Tetrahedron 68 (2012) 5498–5504

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

Synthesis of chromeno[2′,3′:4,5]imidazo[2,1-*a*]isoquinolines via a novel domino reaction of isoquinoline-derived immonium salts. Scope and limitations

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ARTICLE INFO

Article history:
Received 14 February 2012
Received in revised form 31 March 2012
Accepted 23 April 2012
Available online 30 April 2012

Keywords:
Domino reaction
Isoquinoline
Chromene
Salicylic aldehyde
Multi component reaction

ABSTRACT

A one-pot protocol towards chromeno[2′,2′:4,5]imidazo[2,1-*a*]isoquinoline derivatives via a domino reaction of isoquinoline-derived immonium salts and α-hydroxy aromatic aldehydes is elaborated. The scope and limitations of this reaction is discussed.

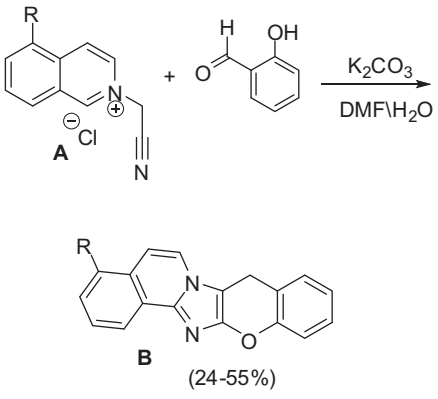
1. Introduction

In modern-day organic chemistry, a growing tendency towards green and sustainable synthesis has been well illustrated by domino reactions,[1] which allow the direct synthesis of complex molecules in a highly efficient way. The synthesis of complex organic substances needs to rely on methods that provide maximum efficiency in research chemistry. Organic reactions are traditionally viewed as linear and stepwise processes, in which isolation and purification of key intermediates often lead to low yields. Domino reactions, on the other hand, allow access to complex molecules in an effective, atom-economical manner.[2]

In the course of our studies on the development of new domino reactions[3] for creation of molecular complexity and diversity whilst combining economic aspects with environmental ones we have recently reported preliminary results on a new synthetic protocol towards previously unknown chromeno[2′,3′:4,5]imidazo[2,1-*a*] isoquinolines.[4]

The target compounds **B** were obtained in moderate yields by the base-catalyzed reaction of isoquinolinium salts **A** with salicylic aldehyde in a DMF\water mixture (Scheme 1).

Herein we report our investigations of this reaction optimization as well as its scope and limitations.



Scheme 1.

2. Results and discussion

We presume that compound **B** is the product of an anionic domino reaction, starting with the Kröhnke condensation of salicylic aldehyde and isoquinolinium salt **A** to produce the styryl derivative **C**. The base-catalyzed deprotonation of the phenol OH yields zwitterion **D**. This then undergoes two consecutive nucleophilic cyclizations, followed by a [1,4]—proton shift to yield the pentacycle **B** (Scheme 2).

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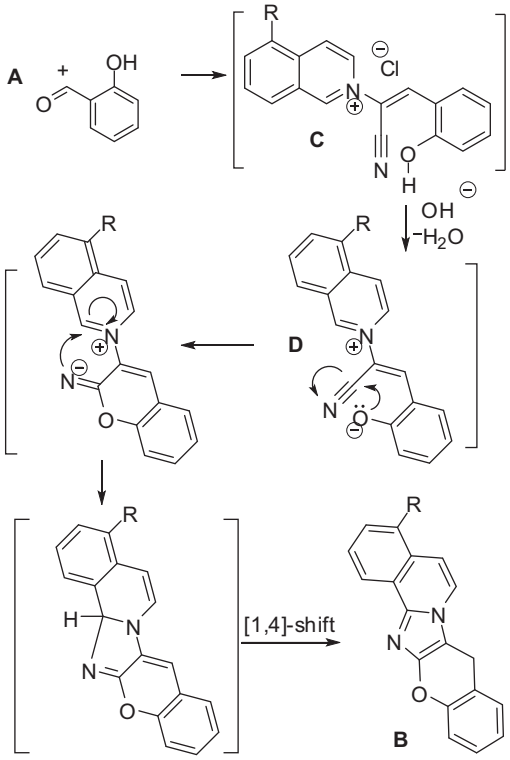
doi:10.1016/j.tet.2012.04.087

