Tetrahedron 67 (2011) 1799–1804

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

2-Aryl-1,9-dihydrochromeno[3,2-*d*]imidazoles: a facile synthesis from salicylaldehydes and arylideneaminoacetonitrile

Marta Costa, Fernanda Proença *

Department of Chemistry, University of Minho, Campos de Gualtar, 4710-057 Braga, Portugal

ARTICLE INFO

Article history:
Received 3 November 2010
Received in revised form 5 January 2011
Accepted 13 January 2011
Available online 19 January 2011

Keywords:
Salicylaldehyde
Arylideneaminoacetonitrile
Chromene
2-Arylimidazole
Cascade reaction

ABSTRACT

2-Aryl-1,9-dihydrochromeno[3,2-*d*]imidazoles were prepared by a one-pot cascade reaction involving salicylaldehydes and arylideneaminoacetonitriles. These novel compounds were isolated in 11–95% yield after reflux in ethanol and triethylamine. A dimeric structure was also identified and partially evolved to the tricyclic product in DMSO solution, according to an evolution study by ^{1}H NMR spectroscopy.

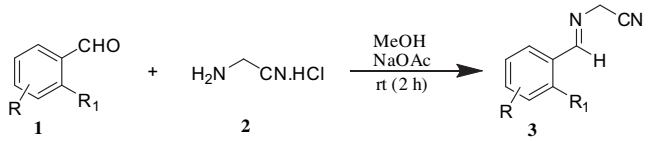
1. Introduction

The chromene scaffold is present in a diversity of natural and synthetic products and a considerable number of molecules is known for their potent biological activity.[1] Chromene derivatives were reported namely as MAO inhibitors,[2] human β-secretase inhibitors,[3] antagonists at 5-HT receptors,[4] and acetylcholinesterase inhibitors.[5] 2-Arylimidazoles have been prepared for over a century[6] and are important building blocks, present in many bioactive compounds. Some recent examples include anticancer,[7] antiviral,[8] antibacterial,[9] antiinflammatory,[10] anticonvulsant,[11] and antihypertensive[12] activity. The association of these two important scaffolds in a single molecule was never reported in the literature. These new fused tricyclic systems combining the chromene and the 2-aryl imidazole can be considered alternative drug candidates with improved pharmacological properties.

2. Results and discussion

As part of our research work on the synthesis of chromene derivatives under ecologically benign conditions, salicylaldehydes **1** were combined with a selection of arylideneaminoacetonitriles **3**. These compounds were prepared from the reaction of aromatic aldehydes **1a**–**k** with the hydrochloride salt of aminoacetonitrile (Table 1, compounds **3a**–**k**). The reaction was performed in methanol and using an excess of sodium acetate as base. Stirring at room temperature resulted in a suspension of the product (for **3a**, **3c**, **3f** and **3g**) that was filtered and used directly without further purification. Compounds **3b**, **3d**, **3e** and **3h**–**k** were soluble in the reaction mixture and the pure product was isolated after dry flash chromatography.

Table 1
Synthesis of arylideneaminoacetonitriles 3



Entry	Aldehyde	R_1	R	Product **3**	Yield (%)
1	**1a**	OH	3-OCH_3	**3a**	99
2	**1b**	OH	H	**3b**	97
3	**1c**	OH	5-Cl	**3c**	97
4	**1d**	OH	3-OH	**3d**	95
5	**1e**	OH	5-OH	**3e**	65
6	**1f**	OH	5-Br	**3f**	90
7	**1g**	OH	3-OCH_3, 5-Br	**3g**	96
8	**1h**	OH	5-OCH_3	**3h**	97
9	**1i**	OH	4-$N(CH_2CH_3)_2$	**3i**	93
10	**1j**	H	3-Cl	**3j**	88
11	**1k**	H	4-Cl	**3k**	98

* Corresponding author. Tel.: +351 253604379; fax: +351 253 604383; e-mail address: fproenca@quimica.uminho.pt (F. Proença).

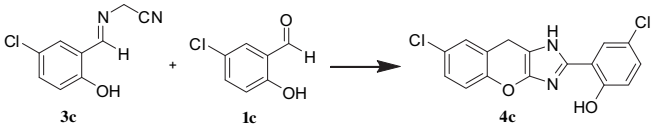
0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.01.035

The reaction of these compounds with salicylaldehydes was initially carried out in 0.05 M aqueous sodium carbonate solution. These experimental conditions had been successfully used in the eco-friendly synthesis of 2-iminochromenes from salicylaldehydes and cyanoacetamides.[13] When 3-methoxysalicylaldehyde **1a** and 3-methoxybenzylideneamino-acetonitrile **3a** were combined in aqueous base, extensive darkening of the reaction mixture was detected after 19 h at room temperature.

Analysis by TLC indicated the complete consumption of compound **3a** and the presence of unreacted aldehyde. Hydrolysis of the imine was considered a possible cause for the unsuccess of this reaction and different organic bases were used in ethanol and acetonitrile.

The optimized reaction conditions were selected from a study using 5-chlorosalicylaldehyde **1c** and the corresponding arylideneaminoacetonitrile **3c**. These reagents were combined in a 1:1 M ratio using acetonitrile as solvent and DBU, 1-methylpiperazine or triethylamine as catalyst (Table 2).

Table 2
Optimization of the reaction conditions for the synthesis of 4-chloro-2-(7-chloro-3,9-dihydrochromeno[3,2-*d*]imidazol-2-yl)phenol **4c**



Equiv **3c**/**1c**	Solvent	Catalyst	Reaction conditions	Product, yield (%)
1:1	CH_3CN	DBU	rt, 23 h	**4c**+5[a]
1:1	CH_3CN	DBU	1. rt, 2 h 2. Reflux,[b] 15 min	**4c**, 29
1:1	CH_3CN	1-Methyl -piperazine	1. rt, 1 h 10 min 2. 10 °C, 2 h 15 min	**4c**+5[c]
1:1.1	CH_3CN	NEt_3	1. rt, 1 h 15 min 2. Reflux,[b] 30 min 3. 80 °C, 21 h	**4c**, 29
2.2:1	CH_3CN	NEt_3	1. rt, 28 h 2. Reflux,[b] 1 h 20 min	**4c**, 24
2:1	CH_3CN	NEt_3	Reflux, 4 h 15 min	**4c**, 71
1:2.2	CH_3CN	NEt_3	1. 80 °C, 20 min 2. 80 °C,[d] 35 min	**4c**, 38[e]
1:1	EtOH	Piperidine	rt, 22 h	**4c**, 11
1:1	EtOH	NEt_3	Reflux, 4 h 15 min	**4c**, 50
1:1.9	EtOH	NEt_3	Reflux, 4 h 30 min	**4c**, 53
1.8:1	EtOH	NEt_3	Reflux, 4 h	**4c**, 74
3:1	EtOH	NEt_3	Reflux, 4 h 20 min	**4c**, 95

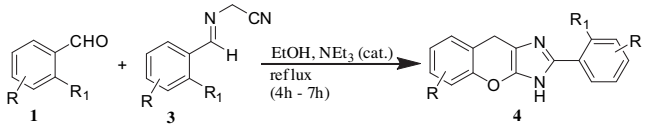
[a] In a 4:1 ratio, by ^{1}H NMR.
[b] Reflux of the solid isolated in step 1, using acetonitrile.
[c] In a 1:2.6 ratio by ^{1}H NMR; traces of **1c** were also present.
[d] Step 1 led to a first crop of **4c** and the mother liquor was heated at 80 °C, leading to a second crop of the same product.
[e] Yield after combining the first and second crops.

