7.77 (ddd, 1H, H-6, J=8.2, 7.2, 1.2 Hz), 7.86 (ddd, 1H, H-7, J=8.2, 7.2, 1.5 Hz), 8.08 (dd, 1H, H-8, J=8.2, 1.0 Hz), 8.62 (dd, 1H, H-5, J=8.2, 1.4 Hz), 9.71 (s, 1H, H-2), 12.74 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 113.2 (C4′/C7′), 118.7 (C7′/C4′), 122.3 (C5′/C6′), 122.7 (C6′/C5′), 123.8 (C3), 128.1 (C8), 128.7 (C5), 129.2 (C7), 132.2 (C4a), 132.7 (C6), 134.9 (C3a′), 137.0 (C8a), 142.8 (7a′), 143.6 (C2), 148.1 (C2′), 177.6 (C4).

*4.2.2. 3-(1,3-Benzothiazol-2-yl)-4H-thiochromen-4-one (**8d**).* This compound was prepared from thiochromone **2** and *o*-aminothiophenol according to the procedure described previously.[6b] Yield 105 mg (28%), mp 183–185 °C (lit.[6b] mp 187–188 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.47 (ddd, 1H, H-6′, J=8.0, 7.2, 1.1 Hz), 7.56 (ddd, 1H, H-5′, J=8.0, 7.2, 1.3 Hz), 7.78 (ddd, 1H, H-6, J=8.1, 7.2, 1.2 Hz), 7.87 (ddd, 1H, H-7, J=8.0, 7.2, 1.5 Hz), 8.06 (ddd, 1H, H-7′, J=8.0, 1.1, 0.7 Hz), 8.10 (ddd, 1H, H-8, J=8.0, 1.2, 0.5 Hz), 8.18 (ddd, 1H, H-4′, J=8.0, 1.3, 0.7 Hz), 8.61 (ddd, 1H, H-5, J=8.1, 1.5, 0.5 Hz), 9.89 (s, 1H, H-2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (ddd, 1H, H-6′, J=8.0, 7.2, 1.0 Hz), 7.51 (ddd, 1H, H-5′, J=8.2, 7.2, 1.2 Hz), 7.64–7.75 (m, 3H, H-6, H-7, H-8), 8.00 (d, 1H, H-7′, J=8.0 Hz), 8.05 (d, 1H, H-4′, J=8.2 Hz), 8.77 (dd, 1H, H-5, J=7.5, 1.8 Hz), 9.56 (s, 1H, H-2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 122.4 (C4′/7′), 122.7 (C7′/4′), 125.4 (C3), 126.4 (C5′/6′), 126.7 (C6′/5′), 128.0 (C8), 128.9 (C5), 129.3 (C7), 131.7 (C4a), 132.7 (C6), 136.4 (C7a′), 136.6 (C8a), 143.7 (C2), 151.6 (C3a′), 160.7 (C2′), 176.7 (C4). Anal. Calcd for $C_{16}H_9NOS_2$: C, 65.06; H, 3.07; N, 4.74. Found: C, 65.09; H, 2.99; N, 4.51.

*4.2.3. 3-[(2-Hydroxyphenyl)iminomethyl]-4H-thiochromen-4-one (**9**).* This compound was prepared from thiochromone **2** and *o*-aminophenol according to the procedure described previously.[6b] Yield 120 mg (91%), mp 193–194 °C (lit.[6b] mp 190–191 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.85 (td, 1H, H-5′, J=7.5, 1.3 Hz), 6.91 (dd, 1H, H-3′, J=8.1, 1.3 Hz), 7.11 (ddd, 1H, H-4′, J=8.1, 7.2, 1.5 Hz), 7.22 (dd, 1H, H-6′, J=7.9, 1.5 Hz), 7.72 (ddd, 1H, H-6, J=8.1, 7.2, 1.2 Hz), 7.82 (ddd, 1H, H-7, J=8.2, 7.2, 1.5 Hz), 8.01 (dd, 1H, H-8, J=8.2, 1.0 Hz), 8.49 (dd, 1H, H-5, J=8.1, 1.5 Hz), 8.99 (s, 1H, HC=N), 9.07 (s, 1H, OH), 9.53 (s, 1H, H-2).