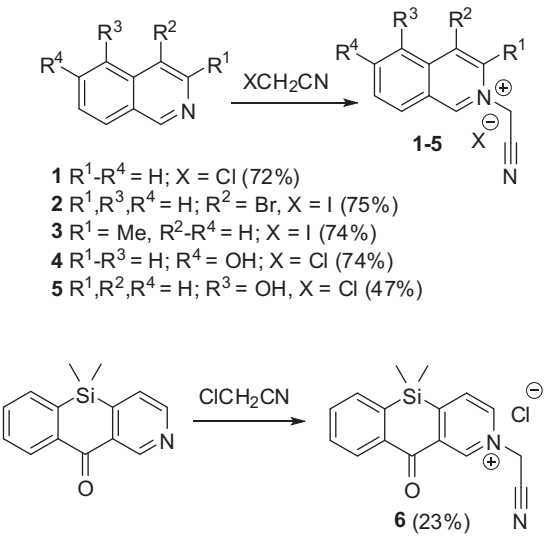


Scheme 2.

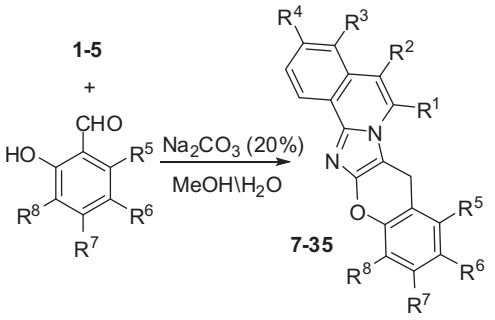
Based on the obtained data we could presume that this anionic domino reaction is influenced by different factors: (a) the electronic and spatial effects of the substituents both on the isoquinoline ring and on the salicylic aldehyde molecule (b) the nature of the solvent.

The quaternary isoquinolinium salts **1**–**4** were obtained by reactions of the commercially available isoquinolines with chloro or iodoacetonitrile in acetonitrile. Due to poor solubility of 5- and 6-hydroxyisoquinolines in acetonitrile, compounds **5**,**6** were obtained by the same procedure in DMF. 2-(Cyanomethyl)-5,5-dimethyl-10-oxo-5,10-dihydro[1]benzosilino[3,2-*c*]pyridin-2-ium chloride (**6**) was obtained from the appropriate benzosilino[3,2-*c*]pyridine[5] and chloroacetonitrile (Scheme 3).

In preliminary experiments we used a DMF\water mixture at reflux as a solvent for this reaction. However, it caused significant tarring and made it necessary to use column chromatography for the isolation of the target products, thus significantly diminishing the main benefit of any domino reaction—the ease of isolation. In a paper published by Proença et al.[6] it was later reported, that in the case of pyridinium salts this reaction could be effectively carried out in water, but our attempts to follow this protocol all failed, mainly due to the low solubility of the starting isoquinolinium salts in water. After several experiments, we found, that the best yields of the chromeno[2′,3′:4,5]imidazo[2,1-*a*]isoquinolines are achieved in a methanol/water mixture in the presence of 20% Na_2CO_3. (Scheme 4) (Table 1).



Scheme 3.



Scheme 4.

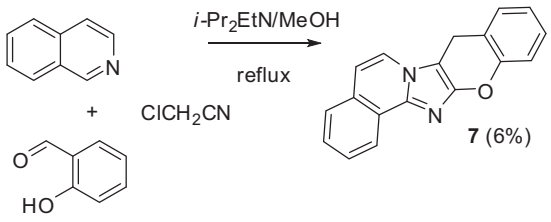
Table 1
Chromeno[2′,3′:4,5]imidazo[2,1-*a*]isoquinolines **7**–**35**