A poor isolated yield of **4c** (29%) or the formation of a dimeric structure identified as **5** (Scheme 2) in part of the experiments led to the selection of different combinations of compounds **1c** and **3c**, with triethylamine catalysis and room temperature or reflux conditions. When these compounds were combined in a 1:2 ratio and refluxed in acetonitrile for approximately 4 h, the product was isolated in 71% yield.

The reaction of 4-chloroacetonitrile **1c** and the corresponding arylideneaminoacetonitrile **3c** was also performed using ethanol as solvent (Table 2). When these reagents were combined in a 1:1 M ratio, using piperidine as catalyst, only 11% of the fused tricyclic product **4c** was isolated after 22 h at room temperature. The yield was improved (50%) with triethylamine catalysis and under reflux conditions for 4 h. These conditions were selected for a set of reactions where the ratio of compounds **1c** and **3c** was varied from 1.9:1 to 1:1.8 and 1:3. A threefold excess of arylideneaminoacetonitrile resulted in 95% yield of **4c**, and these conditions were used to perform all reactions.

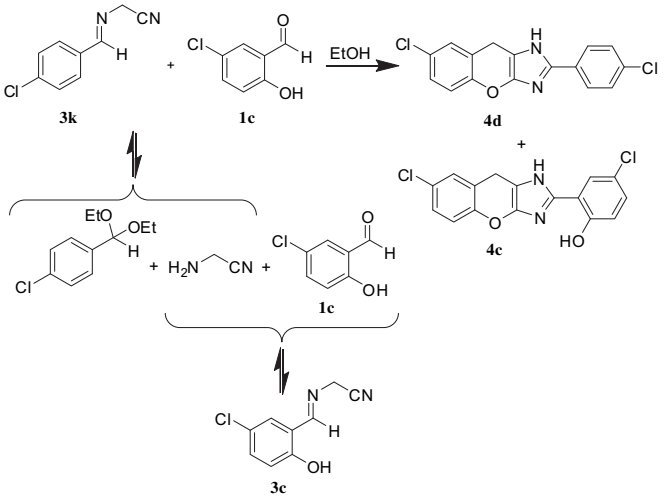
When aldehydes **1a**–**c**, **f**–**h** were combined with 3 M equiv of the corresponding (arylideneamino)acetonitrile **3a**–**c**, **f**–**h** and the ethanolic solution was refluxed for 4 h in the presence of triethylamine, chromeno-imidazophenols **4a**–**c**, **e**–**g** were isolated in 67–95% yield (Table 3).

Table 3
Synthesis of compounds **4**, using 3 M equiv of arylideneamineacetonitrile **3**, NEt_3 catalysis and reflux in ethanol



Entry	Aldehyde **1**	Compound **3**	Product	Yield (%)
1	**1a**	**3a**	**4a**	80
2	**1b**	**3b**	**4b**	68
3	**1c**	**3c**	**4c**	95
4	**1c**	**3k**	**4d**	11
5	**1f**	**3f**	**4e**	94
6	**1g**	**3g**	**4f**	67
9	**1h**	**3h**	**4g**	94

An experiment was carried out combining 2 M equiv of 2-(4-chlorobenzylideneamino)acetonitrile **3k** with 5-chlorosalicylaldehyde **1c** in ethanol and triethylamine (Table 3, entry 4). The reaction mixture was refluxed for 5 h and 40 min leading to a solid material identified by ^{1}H NMR as a mixture of **4c** and **4d** in a 1:3 M ratio (Scheme 1). A pure sample of **4d** was isolated from the solution in 11% yield.



Scheme 1. Products **4c** and **4d** isolated in the reaction of 2-(4-chloro-benzylideneamino)acetonitrile **3k** with 4-chlorosalicylaldehyde **1c**.

The products isolated in this reaction indicate that reflux in ethanol and base can induce cleavage of the imine moiety in the (arylideneamino)acetonitrile **3** to generate the acetal and amino-acetonitrile. A competing reaction with aldehyde **1c** leads to **3c**, the precursor of the tricyclic product **4c** upon reaction with 5-chlorosalicylaldehyde. It is possible that the absence of an hydroxyl group in the 2-position of the aromatic ring of **3k** will be responsible for the poor reactivity of this compound in the reaction with salicylaldehyde. A longer reflux time will lead to a larger extent of alcoholysis, facilitating the corresponding reaction.

The formation of compound **5** in acetonitrile and base was also studied under different reaction conditions (Table 4). The pure solid could be isolated in 45% yield when a threefold excess of compound **3c** was combined with salicylaldehyde **1c** and the acetonitrile solution was stirred at room temperature for 3 h, in the presence of triethylamine.

Table 4
Optimization of the reaction conditions for the synthesis of compound **5**

Equiv **3c**:**1c**	Solvent	Catalyst	Reaction conditions	Product, yield (%)
1:1	CH_3CN	NEt_3	rt, 1 h 15 min	**5**, 25
2.2:1	CH_3CN	NEt_3	rt, 1 h 45 min	**5**, 42
3.2:1	CH_3CN	NEt_3	rt, 3 h	**5**, 45

The structure assigned to this compound was mainly based on the NMR data, including H–C correlation spectra (HMQC and HMBC). Only one set of bands was observed in the ^1H and ^{13}C NMR spectrum, reflecting the symmetrical nature of the molecule. The signal for $C_{2'}$-H (a singlet at δ 6.62 ppm) showed a 3-bond correlation with $C_{5''}$, $C_{12'}$, C_1 and C_3. The proton on $C_{5'}$ (a doublet at δ 5.62 ppm with a coupling constant of 1.6 Hz) correlated with $C_{11'}$, $C_{12'}$ and $C_{7'}$. It was also possible to identify the 2-bond correlation of the N–H proton (δ 8.05 ppm) to $C_{2'}$ and $C_{12'}$ and also the 3-bond correlation to $C_{4'}$.