*4.2.4. 3-[(4-Methoxyphenyl)iminomethyl]-4H-thiochromen-4-one (**10**).* A mixture of **2** (200 mg, 1.05 mmol), *p*-anisidine (135 mg, 1.1 mmol), and ethanol (6 mL) was refluxed for 5 h. After cooling, the resulting solid was filtered, washed with ethanol, and dried. Yield 240 mg (77%), orange powder, mp 152–153 °C; IR (ATR, ZnSe) 1620, 1605, 1589, 1567, 1529, 1498 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.79 (s, 3H, MeO), 7.00 (d, 2H, Ar, J=8.9 Hz), 7.29 (d, 2H, Ar, J=8.9 Hz), 7.71 (ddd, 1H, H-6, J=8.1, 7.2, 1.2 Hz), 7.81 (ddd, 1H, H-7, J=8.2, 7.2, 1.5 Hz), 8.00 (dd, 1H, H-8, J=8.2, 1.0 Hz), 8.48 (dd, 1H, H-5, J=8.1, 1.5 Hz), 8.87 (s, 1H, HC=N), 9.22 (s, 1H, H-2). Anal. Calcd for $C_{17}H_{13}NO_2S$: C, 69.13; H, 4.44; N, 4.74. Found: C, 69.02; H, 4.39; N, 4.56.

4.3. General procedure for the synthesis of 3-di(indol-3-yl) methylthiochromones (11a–c)

A mixture of **2** (200 mg, 1.05 mmol) and the corresponding indole (3.2 mmol) was heated for 7–8 h at 90–95 °C. The resulting solid was recrystallized from xylene–butanol to give compound **11**.

*4.3.1. 3-Di(indol-3-yl)methyl-4H-thiochromen-4-one (**11a**).* Yield 65 mg (22%), pale violet powder, mp 235–236 °C; IR (ATR, ZnSe) 3407, 3388, 3293, 1599, 1576, 1539 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.35 (s, 1H, CH), 6.87 (d, 2H, 2H-2′, J=1.8 Hz), 6.90 (ddd, 2H, 2H-5′, J=7.9, 7.1, 0.9 Hz), 7.05 (ddd, 2H, 2H-6′, J=8.0, 7.1, 1.0 Hz), 7.32 (d, 2H, 2H-4′, J=8.0 Hz), 7.36 (d, 2H, 2H-7′, J=8.1 Hz), 7.61 (ddd, 1H, H-6, J=8.2, 7.2, 1.2 Hz), 7.72 (ddd, 1H, H-7, J=8.2, 7.2, 1.4 Hz), 7.85 (d, 1H, H-8, J=8.2 Hz), 7.95 (s, 1H, H-2), 8.42 (dd, 1H, H-5, J=8.2, 1.4 Hz), 10.85 (d, 2H, 2NH, J=1.8 Hz). Anal. Calcd for $C_{26}H_{18}N_2OS$: C, 76.82; H, 4.46; N, 6.89. Found: C, 76.56; H, 4.52; N, 6.64.