#	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	%
7	H	H	H	H	H	H	H	H	36
8	H	H	H	H			H	H	34
9	H	H	H	H	H	H	H	OEt	15
10	H	H	H	H	H	NO_2	H	H	51
11	H	H	H	H	H	Br	H	H	32
12	H	Br	H	H	H	H	H	H	12
13	H	Br	H	H	H	Br	H	H	56
14	Me	H	H	H	H	H	H	H	13
15	Me	H	H	H			H	H	21
16	Me	H	H	H	H	H	H	OEt	28
17	Me	H	H	H	H	NO_2	H	H	25
18	Me	H	H	H	H	Br	H	H	29
19	Me	H	H	H	H	H	H	Cl	52
20	Me	H	H	H	H	Cl	H	Cl	65
21	H	H	H	OH	H	H	H	H	59
22	H	H	H	OH			H	H	48
23	H	H	H	OH	H	H	H	OEt	37
24	H	H	H	OH	H	H	OMe	H	3
25	H	H	H	OH	H	NO_2	H	H	49
26	H	H	H	OH	H	Br	H	H	51
27	H	H	H	OH	H	H	H	Cl	76
28	H	H	H	OH	H	Cl	H	Cl	48
29	H	H	OH	H	H	H	H	H	34
30	H	H	OH	H			H	H	51
31	H	H	OH	H	H	H	H	OEt	12
32	H	H	OH	H	H	NO_2	H	H	31
33	H	H	OH	H	H	Br	H	H	38
34	H	H	OH	H	H	H	H	Cl	41
35	H	H	OH	H	H	Cl	H	Cl	67

In a typical experiment, a mixture of the isoquinolinium salt and salicylic aldehyde is dissolved in methanol/water and solid Na_2CO_3 is then added, followed by intensive stirring at reflux. In most cases, the precipitation of the target product starts in 5 min and the reaction takes 1–2 h to complete (TLC monitoring). The products thus formed are the target chromeno[2′,3′:4,5]imidazo[2,1-*a*]isoquinolines (90–95% purity as judged by NMR spectroscopic analysis). The addition of water to methanol is mandatory to achieve homogeneity of the reaction mixture. The use of other bases, i.e., TEA, Hünig base, pyridine or KOH in all cases led to the formation of by-products, thus complicating the product isolation procedure.

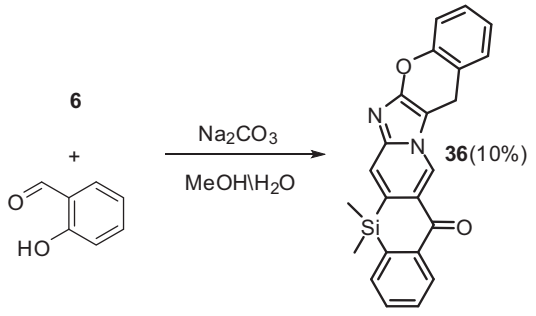
The experiments demonstrate that the best results are achieved when the molecule of salicylic aldehyde bears electron withdrawing substituents (Table 1, entries **10**, **13**, **19**, **20**, **22**, **25**–**28**, **30**, **35**). We presume, that electron withdrawing groups increase the acidity of the phenolic OH, thus facilitating the formation of the zwitterionic intermediate **D** (Scheme 2) and subsequent nucleophilic cyclizations. This assumption is indirectly proved by low-to-moderate yields of the target products in the case of OMe or OEt substituted aldehydes (Table 1, entries **9**, **16**, **24**, **31**). In all cases the only products isolated were obtained by cyclization onto the C-1 atom of the isoquinolines ring.

We have also tried to work out the MCR variant of this reaction. Thus, simply mixing the equimolar amounts of isoquinoline, chloroacetonitrile, salicylic aldehyde and Hünig base in methanol resulted in precipitation of the target **7** in 6% yield (Scheme 5).



Scheme 5.

To further explore this reaction scope, we investigated the reaction of 2-(cyanomethyl)-5,5-dimethyl-10-oxo-5,10-dihydro[1]benzosilino[3,2-*c*]pyridin-2-ium chloride (**6**) with salicylic aldehyde. The target hexacyclic product was isolated in only 10% yield (Scheme 6).



Scheme 6.

3. Conclusion

We have elaborated and optimized a new method for the synthesis of polycyclic chromeno[2′,3′:4,5]imidazo[2,1-*a*]isoquinolines derivatives based on a new anionic domino reaction of cycloimmonium salts with *o*-hydroxybenzaldehydes. This reaction is especially effective in the case of salicylic aldehydes bearing electron withdrawing groups. We have demonstrated the possibility of the target products synthesis in the MCR mode, however very low yields caused by side reactions complicate its further usage. Further work aimed in using 1,3-azolium salts in this reaction is underway and will be reported in due course.