A mixture containing compound **4c** and dimer **5** (in a 1:4 M ratio) was solubilized in DMSO-d_6 (5 mg in 650 μL) and the ^1H NMR spectrum was registered daily during 3 days.

The N–H and C–H signals (δ 8.06, 6.62 and 5.62 ppm) for compound **5** and the CH_2 signal for compound **4c** (δ 4.15 ppm) were used to quantify these compounds. A singlet at δ 4.86 ppm progressively increasing with time indicated the formation of a new molecule in a noticeable amount. Considering that oxidation is also a possible competing process in DMSO, attempts were made to prepare and fully characterize this minor product.

In a separate experiment, dimer **5** was combined with manganese dioxide (1.6 M equiv), in THF. The mixture was stirred at room temperature until the presence of the starting material was no longer detected by TLC. The NMR of the first solid crop isolated from the reaction mixture showed a singlet at δ 4.86 ppm and two singlets at δ 12.09 and 11.45 ppm, together with signals for two substituted aromatic rings.

These signals were identical to those assigned to the minor compound, in the NMR study on the evolution of dimer **5**. This new compound was fully characterized by elemental analysis and spectroscopic techniques, including C–H correlation NMR spectra (HMQC and HMBC). Structure **6** was assigned to the compound considering that only one set of bands was observed in the ^1H and ^{13}C NMR spectrum and that the proton on $C_{5'}$ (δ_H 4.86 ppm, δ_C 42.8 ppm) showed an intense 3-bond correlation with $C_{7'}$, $C_{11'}$, $C_{12'}$, $C_{4''}$ and $C_{6''}$. A decisive observation was that the proton at δ 4.88 ppm showed a faint correlation with the carbon at δ 42.8 ppm, suggesting a 2-bond correlation between $C_{5'}$-H and $C_{5''}$-H (and vice-versa).

The evolution registered in Fig. 1 confirmed that compound **5** evolves to the monomeric species **4c** as a result of tautomeric equilibrium. In DMSO solution, oxidation is also a possible competing process, leading to the formation of **6**. After 3 days at room temperature, the solution contained approximately 20% of the dimer **5**, a similar amount of **6** and 60% of the chromeno-imidazole **4c**.

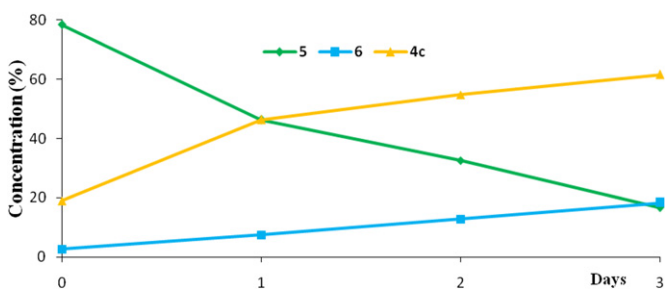
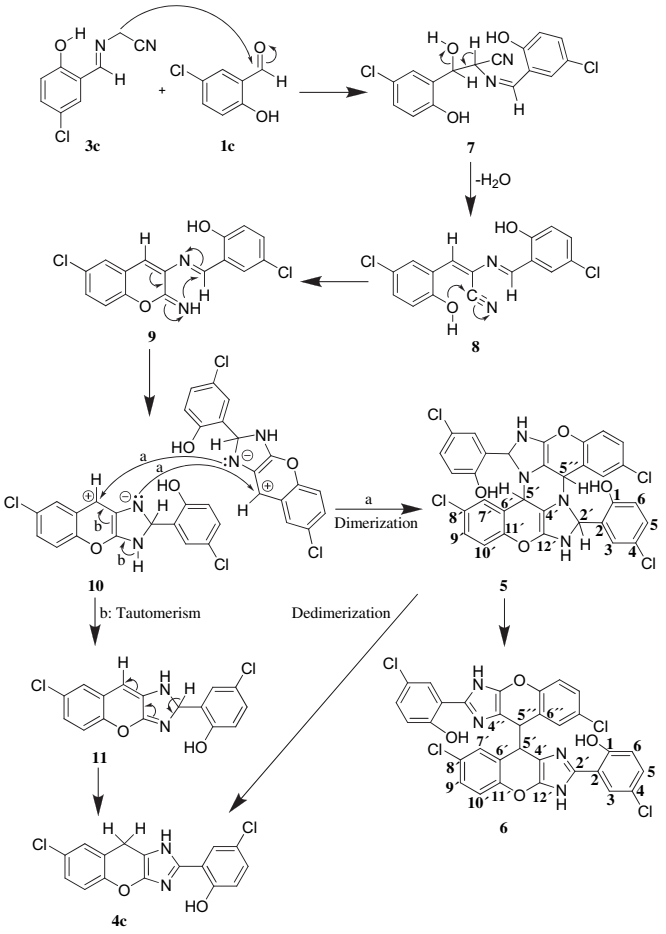


Fig. 1. Evolution of a mixture containing compound **4c** and dimer **5** (in a 1:4 M ratio) in DMSO-d_6 at room temperature for 3 days.

This study supports the reaction mechanism presented in Scheme 2 for the formation of chromeno[3,2-*d*]imidazoles **4** from the reaction of (arylideneamino)acetonitrile and salicylaldehydes.



Scheme 2. Proposed mechanism for the reaction of aldehyde **1c** with arylideneaminoacetonitrile **3c**.

The reaction starts with nucleophilic attack of the methylene carbon atom to the carbonyl group of salicylaldehyde. A cascade cyclization process is initiated after dehydration of intermediate **7**, leading to betaine **10**. This molecule can dimerize to compound **5**, isolated due to the poor solubility of this high molecular weight structure in acetonitrile.

Tautomeric equilibrium in compound **10** is a competing process assisted by the use of ethanol as solvent and leads directly to monomer **4**, usually isolated as the major product. The formation of **4** also occurs from dimer **5** upon proton transfer and C–N bond cleavage. Oxidation of dimer **5** to generate **6** was a minor competing process, detected when a DMSO solution of compound **5** was kept at room temperature. The formation of **6** was negligible when the reaction was performed under heating conditions.

3. Conclusion

A simple and mild procedure was developed for the synthesis of 2-aryl-1,9-dihydrochromeno[3,2-*d*]imidazoles through a one-pot cascade reaction initiated by the condensation of a salicylaldehyde

with an arylideneaminoacetonitrile. This synthetic approach requires reflux conditions in ethanol and triethylamine as catalyst. Different aromatic substituents in the salicylaldehyde and in the nitrile led to a mixture of products due to imine alcoholysis and the formation of two different arylideneaminoacetonitrile derivatives. A good yield of the tricyclic product **4** was obtained when the same aromatic moiety was present in both reagents.