*4.3.2. 3-Di(2-methylindol-3-yl)methyl-4H-thiochromen-4-one (**11b**).* Yield 330 mg (73%), yellow powder, mp 310–312 °C; IR (KBr) 3404, 3258, 1603, 1586, 1539 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.08 (s, 6H, 2 Me), 6.17 (s, 1H, CH), 6.71 (ddd, 2H, 2H-5′, J=7.8, 7.1, 0.9 Hz), 6.90 (ddd, 2H, 2H-6′, J=8.0, 7.1, 1.0 Hz), 6.98 (d, 2H, 2H-4′, J=8.0 Hz), 7.22 (d, 2H, 2H-7′, J=8.0 Hz), 7.59 (ddd, 1H, H-6, J=8.2, 7.2, 1.1 Hz), 7.71 (ddd, 1H, H-7, J=8.3, 7.2, 1.4 Hz), 7.80 (s, 1H, H-2), 7.87 (d, 1H, H-8, J=8.2 Hz), 8.32 (dd, 1H, H-5, J=8.2, 1.4 Hz), 10.77 (s, 2H, 2 NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.5, 35.3, 110.5, 111.0, 118.4, 118.7, 120.1, 127.6, 128.1, 128.7, 128.8, 131.4, 131.9, 132.9, 135.5, 136.1, 137.5, 138.6, 178.0. Anal. Calcd for $C_{28}H_{22}N_2OS$: C, 77.39; H, 5.10; N, 6.45. Found: C, 77.10; H, 5.04; N, 6.31.

*4.3.3. 3-Di(1-methylindol-3-yl)methyl-4H-thiochromen-4-one (**11c**).* Yield 200 mg (58%), pink powder, mp 284–286 °C; IR (KBr) 1613, 1588, 1547 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.69 (s, 6H, 2 Me), 6.33 (s, 1H, CH), 6.87 (s, 2H, 2H-2′), 6.95 (ddd, 2H, 2H-5′, J=7.9, 7.1, 0.9 Hz), 7.13 (ddd, 2H, 2H-6′, J=8.1, 7.1, 1.0 Hz), 7.33 (d, 2H, 2H-4′, J=7.9 Hz), 7.39 (d, 2H, 2H-7′, J=8.2 Hz), 7.62 (ddd, 1H, H-6, J=8.2, 7.2, 1.2 Hz), 7.72 (ddd, 1H, H-7, J=8.2, 7.2, 1.4 Hz), 7.86 (d, 1H, H-8, J=8.2 Hz), 7.94 (s, 1H, H-2), 8.41 (dd, 1H, H-5, J=8.2, 1.4 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 32.8, 33.7, 110.2, 116.0, 119.0, 119.4, 121.7, 127.2, 127.7, 128.1, 128.8, 128.9, 131.6, 131.9, 136.4, 137.6 (2C), 138.7, 177.8. Anal. Calcd for $C_{28}H_{22}N_2OS$: C, 77.39; H, 5.10; N, 6.45. Found: C, 77.24; H, 4.99; N, 6.34.

*4.3.4. 2-[(4-Oxo-4H-thiochromen-3-yl)methylene]malononitrile (**12**).* A mixture of **2** (200 mg, 1.05 mmol), malononitrile (70 mg, 1.06 mmol), and water (7 mL) was heated to reflux for 3 h. After cooling, the resulting solid was filtered, dried, and recrystallized from xylene. Yield 170 mg (68%), brown cubic crystals, mp 220–222 °C; IR (KBr) 3019, 2226, 2172, 1623, 1585, 1559, 1515 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (t, 1H, H-6, J=7.6 Hz), 7.86 (t 1H, H-7, J=7.6 Hz), 8.04 (d, 1H, H-8, J=8.0 Hz), 8.42 (s, 1H, =CH), 8.43 (d, 1H, H-5, J=8.0 Hz), 9.36 (s, 1H, H-2). Anal. Calcd for $C_{13}H_6N_2OS$: C, 65.53; H, 2.54; N, 11.76. Found: C, 65.58; H, 2.30; N, 11.50.