4. Experimental section

4.1. General

All solvents were distilled and dried before use, chloroacetonitrile and iodoacetonitrile were purchased from ACROS ORGANICS and were used without any additional purification. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, DMSO-d_6, HMPA-d_{18} solutions, at 25 °C, using a 400 or 600 MHz NMR spectrometer, peak positions are given in parts per million (δ) with tetramethylsilane used as the internal standard. Mass-spectra were registered using ESI or EI techniques, peaks of molecular ions of halogen-containing compounds are indicated for ^{35}Cl and ^{79}Br. Melting points were determined in a capillary tube and are uncorrected.

4.2. General procedure for the synthesis of isoquinolinium and benzosilinopyridinium salts 1–3, 6

Chloroacetonitrile (9.2 mmol) or iodoacetonitrile (9.2 mmol) was added to a stirred solution of isoquinoline (7.7 mmol) or benzosilinopyridine (7.7 mmol) in acetonitrile (5 mL). The reaction mixture was heated at reflux for 3–18 h (TLC monitoring). The target salt was filtered, washed with acetonitrile and dried in vacuo.

*4.2.1. 2-(Cyanomethyl)isoquinolinium chloride **1**.* Yield 1.15 g (72%); as beige solid; mp 204–205 °C (dec); [Found: C, 64.72; H, 4.31; N, 13.85. $C_{11}H_9ClN_2$ requires C, 64.56; H, 4.43; N, 13.69%]; δ_H (400 MHz, DMSO-d_6) 6.37 (s, 2H, CH_2), 8.07 (t, J=8.0 Hz, 1H, H-7), 8.28 (t, J=8.0 Hz, 1H, H-6), 8.38 (d, J=8.0 Hz, 1H, H-5), 8.56 (d, J=8.0 Hz, 1H, H-8), 8.69 (d, J=6.8 Hz, 1H, H-4), 8.97 (d, J=6.8 Hz, 1H, H-3), 10.44 (s, 1H, H-1); δ_C (100 MHz, DMSO-d_6): 47.9, 115.0, 126.8, 127.6, 128.0, 131.5, 132.2, 135.2, 138.0, 138.5, 152.2; *m*/*z* (%)=170 (20), 169 (70) $[M-Cl]^+$, 130 (27), 129 (100), 128 (24), 115(12), 103 (22), 102 (13), 101 (30), 77 (17), 76 (12), 75 (13), 63 (16), 59 (17), 51 (37), 50 (22), 48 (22), 43 (59), 42 (51).

*4.2.2. 4-Bromo-2-(cyanomethyl)isoquinolinium iodide **2**.* Yield 2.17 g (75%); as yellow solid; mp 184–185 °C (dec); [Found: C, 35.43; H, 2.19; N, 7.58. $C_{11}H_8BrIN_2$ requires C, 35.23; H, 2.15; N, 7.47%]; δ_H (400 MHz, DMSO-d_6) 5.18 (s, 2H, CH_2), 7.34 (t, J=7.0 Hz, 1H, H-6), 7.54 (d, J=8.3 Hz, 1H, H-7), 7.61 (td, J=7.0, 1.3 Hz, 1H, H-5), 7.81 (d, J=8.3 Hz, 1H, H-8), 8.49 (d, J=1.3 Hz, 1H, H-1), 9.42 (s, 1H, H-3); δ_C (100 MHz, DMSO-d_6): 47.9, 114.4, 122.3, 126.6, 127.6, 132.8, 133.0, 136.3, 136.8, 140.3, 152.0; *m*/*z* (%)=248 (2) $[M-I]^+$, 210(16), 209 (100), 208 (15), 207 (99), 129 (12), 128 (43), 127 (11), 101 (17), 50 (14), 43 (23).

*4.2.3. 2-(Cyanomethyl)-3-methylisoquinolinium iodide **3**.* Yield 1.77 g (74%); as orange solid; mp 197–198 °C (dec); [Found: C, 46.43; H, 3.44; N, 9.15. $C_{12}H_{11}IN_2$ requires C, 46.47; H, 3.58; N, 9.03%]; δ_H (400 MHz, DMSO-d_6) 2.95 (s, 3H, CH_3), 6.13 (s, 2H, CH_2), 8.02–8.06 (m, 1H, H-6), 8.24–8.31 (m, 2H, H-5, H-7), 8.52–8.56 (m, 2H, H-4, H-8), 10.15 (s, 1H, H-1); δ_C (150.9 MHz, DMSO-d_6) 19.5, 45.9, 114.2, 126.5, 126.9, 127.0, 131.1, 131.4, 138.6, 139.0, 144.5, 152.9; *m*/*z* (%)=183 (15) $[M-I]^+$, 167 (46), 144 (15), 143 (100), 142 (15), 129 (19), 128 (25), 127 (67), 116 (31), 115 (37), 101 (15), 79 (10), 63 (14), 59 (14), 55 (11), 51 (14).