4. Experimental section

4.1. General

All compounds were fully characterized by elemental analysis and spectroscopic data. The NMR spectra were recorded at room temperature, on a Varian Unity Plus (^{1}H: 300 MHz, ^{13}C: 75 MHz) and Bruker Avance 3400 (^{1}H: 400 MHz, ^{13}C: 100 MHz), including the ^{1}H–^{13}C correlation spectra (HMQC and HMBC) and deuterated DMSO was used as solvent. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet and br, broad. The coupling constants, *J*, are reported in hertz (Hz). IR spectra were recorded on an FT-IR Bomem MB 104 using Nujol mulls and NaCl cells. The reactions were monitored by thin layer chromatography (TLC) using silica gel 60 F_{254} (Merck). The melting points were determined on a Stuart SMP3 melting point apparatus and are uncorrected. Elemental analyses were performed on a LECO CHNS-932 instrument.

4.2. General procedure for the synthesis of (arylideneamino) acetonitriles 3

2-Aminoacetonitrile hydrochloride **2** (7.0 mmol) and sodium acetate (8.0 mmol) were dissolved in 35 mL of methanol. Aldehyde **1** (7.0 mmol) was added to the grey solution, and the reaction mixture was stirred at room temperature. A solid suspension was formed after a few minutes (for compounds **3a**, **3c**, **3f** and **3g**). The suspension was stirred for 2 h and the solid filtered and washed with cold methanol, leading to the pure product **3**. A second crop was isolated from the mother liquor after complete removal of methanol in the rotary evaporator, addition of dichloromethane (40 mL) and dry flash chromatography of the solution using dichloromethane (4×10 mL) as eluent. The solution was concentrated in the rotary evaporator and the yellow oil was kept at 0 °C leading to the product **3** that was filtered and washed with cold diethyl ether. For compounds **3b**, **3d**, **3e** and **3h**–**k**, the reaction mixture was stirred at room temperature for 2 h. The solvent was removed in the rotary evaporator and dichloromethane (40 mL) was added to the mixture. Dry flash chromatography of this mixture was performed using 20 mL of dichloromethane as eluent. The solvent was removed in the rotary evaporator leading to a solid product. Cold diethyl ether was added to the suspension, kept for a few minutes in an ice bath. The solid was filtered and washed with cold diethyl ether, leading to the pure (arylideneamino)acetonitrile **3**.

*4.2.1. (2-Hydroxy-3-methoxybenzylideneamino) acetonitrile (**3a**).* Yellow solid. Mp 118–120 °C; IR (Nujol mull) 3500–3200 (br), 2201, 1643, 1585, 1461, 1407; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.80 (s, 3H), 4.85 (d, *J*=1.5 Hz, 2H), 6.87 (t, *J*=8.1 Hz, 1H), 7.11 (dd, *J*=8.1 , 1.5 Hz, 1H), 7.15 (dd, *J*=7.5 , 1.5 Hz, 1H), 8.70 (t, *J*=1.5 Hz, 1H), 11.89 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 44.4, 55.8, 115.4, 117.1, 118.8 (2C), 122.6, 147.8, 149.5, 168.1. Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.16; H, 5.26; N, 14.74. Found: C, 63.11; H, 5.39; N, 14.76.

*4.2.2. (2-Hydroxy-benzylideneamino)acetonitrile (**3b**).* Yellow solid. Mp 51–53 °C; IR (Nujol mull) 3500–3200 (br), 2244, 1638, 1582, 1462, 1420, 1404; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.85 (d, *J*=1.8 Hz, 2H), 6.90–6.96 (m, 2H), 7.38 (td, *J*=8.1 , 1.8 Hz, 1H), 7.57 (dd, *J*=8.1 , 1.8 Hz, 1H), 8.70 (t, *J*=1.5 Hz, 1H), 11.97 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 44.4, 116.5, 117.1, 118.8, 119.2, 131.4, 133.3, 159.5, 168.0. Anal. Calcd for $C_9H_8N_2O$: C, 67.50; H, 5.00; N, 17.50. Found: C, 67.19; H, 4.79; N, 17.40.

*4.2.3. (2-Hydroxy-5-chlorobenzylideneamino) acetonitrile (**3c**).* Yellow-greyish solid. Mp 129–130 °C; IR (Nujol mull) 3500–3200 (br), 3071, 2240, 1641, 1621, 1577, 1514, 1466, 1415; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.86 (d, *J*=1.6 Hz, 2H), 6.96 (d, *J*=8.8 Hz, 1H), 7.40 (dd, *J*=8.8 , 2.8 Hz, 1H), 7.64 (d, *J*=2.8 Hz, 1H), 8.69 (t, *J*=1.6 Hz, 1H), 11.85 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 44.5, 116.9, 118.5, 120.4, 122.7, 129.5, 132.7, 157.9, 165.6. Anal. Calcd for $C_9H_7N_2OCl$: C, 55.53; H, 3.60; N, 14.40. Found: C, 55.90; H, 3.71; N, 14.56.

*4.2.4. (2,3-Dihydroxy-benzylideneamino) acetonitrile (**3d**).* Yellow solid. Mp 138–140 °C; IR (Nujol mull) 3500–3200 (br), 2263, 1635, 1595, 1466, 1410; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.84 (d, *J*=1.2 Hz, 2H), 6.75 (t, *J*=7.6 Hz, 1H), 6.92 (dd, *J*=7.6 , 1.6 Hz, 1H), 6.99 (dd, *J*=8.0 , 1.6 Hz, 1H), 8.65 (s, 1H), 8.90–9.60 (br s, 1H), 11.60–12.20 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 44.3, 117.1, 118.8, 118.9, 119.0, 122.7, 146.1, 148.4, 168.8. Anal. Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.54; N, 15.91. Found: C, 61.22; H, 4.41; N, 15.93.

*4.2.5. (2,5-Dihydroxy-benzylideneamino) acetonitrile (**3e**).* Yellow solid. Mp 169–171 °C; IR (Nujol mull) 3400–3300 (br), 2265, 1645, 1597, 1502, 1459, 1409; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.80 (d, *J*=1.6 Hz, 2H), 6.75 (d, *J*=8.8 Hz, 1H), 6.82 (dd, *J*=8.6 , 2.8 Hz, 1H), 6.94 (d, *J*=2.8 Hz, 1H), 8.61 (t, *J*=1.2 Hz, 1H), 9.05 (s, 1H), 11.08 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 44.6, 116.0, 117.2 (2C), 118.9, 121.0, 149.7, 152.1, 167.1. Anal. Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.54; N, 15.91. Found: C, 60.99; H, 4.36; N, 15.78.