4.4. Compounds 13, 15–19

*4.4.1. 4-Oxo-4H-thiochromene-3-carbaldehyde N-phenylhydrazone (**13**).* A solution of **2** (150 mg, 0.79 mmol) and phenylhydrazine (90 mg, 0.83 mmol) in benzene (4 mL) was heated to reflux for 4 h. After cooling, the resulting solid was filtered, washed with benzene, and dried. Yield 130 mg (57%), orange cubic crystals, mp 222–224 °C; IR (KBr) 3244, 1603, 1587, 1573, 1554, 1526, 1494 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.77 (tt, 1H, H-4′, J=7.3, 1.1 Hz), 7.10 (dd, 2H, H-2′, H-6′, J=8.5, 1.1 Hz), 7.23 (dd, 2H, H-3′, H-5′, J=8.5, 7.3 Hz), 7.66 (ddd, 1H, H-6, J=8.1, 7.1, 1.2 Hz), 7.76 (ddd, 1H, H-7, J=8.2, 7.1, 1.5 Hz), 7.95 (dd, 1H, H-8, J=8.2, 0.8 Hz), 8.24 (s, 1H, HC=N), 8.45 (dd, 1H, H-5, J=8.1, 1.5 Hz), 8.88 (s, 1H, H-2), 10.61 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 112.6, 119.5, 128.0, 128.5, 128.6, 129.6, 129.7, 131.3, 131.6, 132.2, 133.4, 137.2, 145.5, 177.5. Anal. Calcd for $C_{16}H_{12}N_2OS$: C, 68.55; H, 4.31; N, 9.99. Found: C, 68.17; H, 4.00; N, 9.87.

*4.4.2. 4-Oxo-4H-thiochromene-3-carbonitrile (**15**).* This compound was prepared according to the procedure described earlier.[9] Yield 570 mg (83%), orange crystals, mp 227–229 °C (lit.[9] mp 229–230 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (ddd, 1H, H-6, J=8.1, 7.2, 1.2 Hz), 7.87 (ddd, 1H, H-7, J=8.2, 7.2, 1.5 Hz), 8.05 (ddd,

1H, H-8, *J*=8.2, 1.2, 0.5 Hz), 8.40 (ddd, 1H, H-5, *J*=8.1, 1.5, 0.5 Hz), 9.45 (s, 1H, H-2).

*4.4.3. 2-Amino-4-oxo-4H-thiochromene-3-carbaldehyde N-phenylhydrazone (**16**).* A mixture of **15** (200 mg, 1.07 mmol), phenylhydrazine (140 mg, 1.28 mmol), and two drops of triethylamine in toluene (5 mL) was heated to reflux for 5 h. After cooling, the resulting solid was filtered, washed with toluene, and dried. Yield 210 mg (67%), gold plates, mp 250–252 °C; IR (KBr) 3251, 1600, 1573, 1530, 1509, 1488 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 6.72 (t, 1H, H-4′, *J*=7.3 Hz), 6.87 (dd, 2H, H-2′, H-6′, *J*=8.4, 1.0 Hz), 7.22 (dd, 2H, H-3′, H-5′, *J*=7.4, 8.4 Hz), 7.49 (ddd, 1H, H-6, *J*=8.2, 6.9, 1.5 Hz), 7.61 (td, 1H, H-7, *J*=7.5, 1.5 Hz), 7.65 (dd, 1H, H-8, *J*=8.0, 1.0 Hz), 8.30 (dd, 1H, H-5, *J*=8.0, 1.5 Hz), 8.69 (s, 1H, HC=N), 9.35 (br s, 2H, NH_2), 10.15 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 103.4, 111.8, 118.7, 126.2, 127.3, 128.5, 129.2, 129.7, 131.6, 131.8, 139.7, 145.6, 157.8, 176.8. Anal. Calcd for $C_{16}H_{13}N_3OS$: C, 65.06; H, 4.44; N, 14.23. Found: C, 65.05; H, 4.16; N, 14.15.