*4.2.4. 2-(Cyanomethyl)-5,5-dimethyl-10-oxo-5,10-dihydro[1]benzosilino[3,2-c]pyridin-2-ium chloride **6**.* Analytical sample was recrystallyzed from CH_3CN. Yield 560 mg (23%); as beige solid; mp

170–171 °C (dec); [Found: C, 60.81; H, 4.95; N, 8.77. $C_{16}H_{15}ClN_2OSi$ requires C, 61.04; H, 4.80; N, 8.90%]; δ_H (400 MHz, DMSO-d_6) 0.61 (s, 6H, $(CH_3)_2Si$), 6.19 (s, 2H, CH_2), 7.73 (t, J=7.7 Hz, 1H, H-8), 7.81 (t, J=7.7 Hz, 1H, H-7), 7.61 (d, J=7.7 Hz, 1H, H-6), 8.34 (d, J=7.7 Hz, 1H, H-9), 8.84 (d, J=6.1 Hz, 1H, H-4), 9.42 (d, J=6.1 Hz, 1H, H-3), 9.82 (s, 1H, H-1); δ_C (100 MHz, DMSO-d_6) −2.2(2C), 48.5, 114.6, 129.6, 131.5, 133.6, 134.2, 135.0, 138.2, 139.0, 139.6, 144.6, 145.8, 163.0, 183.6; IR (KBr), ν: 1658 (C=O) cm^{-1}; m/z (%)=279 (5) $[M-Cl]^+$, 239 (29), 225 (18), 224 (100), 59 (10), 48 (13), 43 (34).

4.3. General procedure for the synthesis of isoquinolinium salts 4,5

Chloroacetonitrile (7.6 mmol) was added to a stirred solution of 5- or 6-hydroxyisoquinoline (6.9 mmol) in DMF (7 mL). The reaction mixture was heated at reflux for 4 h (TLC monitoring). The target salt was filtered, washedsubsequently with DMF and $CHCl_3$ and dried in vacuo.

4.3.1. 2-(Cyanomethyl)-6-hydroxyisoquinolinium chloride ***4***. Yield 1.12 g (74%); as grey solid; mp 234–235 °C (dec); [Found: C, 60.02; H, 4.14; N, 12.56. $C_{11}H_9ClN_2O$ requires C, 59.88; H, 4.11; N, 12.70%]; δ_H (400 MHz, DMSO-d_6) 5.99 (s, 2H, CH_2), 7.52 (d, J=2.1 Hz, 1H, H-5), 7.63 (dd, J=8.0, 2.1 Hz, 1H, H-7), 8.26 (d, J=8.0 Hz, 1H, H-8), 8.37 (d, J=8.1 Hz, 1H, H-4), 8.58 (dd, J=8.1, 1.3 Hz, 1H, H-3), 9.85 (bs, 1H, H-1), 12.60 (bs, 1H, OH); δ_C (100 MHz, DMSO-d_6): 46.8, 109.3, 115.0, 121.8, 123.8, 125.0, 134.2, 134.5, 140.8, 149.2, 167.5; m/z (%)=186 (14), 185 (37) $[M-Cl]^+$, 145 (100), 90 (16), 63 (16), 59 (14), 44 (10), 43 (62), 42 (19).

4.3.2. 2-(Cyanomethyl)-5-hydroxyisoquinolinium chloride ***5***. Yield 710 mg (47%); as yellow solid; mp 239–240 °C (dec); [Found: C, 59.95; H, 4.15; N, 12.45. $C_{11}H_9ClN_2O$ requires C, 59.88; H, 4.11; N, 12.70%]; δ_H (400 MHz, DMSO-d_6) 6.15 (s, 2H, CH_2), 7.69 (d, J=7.7 Hz, 1H, H-6), 7.91–7.99 (m, 2H, H-7, H-8), 8.64 (d, J=7.1 Hz, 1H, H-4), 8.75 (dd, J=7.1, 1.1 Hz, 1H, H-3), 10.16 (bs, 1H, H-1), 11.92 (s, 1H, OH); δ_C (150.9 MHz, DMSO-d_6) 47.9, 114.9, 120.0, 121.2, 121.9, 128.6, 128.9, 133.4, 133.8, 151.6, 153.9; m/z (%)=186 (26), 185 (100) $[M-Cl]^+$, 146 (19), 145 (91), 117 (21), 91 (17), 89 (15), 59 (14), 57 (14).