*4.2.6. (2-Hydroxy-5-bromobenzylideneamino) acetonitrile (**3f**).* Grey solid. Mp 122–124 °C; IR (Nujol mull) 3500–3000 (br), 2238, 1644, 1619, 1567, 1505, 1465; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.86 (d, *J*=1.2 Hz, 2H), 6.91 (d, *J*=8.8 Hz, 1H), 7.51 (dd, *J*=8.8 , 2.4 Hz, 1H), 7.79 (d, *J*=2.8 Hz, 1H), 8.68 (t, *J*=1.2 Hz, 1H), 11.86 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 44.5, 116.9, 119.0, 110.1, 121.0, 132.4, 135.5, 158.3, 165.4. Anal. Calcd for $C_9H_7N_2OBr\cdot 0.2H_2O$: C, 44.52; H, 3.05; N, 11.54. Found: C, 44.38; H, 2.98; N, 11.60.

*4.2.7. (2-Hydroxy-3-methoxy-5-bromobenzylideneamino)acetonitrile (**3g**).* Beige solid. Mp 165–167 °C; IR (Nujol mull) 3500–3100 (br), 2244, 1646, 1631, 1573, 1467, 1415; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.82 (s, 3H), 4.86 (d, *J*=1.6 Hz, 2H), 7.23 (d, *J*=2.4 Hz, 1H), 7.38 (dd, *J*=2.4 Hz, 1H), 8.67 (t, *J*=1.6 Hz, 1H), 11.77 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 44.4, 56.2, 109.7, 116.9, 117.6, 120.2, 123.6, 148.7, 149.1, 165.8. Anal. Calcd for $C_{10}H_9N_2O_2Br$: C, 44.61; H, 3.35; N, 10.41. Found: C, 44.51; H, 3.43; N, 10.32.

*4.2.8. (2-Hydroxy-5-methoxybenzylideneamino) acetonitrile (**3h**).* Yellow solid. Mp 102–104 °C; IR (Nujol mull) 3500–3000 (br), 2257, 1636, 1621, 1588, 1487, 1456, 1409; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.71 (s, 3H), 4.85 (d, *J*=1.5 Hz, 2H), 6.86 (d, *J*=9.3 Hz, 1H), 6.96 (dd, *J*=9.2 , 3.3 Hz, 1H), 7.17 (d, *J*=3.0 Hz, 1H), 8.68 (s, 1H), 11.28 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 44.5, 55.5, 113.7, 117.5, 118.8, 120.4, 151.9, 153.4, 166.8. Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.16; H, 5.26; N, 14.74. Found: C, 62.98; H, 5.32; N, 14.59.

*4.2.9. (4-Diethylamino-2-hydroxybenzylideneamino) acetonitrile (**3i**).* Yellow solid. Mp 73–75 °C; IR (Nujol mull) 3500–3000 (br), 2252, 1634, 1560, 1523, 1459, 1420; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.09 (t, *J*=6.9 Hz, 6H), 3.35 (q, *J*=6.9 Hz, 4H), 4.68 (d, *J*=0.9 Hz, 2H), 6.04 (d, *J*=2.1 Hz, 1H), 6.25 (dd, *J*=8.4 , 2.4 Hz, 1H), 7.21 (d, *J*=9.0 Hz, 1H), 8.38 (s, 1H), 12.39 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 12.5 (2C), 43.7, 43.8 (2C), 96.8, 103.5, 107.4, 117.7, 133.4, 151.3, 162.1, 167.7.

Anal. Calcd for $C_{13}H_{17}N_3O$: C, 67.53; H, 7.36; N, 18.18. Found: C, 67.56; H, 7.31; N, 18.07.

*4.2.10. 2-(3-Chlorobenzylideneamino)acetonitrile (**3j**).* White solid. Mp 51–53 °C; IR (Nujol mull) 3061, 2245, 1651, 1645, 1621, 1584, 1568, 1538, 1466, 1434, 1409; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.83 (d, J=1.8 Hz, 2H), 7.52 (d, J=8.1 Hz, 1H), 7.59 (dt, J=8.4 Hz, 1H), 7.76 (d, J=7.8 Hz, 1H), 7.83 (t, J=1.5 Hz, 1H), 8.48 (t, J=1.5 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 45.4, 117.3, 127.0, 127.6, 130.8, 131.3, 133.7, 137.0, 163.9. Anal. Calcd for $C_9H_7N_2Cl\cdot 0.1H_2O$: C, 59.83; H, 4.00; N, 15.51. Found: C, 60.07; H, 3.86; N, 15.18.

*4.2.11. 2-(4-Chlorobenzylideneamino)acetonitrile (**3k**).* White solid. Mp 79–81 °C; IR (Nujol mull) 1653, 1594, 1569, 1459, 1413, 1404; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.81 (d, J=1.5 Hz, 2H), 7.54 (dd, J=6.6 , 1.8 Hz, 2H), 7.81 (dd, J=7.1 , 1.5 Hz, 2H), 8.48 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 45.4, 117.4, 129.0 (2C), 129.9 (2C), 133.8, 136.3, 164.0. Anal. Calcd for $C_9H_7N_2Cl\cdot 0.02H_2O$: C, 60.38; H, 3.94; N, 15.65. Found: C, 60.38; H, 3.67; N, 15.25.

4.3. General procedure for the synthesis of chromeno([2,3-*d*] imidazol-2-yl)phenol 4

Salicylaldehyde **1** (0.40 mmol) was added to a yellow solution of arylideneaminoacetonitrile **3** (1.20 mmol) in ethanol (15 mL) and triethylamine (0.08 mmol) and the reaction mixture was refluxed for 4–7 h. A solid gradually precipitated from solution and was filtered and washed with ethanol, leading to the pure product **4**.

*4.3.1. 2-Methoxy-6-(5-methoxy-3,9-dihydrochromeno[2,3-d]imidazol-2-yl)phenol (**4a**).* Yellow solid. Mp 238–239 °C; IR (Nujol mull) 3258, 1648, 1622, 1600, 1575, 1534, 1463, 1438, 1419; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.79 (s, 3H), 3.82 (s, 3H), 4.14 (s, 2H), 6.88 (d, J=6.0 Hz, 1H), 6.85 (t, J=8.0 Hz, 1H), 6.93 (dd, J=8.2 , 1.6 Hz, 1H), 6.96 (dd, J=8.0 , 1.2 Hz, 1H), 7.03 (t, J=7.6 Hz, 1H), 7.40 (dd, J=7.8 , 1.6 Hz, 1H), 10.5–13.5 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.5, 55.6, 55.7, 103.2, 110.5, 112.0, 113.6, 115.9, 118.7, 119.3, 121.8, 123.0, 139.6, 140.9, 145.3, 145.5, 148.3, 148.4. Anal. Calcd for $C_{18}H_{16}N_2O_4\cdot 0.2H_2O$: C, 65.93; H, 5.01; N, 8.55. Found: C, 65.78; H, 5.22; N, 8.42.