*4.4.4. 2-Amino-3-[(benzyl)iminomethyl]-4H-thiochromen-4-one (**17**).* A mixture of **15** (150 mg, 0.8 mmol), benzylamine (85 mg, 0.8 mmol), and two drops of triethylamine in toluene (3 mL) was heated to reflux for 1 h. After cooling, the resulting solid was filtered, washed with toluene, then ether and dried. Yield 170 mg (73%), pale yellow powder, mp 218–219 °C; IR (KBr) 3236, 3210, 1615, 1590, 1576, 1527, 1509 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 4.73 (s, 2H, CH_2), 7.24–7.38 (m, 5H, Ph), 7.45–7.50 (m, 1H, H-6), 7.58–7.62 (m, 2H, H-7, H-8), 8.28 (d, 1H, H-5, *J*=7.7 Hz), 9.03 (s, 1H, HC=N), 9.08 (br s, 1H, NH), 11.81 (br s, 1H, NH). Anal. Calcd for $C_{17}H_{14}N_2OS$: C, 69.36; H, 4.79; N, 9.52. Found: C, 68.94; H, 4.52; N, 9.22.

*4.4.5. 2-Amino-3-[(4-methoxyphenyl)iminomethyl]-4H-thiochromen-4-one (**18**).* A mixture of **15** (150 mg, 0.8 mmol), *p*-anisidine (110 mg, 0.9 mmol), and two drops of triethylamine in toluene (4 mL) was heated to reflux for 12 h. After cooling, the resulting solid was filtered, washed with toluene, and recrystallized from butanol. Yield 70 mg (28%), pale yellow powder, mp 203–205 °C; IR (KBr) 3178, 3056, 1638, 1601, 1590, 1575, 1544, 1505 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.77 (s, 3H, MeO), 6.97 (d, 2H, H-3′, H-5′, *J*=8.9 Hz), 7.22 (d, 2H, H-2′, H-6′, *J*=8.9 Hz), 7.48–7.53 (m 1H, H-6), 7.61–7.66 (m, 2H, H-7, H-8), 8.30 (d, 1H, H-5, *J*=8.0 Hz), 9.15 (s, 1H, HC=N), 9.30 (br s, 1H, NH), 11.73 (br s, 1H, NH). Anal. Calcd for $C_{17}H_{14}N_2O_2S$: C, 65.79; H, 4.55; N, 9.03. Found: C, 65.44; H, 4.24; N, 8.84.

*4.4.6. 2-Amino-3-[(2-aminophenyl)iminomethyl]-4H-thiochromen-4-one (**19**).* A mixture of **15** (200 mg, 1.07 mmol), *o*-phenylenediamine (240 mg, 2.22 mmol), and two drops of triethylamine in toluene (5 mL) was heated to reflux for 7 h. After cooling, the resulting solid was filtered, washed with toluene, and dried. Yield 200 mg (64%), yellow powder, mp 208–210 °C; IR (ATR, ZnSe) 3395, 1576, 1549, 1486 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 4.99 (s, 2H, NH_2), 6.59 (td, 1H, H-4′, *J*=7.6, 1.3 Hz), 6.72 (dd, 1H, H-3′, *J*=7.9, 1.2 Hz), 6.88 (dd, 1H, H-6′, *J*=7.8, 1.2 Hz), 6.93 (td, 1H, H-5′, *J*=7.5, 1.3 Hz), 7.48–7.53 (m, 1H, H-6), 7.61–7.66 (m, 2H, H-7, H-8), 8.31 (d, 1H, H-5, *J*=8.0 Hz), 9.10 (s, 1H, HC=N), 9.25 (br s, 1H, NH), 11.46 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 104.5, 115.2, 117.3, 118.5, 126.3, 126.8, 127.6, 128.5, 129.4, 131.9, 132.1, 138.0, 142.7, 158.3, 163.1, 177.9. Anal. Calcd for $C_{16}H_{13}N_3OS$: C, 65.06; H, 4.44; N, 14.23; S, 11.06. Found: C, 65.11; H, 4.41; N, 14.21; S, 10.99.

*4.4.7. 16-Benzyl-6,7,14,15-tetrahydro-7,15-epiminobis(8H,16H-dithiochromeno)[2,3-b:2,3-f][1,5]diazocine-8,16-dione (**20**).* A mixture of **17** (150 mg, 0.51 mmol), benzylamine (55 mg, 0.51 mmol), and two drops of triethylamine in toluene (3 mL) was heated to reflux for 12 h. After cooling, the resulting solid was filtered, washed with toluene, and dried. Yield 70 mg (28%), a colorless powder, mp 242–243 °C; IR (ATR, ZnSe) 3243, 3211, 1595, 1574, 1561, 1504 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.64 (AB-system, 2H, CH_2, *J*=13.0 Hz), 5.35 (s, 2H, 2 CH), 7.27–7.38 (m, 5H, Ph), 7.46 (ddd, 2H, 2H-6, *J*=8.0, 7.3, 1.2 Hz), 7.56 (td, 2H, 2H-7, *J*=7.5, 1.5 Hz), 7.63 (dd, 2H, 2H-8, *J*=8.0, 1.0 Hz), 8.24 (dd, 2H, 2H-5, *J*=8.0, 1.5 Hz), 9.50 (br s, 2H, 2 NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 53.1, 61.0, 106.2, 126.0, 126.8, 127.5, 128.4, 129.1, 129.4, 131.0, 132.2, 137.2, 153.4, 174.6. Anal. Calcd for $C_{27}H_{19}N_3O_2S_2$: C, 67.34; H, 3.98; N, 8.73. Found: C, 66.95; H, 3.63; N, 8.62.

4.5. General procedure for the synthesis of 2-amino-3-[(2-aminophenyl)iminomethyl]-4*H*-chromen-4-ones (21a–c)

A solution of the corresponding 3-cyanochromone (1.0 mmol), *o*-phenylenediamine (1.0 mmol) and two drops of triethylamine in benzene or ethanol (5 mL) was heated to reflux for 3–4 h. Then the reaction mixture was cooled and the formed precipitate filtered, washed with benzene, and dried.

*4.5.1. 2-Amino-3-[(2-aminophenyl)iminomethyl]-4H-chromen-4-one (**21a**).* Yield 230 mg (48%), yellow cubic crystals, mp 218–219 °C (ethanol) (lit.[32] mp 217 °C); IR (KBr) 3330, 3180, 1664, 1601, 1559, 1521, 1498, 1462 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 5.02 (s, 2H, NH_2), 6.59 (ddd, 1H, H-5′, *J*=7.8, 7.3, 1.0 Hz), 6.73 (dd, 1H, H-3′, *J*=7.8, 0.8 Hz), 6.87 (dd, 1H, H-6′, *J*=7.8, 0.8 Hz), 6.93 (ddd, 1H, H-4′, *J*=7.8, 7.3, 1.0 Hz), 7.41–7.47 (m, 2H, H-6, H-8), 7.71 (ddd, 1H, H-7, *J*=8.2, 7.4, 1.6 Hz), 8.06 (dd, 1H, H-5, *J*=7.7, 1.6 Hz), 8.91 (s, 1H, HC=N), 9.30 (s, 1H, NH), 10.39 (s, 1H, NH). Anal. Calcd for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.05. Found: C, 69.04; H, 4.67; N, 15.09.