*4.3.2. 2-(3,9-Dihydrochromeno[3,2-d]imidazol-2-yl)phenol (**4b**).* Orange solid. Mp 270–272 °C; IR (Nujol mull) 3208, 3176, 1655, 1622, 1590, 1575, 1536, 1493, 1484, 1465, 1458, 1408; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.16 (s, 2H), 6.88–6.95 (m, 2H), 7.08–7.15 (m, 2H), 7.21 (td, J=8.0 , 1.6 Hz, 1H), 7.27 (td, J=7.6 , 1.6 Hz, 1H), 7.34 (dd, J=7.6 , 1.2 Hz, 1H), 7.82 (dd, J=7.8 , 1.2 Hz, 1H), 11.70 (s, 1H), 12.63 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.4, 103.1, 113.7, 116.7, 119.2, 117.3, 118.6, 123.3, 124.4, 127.9, 129.5, 130.7, 139.4, 145.6, 151.2, 155.3. Anal. Calcd for $C_{16}H_{12}N_2O_2\cdot 0.1H_2O$: C, 72.23; H, 4.59; N, 10.53. Found: C, 72.10; H, 4.64; N, 10.25.

*4.3.3. 4-Chloro-2-(7-chloro-3,9-dihydrochromeno[3,2-d]imidazol-2-yl)phenol (**4c**).* Beige solid. Mp 290–292 °C; IR (Nujol mull) 3316, 1650, 1629, 1609, 1572, 1536, 1478, 1463, 1415; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.15 (s, 2H), 6.95 (d, J=8.7 Hz, 1H), 7.15 (d, J=8.7 Hz, 1H), 7.21 (dd, J=8.7 , 2.7 Hz, 1H), 7.30 (dd, J=8.8 , 2.7 Hz, 1H), 7.42 (d, J=2.4 Hz, 1H), 7.87 (d, J=2.4 Hz, 1H), 11.0–13.0 (br s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 23.2, 103.4, 115.2, 118.2, 118.8, 120.7, 122.7, 123.7, 126.6, 127.5, 128.6, 129.9, 137.9, 145.6, 149.9, 153.8. Anal. Calcd for $C_{16}H_{10}N_2O_2Cl_2$: C, 57.66; H, 3.00; N, 8.41. Found: C, 57.51; H, 3.31; N, 8.26.

*4.3.4. 7-Chloro-2-(4-chlorophenyl)-3,9-dihydrochromeno[3,2-d]imidazole (**4d**).* After refluxing for 5 h and 40 min a yellow solid was isolated from the reaction mixture and identified as a mixture of 7-chloro-2-(4-chlorophenyl)-3,9-dihydrochromeno[3,2-*d*]imidazole **4c** and 4-chloro-2-(7-chloro-3,9-dihydrochromeno[3,2-*d*] imidazol-2-yl)phenol **4d** (28.40 mg) in a 3:1 ratio, by ^{1}H NMR. The mother liquor was concentrated in the rotary evaporator and kept at 0 °C for 12 h. An orange solid precipitated and was filtered and washed with ethanol, leading to the pure 7-chloro-2-(4-chlorophenyl)-3,9-dihydrochromeno[3,2-*d*]imidazole **4d** (0.06 mmol, 11%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.33 (s, 2H), 7.13 (d, J=8.8 Hz, 1H), 7.29 (dd, J=8.6 , 2.8 Hz, 1H), 7.42 (d, J=2.8 Hz, 1H), 7.50 (dd, J=6.8 , 2.0 Hz, 2H), 7.85 (dd, J=6.8 , 2.0 Hz, 2H), 12.58 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.4, 103.9, 119.1, 121.0, 125.9 (2C), 126.5, 127.7, 128.8 (2C), 129.2, 130.1, 132.3, 138.8, 148.1, 150.4. Anal. Calcd for $C_{16}H_{10}N_2OCl_2\cdot 0.6H_2O$: C, 58.57; H, 3.42; N, 8.54. Found: C, 58.70; H, 3.50; N, 8.38. Due to the small amount of solid isolated, the melting point and IR spectrum could not be obtained.

*4.3.5. 4-Bromo-2-(7-bromo-3,9-dihydrochromeno [3,2-d]imidazol-2-yl)phenol (**4e**).* Beige solid. Mp 298–300 °C; IR (Nujol mull) 3332, 1650, 1625, 1603, 1579, 1566, 1531, 1473, 1460, 1409; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.16 (s, 2H), 6.90 (d, J=8.7 Hz, 1H), 7.09 (d, J=8.4 Hz, 1H), 7.33 (dd, J=8.6 , 2.4 Hz, 1H), 7.42 (dd, J=8.7 , 2.4 Hz, 1H), 7.56 (d, J=2.4 Hz, 1H), 8.00 (d, J=2.4 Hz, 1H), 11.0–13.0 (br s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 23.1, 103.5, 110.1, 114.4, 115.8, 118.7, 119.2, 121.2, 126.6, 130.4, 131.5, 132.7, 137.8, 145.7, 150.4, 154.2. Anal. Calcd for $C_{16}H_{10}N_2O_2Br_2$: C, 45.50; H, 2.37; N, 6.64. Found: C, 45.26; H, 2.48; N, 6.76.

*4.3.6. 4-Bromo-2-(7-bromo-5-methoxy-3,9-dihydrochromeno[2,3-d] imidazol-2-yl)-6-methoxyphenol (**4f**).* Beige solid. Mp 274–276 °C; IR (Nujol mull) 3550–3000 (br), 1654, 1604, 1573, 1527, 1463, 1418; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.81 (s, 3H), 3.85 (s, 3H), 4.11 (s, 2H), 7.05 (d, J=2.0 Hz, 1H), 7.11 (d, J=11.4 Hz, 1H), 7.60 (d, J=2.4 Hz, 1H), 11.72 (s, 1H), 12.74 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.2, 56.0, 52.2, 103.6, 110.0, 113.6, 114.4, 114.5, 114.9, 118.1, 121.2, 124.0, 138.2, 140.2, 144.6, 145.2, 149.1, 149.4. Anal. Calcd for $C_{18}H_{14}N_2O_4Br_2\cdot 2.5H_2O$: C, 40.99; H, 3.61; N, 5.31. Found: C, 41.03; H, 3.54; N, 5.48.

*4.3.7. 4-Methoxy-2-(7-methoxy-3,9-dihydrochromeno[2,3-d]imidazol-2-yl)phenol (**4g**).* Yellow solid. Mp 274–276 °C; IR (Nujol mull) 3204, 3168, 1650, 1635, 1596, 1536, 1490, 1465; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.74 (s, 3H), 3.73 (s, 3H), 4.13 (s, 2H), 6.79–6.87 (m, 3H), 6.90 (d, J=3.2 Hz, 1H), 7.06 (d, J=8.8 Hz, 1H), 7.41 (d, J=2.4 Hz, 1H), 11.24 (s, 1H), 12.59 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.6, 55.4, 55.5, 102.7, 108.4, 113.6, 114.1, 114.4, 116.1, 117.5, 118.1, 119.3, 139.3, 145.1, 146.0, 149.4, 152.1, 154.9. Anal. Calcd for $C_{18}H_{16}N_2O_4\cdot 0.1H_2O$: C, 66.30; H, 4.97; N, 8.59. Found: C, 66.24; H, 4.98; N, 8.68.

4.4. Synthesis of 2,2′-(3,10-dichloro-6,11b,12,13-tetrahydro-4b*H*,5*H*-7,14-dioxa-4c,6,11c,13-tetraazadibenzo[*e*,*l*] cyclopenta [*h*,*i*]aceanthrylene-5,12-diyl)bis(4-chlorophenol) 5

5-Clorosalicylaldehyde **1c** (0.06 g, 0.38 mmol) was added to a solution of (5-chloro-2-hydroxybenzylideneamino)acetonitrile **3c** (0.24 g, 1.23 mmol) in acetonitrile (5 mL) and triethylamine (0.01 g, 0.08 mmol, 14.0 μL), and the yellow solution was stirred at room temperature. After 10 min a yellow solid started to precipitate. The reaction mixture was stirred for a further 2 h and 50 min and the yellow solid was filtered and washed with acetonitrile, leading to the pure product **5** (0.06 g, 0.17 mmol, 45%): mp higher then 300 °C; IR (Nujol mull) 3332, 3312, 3101, 1644, 1609, 1595, 1565, 1479, 1463, 1415 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.62 (d, J=1.6 Hz, 2H), 6.62 (s, 2H), 6.87 (d, J=8.8 Hz, 2H), 6.98 (dd, J=8.6 , 2.8 Hz, 2H), 7.06 (d, J=2.8 Hz, 2H), 7.10 (d, J=8.4 Hz, 2H), 7.17 (dd, J=8.4 , 2.8 Hz, 2H), 7.21 (d, J=2.4 Hz, 2H), 8.04 (s, 2H), 10.13 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 77.8 (2C), 87.7 (2C), 117.0 (2C), 117.1

(2C), 122.4 (2C), 122.7 (2C), 123.1 (2C), 126.2 (2C), 126.8 (2C), 128.2 (2C), 128.5 (2C), 128.7 (2C), 138.0 (2C), 146.0 (2C), 153.7 (2C), 162.8 (2C). Anal. Calcd for $C_{32}H_{20}N_4O_4Cl_4$: C, 57.66; H, 3.00; N, 8.41. Found: C, 57.28; H, 2.96; N, 8.56.

4.5. Synthesis of 2,2′-(7,7′-dichloro-3,3′,9,9′-tetrahydro-9,9′-bichromeno[2,3-*d*]imidazole-2,2′-diyl)bis(4-chlorophenol) 6

Manganese dioxide (15.72 mg, 0.18 mmol) was added to a yellow solution of dimer **5** (0.07 g, 0.11 mmol) in THF (60 mL). The reaction mixture was stirred at room temperature for 4.5 h. Flash chromatography using THF (4×10 mL) as eluent was performed and the yellow solution was concentrated in the rotary evaporator leading to a yellow solid. The suspension was kept in an ice bath for a few minutes and the solid was filtered and washed with THF, leading to the pure product **6** (13.10 mg, 0.02 mmol, 18%). The mother liquor was concentrated in the rotary evaporator leading to a second crop of a yellow solid, identified as a complex mixture containing compound **6**, by ^{1}H NMR. Mp 285–287 °C; IR (Nujol mull) 3296, 1636, 1585, 1558, 1536; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.86 (s, 2H), 6.95 (br s, 2H), 6.99 (d, J=8.8 Hz, 2H), 7.06 (d, J=8.8 Hz, 2H), 7.25 (dd, J=8.8 , 2.4 Hz, 2H), 7.33 (dd, J=8.8 , 2.4 Hz, 2H), 7.83 (d, J=2.4 Hz, 2H), 10.45 (s, 2H), 12.09 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 42.8 (2C), 104.4 (2C), 116.0 (2C), 118.47 (2C), 118.50 (2C), 122.2 (2C), 122.9 (2C), 124.6 (2C), 126.7 (2C), 128.4 (2C), 128.8 (2C), 129.0 (2C), 138.9 (2C), 147.5 (2C), 151.2 (2C), 153.8 (2C). Anal. Calcd for $C_{32}H_{18}N_4O_4Cl_4$: C, 57.83; H, 2.71; N, 8.43. Found: C, 57.63; H, 2.78; N, 8.18.

Acknowledgements

We gratefully acknowledge the financial support from Fundação para a Ciência e a Tecnologia and a Ph.D. grant awarded to M.C. (SFRH/BD/31531/2006).

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.01.035.