*4.5.2. 2-Amino-3-[(2-aminophenyl)iminomethyl]-6-methyl-4H-chromen-4-one (**21b**).* Yield 180 mg (38%), yellow powder, mp 244–245 °C (ethanol); IR (KBr) 3340, 1663, 1607, 1561, 1499, 1474 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.41 (s, 3H, Me), 4.99 (s, 2H, NH_2), 6.58 (td, 1H, H-5′, *J*=7.5, 1.4 Hz), 6.72 (dd, 1H, H-3′, *J*=7.9, 1.4 Hz), 6.86 (dd, 1H, H-6′, *J*=7.9, 1.4 Hz), 6.92 (td, 1H, H-4′, *J*=7.5, 1.4 Hz), 7.34 (d, 1H, H-8, *J*=8.4 Hz), 7.51 (ddq, 1H, H-7, *J*=8.4, 2.3, 0.6 Hz), 7.84 (dq, 1H, H-5, *J*=2.3, 0.6 Hz), 8.90 (s, 1H, HC=N), 9.22 (br s, 1H, NH), 10.35 (br s, 1H, NH). Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.84; H, 5.06; N, 14.49.

*4.5.3. 2-Amino-6-chloro-3-[(2-aminophenyl)iminomethyl]-4H-chromen-4-one (**21c**).* Yield 295 mg (64%), yellow powder, mp 248–250 °C; IR (KBr) 3212, 1654, 1605, 1553, 1497, 1457 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 5.01 (s, 2H, NH_2), 6.58 (td, 1H, H-5′, *J*=7.5, 1.4 Hz), 6.72 (dd, 1H, H-3′, *J*=7.9, 1.4 Hz), 6.87 (dd, 1H, H-6′, *J*=7.9, 1.4 Hz), 6.92 (td, 1H, H-4′, *J*=7.5, 1.4 Hz), 7.51 (d, 1H, H-8, *J*=8.8 Hz), 7.74 (dd, 1H, H-7, *J*=8.8, 2.7 Hz), 7.96 (d, 1H, H-5, *J*=2.7 Hz), 8.88 (s, 1H, HC=N), 9.40 (br s, 1H, NH), 10.42 (br s, 1H, NH). Anal. Calcd for $C_{16}H_{12}ClN_3O_2$: C, 61.25; H, 3.86; N, 13.39. Found: C, 61.36; H, 3.76; N, 13.10.

4.6. 3-(Benzimidazol-2-yl)chromones 22a,b

*4.6.1. 3-(1H-Benzimidazol-2-yl)-4H-chromen-4-one (**22a**).* A solution of **21a** (480 mg, 1.72 mmol), in acetic acid (10 mL) was heated to reflux for 3 h. Then the reaction mixture was evaporated and 5 mL of water was added. After cooling, the resulting solid was filtered, washed with diluted acetic acid, and dried. Yield 370 mg (82%), yellow powder, mp 270–272 °C (lit.[32] mp 270 °C, lit.[15c] mp 268 °C); ^1H NMR (400 MHz, DMSO-d_6) δ 7.18–7.23 (m, 2H, H-5′, H-6′), 7.63 (ddd, 1H, H-6, *J*=8.0, 7.1, 1.0 Hz), 7.63–7.70 (m, 2H, H-4′, H-7′), 7.82 (dd, 1H, H-8, *J*=8.6, 0.8 Hz), 7.93 (ddd, 1H, H-7, *J*=8.6, 7.1,

1.7 Hz), 8.28 (dd, 1H, H-5, *J*=8.0, 1.7 Hz), 9.38 (s, 1H, H-2), 12.64 (s, 1H, NH).

*4.6.2. 3-(1H-Benzimidazol-2-yl)-6-methyl-4H-chromen-4-one (**22b**).* This compound was prepared from **21b** according to the procedure described for compound **22a**. Yield 145 mg (43%), yellow powder, mp 258–260 °C (lit.[15c] mp 256 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.50 (s, 3H, Me), 7.18–7.23 (m, 2H, H-5′, H-6′), 7.62–7.69 (m, 2H, H-4′, H-7′), 7.71 (d, 1H, H-8, *J*=8.6 Hz), 7.74 (dd, 1H, H-7, *J*=8.6, 2.0 Hz), 8.05 (dq, 1H, H-5, *J*=2.0, 0.8 Hz), 9.35 (s, 1H, H-2), 12.61 (s, 1H, NH).

Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.06.066.

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