References and notes

1. For recent examples of biologically active chromene derivatives see: (a) Robert, S.; Bertolla, C.; Masereel, B.; Dogné, J.; Pochet, L. *J. Med. Chem.* **2008**, *51*, 3077–3080; (b) Abrunhosa, L.; Costa, M.; Areias, F.; Venâncio, A.; Proença, F. *J. Ind. Microbiol. Biotechnol.* **2007**, *34*, 787–792; (c) Chimenti, F.; Bizzarri, B.; Bolasco, A.; Secci, D.; Chimenti, P.; Granese, A.; Carradori, S.; Rivanera, D.; Zicari, A.; Scaltrito, M.; Sisto, F. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4922–4926; (d) Behrenswerth, A.; Volz, N.; Toräng, J.; Hinz, S.; Bräse, S.; Müller, C. *Bioorg. Med. Chem.* **2009**, *17*, 2842–2851; (e) Erichsen, M.; Huynh, T.; Abrahamsen, B.; Bastlund, J.; Bundgaard, C.; Monrad, O.; Bekker-Jensen, A.; Nielsen, C.; Frydenvang, K.; Jensen, A.; Bunch, L. *J. Med. Chem.* **2010**, *53*, 7180–7191; (f) Jain, N.; Xu, J.; Kanojia, R.; Du, F.; Jian-Zhong, G.; Pacia, E.; Lai, M.; Musto, A.; Allan, G.; Reuman, M.; Li, X.; Hahn, D.; Cousineau, M.; Peng, S.; Ritchie, D.; Russell, R.; Lundeen, S.; Sui, Z. *J. Med. Chem.* **2009**, *52*, 7544–7569; (g) Endo, S.; Matsunaga, T.; Kuwata, K.; Zhao, H.; El-Kabbani, O.; Kitade, Y.; Hara, A. *Bioorg. Med. Chem.* **2010**, *18*, 2485–2490; (h) Tang, J.; Qian, K.; Zhang, B.; Chen, Y.; Xia, P.; Yu, D.; Xia, Y.; Yang, Z.; Chen, C.; Morris-Natschke, S.; Lee, K. *Bioorg. Med. Chem.* **2010**, *18*, 4363–4373; (i) Conti, C.; Desideri, N. *Bioorg. Med. Chem.* **2010**, 6480–6488.
2. (a) Santana, L.; Uriarte, E.; González-Díáz, H.; Zagotto, G.; Soto-Otero, R.; Médez-Álvarez, E. *J. Med. Chem.* **2006**, *49*, 1149–1156; (b) Catto, M.; Nicolotti, O.; Leonetti, F.; Carotti, A.; Favia, A.; Soto-Otero, R.; Méndez-Álvarez, E.; Carotti, A. *J. Med. Chem.* **2006**, *49*, 4912–4925; (c) Brűhlmann, C.; Ooms, F.; Carrupt, P.; Testa, B.; Catto, M.; Leonetti, F.; Altomare, C.; Carotti, A. *J. Med. Chem.* **2001**, *44*, 3195–3198; (d) Chimenti, F.; Secci, D.; Bolasco, A.; Chimenti, P.; Bizzarri, B.; Granese, A.; Carradori, S.; Yánez, M.; Orallo, F.; Ortuso, F.; Alcaro, S. *J. Med. Chem.* **2009**, *52*, 1935–1942.
3. Maier, D.; Briner, C.; Ding, M.; Powell, M.; Jiang, Q.; Hill, G.; Heys, J.; Elmore, C.; Pierson, M.; Mrzljak, L. *J. Pharmacol. Exp. Ther.* **2009**, *330*, 342–351.
4. (a) Garino, C.; Tomita, T.; Pietrancosta, N.; Laras, Y.; Rosas, R.; Herbette, G.; Maigret, B.; Quéléver, G.; Iwatsubo, T.; Kraus, J. *J. Med. Chem.* **2006**, *49*, 4275–4285; (b) Garino, C.; Tomita, T.; Pietrancosta, N.; Laras, Y.; Rosas, R.; Herbette, G.; Maigret, B.; Quéléver, G.; Iwatsubo, T.; Kraus, J. *Bioorg. Med. Chem.* **2006**, *16*, 1995–1999.
5. Zhou, X.; Wang, X.; Wang, T.; Kong, L. *Bioorg. Med. Chem.* **2008**, *16*, 8011–8021.
6. Radziszewski, B. *Ber.* **1882**, *15*, 2706–2709.
7. (a) Tong, Y.; Bouska, J. J.; Ellis, P. A.; Johnson, E. F.; Leverson, J.; Liu, X.; Marcotte, P. A.; Olson, A. M.; Osterling, D. J.; Przytulinska, M.; Rodriguez, L. E.; Shi, Y.; Soni, N.; Stavropoulos, J.; Thomas, S.; Donawho, C. K.; Frost, D. J.; Luo, Y.; Giranda, V. L.; Penning, T. D. *J. Med. Chem.* **2009**, *52*, 6803–6813; (b) Niculescu-Duvaz, D.; Niculescu-Duvaz, I.; Suijkerbuijk, B. M. J. M.; Ménard, D.; Zambon, A.; Nourry, A.; Davies, L.; Manne, H. A.; Friedlos, F.; Ogilvie, L.; Hedley, D.; Takle, A. K.; Wilson, D. M.; Pons, J.-F.; Coulter, T.; Kirk, R.; Cantarino, N.; Whittaker, S.; Marais, R.; Springer, C. J. *Bioorg. Med. Chem.* **2010**, *18*, 6934–6952; (c) Lee, J.; Kim, H.; Yu, H.; Chung, J. Y.; Oh, C.-H.; Yoo, K. H.; Sim, T.; Hah, J.-M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1573–1577; (d) Bressi, J. C.; Jong, R.; Wu, Y.; Jennings, A. J.; Brown, J. W.; O'Connell, S.; Tari, L. W.; Skene, R. J.; Vu, P.; Navre, M.; Cao, X.; Gangloff, A. R. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3138–3141; (e) Potter, A.; Oldfield, V.; Nunns, C.; Fromont, C.; Ray, S.; Northfield, C. J.; Bryant, C. J.; Scrace, S. F.; Robinson, D.; Matossova, N.; Baker, L.; Dokurno, P.; Surgenor, A. E.; Davis, B.; Richardson, C. M.; Murray, J. B.; Moore, J. D. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6483–6488.
8. (a) Banie, H.; Sinha, A.; Thomas, R. J.; Sircar, J. C.; Richards, M. L. *J. Med. Chem.* **2007**, *50*, 5984–5993; (b) Tonelli, M.; Simone, M.; Tasso, B.; Novelli, F.; Boido, V.; Sparatore, F.; Paglietti, G.; Pricl, S.; Giliberti, G.; Blois, S.; Ibba, C.; Sanna, G.; Loddo, R.; Colla, P. *Bioorg. Med. Chem. Lett.* **2010**, *18*, 2937–2953.
9. Keurulainen, L.; Salin, O.; Siiskonen, A.; Kern, J. M.; Alvesalo, J.; Kiuru, P.; Maass, M.; Yli-Kauhaluoma, J.; Vuorela, P. *J. Med. Chem.* **2010**, *53*, 7664–7674.
10. (a) Gleave, R. J.; Walter, D. S.; Beswick, P. J.; Fonfria, E.; Michel, A. D.; Roman, S. A.; Tang, S.-P. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4951–4954; (b) Wu, T. Y. H.; Juteau, H.; Ducharme, Y.; Friesen, R. W.; Guiral, S.; Dufresne, L.; Poirier, H.; Salem, M.; Riendeau, D.; Mancini, J.; Brideau, C. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6978–6982.
11. Zuliani, V.; Fantini, M.; Nigam, A.; Stables, J. P.; Patel, M. K.; Rivara, M. *Bioorg. Med. Chem.* **2010**, *18*, 7957–7965.
12. Navarrete-Vázquez, G.; Hidalgo-Figueroa, S.; Torres-Piedra, M.; Vergara-Galicia, J.; Rivera-Leyva, J. C.; Estrada-Soto, S.; León-Rivera, I.; Aguilar-Guardarrama, B.; Rios-Gómez, Y.; Villalobos-Molina, R.; Ibarra-Barajas, M. *Bioorg. Med. Chem.* **2010**, *18*, 3985–3991.
13. Proença, F.; Costa, M. *Green Chem.* **2008**, *10*, 995–998.