4.4. General procedure for the synthesis of chromeno [2′,3′:4,5]imidazo[2,1-*a*]isoquinolines 7–35

To a stirred solution of isoquinolinium salt (1 mmol) **1**–**5** and aldehyde (0.9 mmol) in a mixture of of methanol (**A** mL) and water (**B** mL), solid Na_2CO_3 (0.2 mmol) was added at reflux. The reaction mixture was heated at reflux for 1–2 h (TLC monitoring). After cooling, the precipitate was filtered-off, washed with water (3x) and with methanol once to give the target chromeno[2′,3′:4,5] imidazo[2,1-a]isoquinolines **7**–**35**.

4.4.1. 8H-Chromeno[2′,3′:4,5]imidazo[2,1-a]isoquinoline ***7***. **A**=2.5 mL, **B**=2.5 mL. Yield 0.09 g (36%). The physical characteristics and spectroscopic data were in good agreement with those reported earlier.[4b]

4.4.2. 16H-Benzo[5′,6′]chromeno[2′,3′:4,5]imidazo[2,1-a]isoquinoline ***8***. **A**=2.5 mL, **B**=2.5 mL. Yield 0.10 g (34%). The physical characteristics and spectroscopic data were in good agreement with reported earlier.[4b]

4.4.3. 12-Ethoxy-8H-chromeno[2′,3′:4,5]imidazo[2,1-a]isoquinoline ***9***. **A**=1.3 mL, **B**=1.3 mL. Yield 40 mg (15%); as light-brown solid; mp 108–109 °C (dec); [Found: C, 75.85; H, 5.16; N, 8.64. $C_{20}H_{16}N_2O_2$ requires C, 75.93; H, 5.10; N, 8.86%]; δ_H (400 MHz, $CDCl_3$) 1.50 (t, J=7.2 Hz, 3H, OCH_2CH_3), 4.16 (q, J=7.2 Hz, 2H, OCH_2CH_3), 4.29 (s, 2H, H-8), 6.87 (d, J=7.5 Hz, 2H, H-9, H-11), 7.00 (t, J=7.5, 1H, H-10), 7.12 (d, J=7.5 Hz, 1H, H-5), 7.53 (t, J=7.5 Hz, 1H, H-2), 7.62 (t, J=7.5 Hz, 1H, H-3), 7.67–7.71(m, 2H, H-4, H-6), 8.61 (d, J=7.5 Hz, 1H, H-1); δ_C (100 MHz, $CDCl_3$): 15.1, 23.4, 65.0, 99.3, 112.4, 112.6, 114.4, 116.8, 118.7, 120.3, 121.8, 123.0, 123.1, 125.0, 127.0, 127.6, 128.1, 129.0, 148.6, 150.5; m/z (%)=317 (14), 316 (100) $[M]^+$, 315 (54), 301 (15), 287 (16), 144 (11), 58 (16), 43 (20).

4.4.4. 10-Nitro-8H-chromeno[2′,3′:4,5]imidazo[2,1-a]isoquinoline ***10***. **A**=7 mL, **B**=0.7 mL. Analytical sample was recrystallyzed from *i*-PrOH/DMF. Yield 150 mg (51%); as light-yellow solid; mp 239–240 °C (dec); [Found: C, 68.03; H, 3.55; N, 13.37. $C_{18}H_{11}N_3O_3$ requires C, 68.14; H, 3.49; N, 13.24%]; δ_H (400 MHz, DMSO-d_6) 4.49 (s, 2H, H-8), 7.38–7.44 (m, 2H, H-5, H-12), 7.59–7.67 (m, 2H, H-9, H-11), 7.87–7.93 (m, 2H, H-2, H-3), 8.15–8.18 (m, 1H, H-6), 8.30–8.38 (m, 2H, H-1, H-4); δ_C (100 MHz, CF_3COOH+$CDCl_3$): 20.8, 101.9, 115.7, 117.9, 118.6, 118.8, 119.3, 121.6, 124.5, 126.2, 128.0, 130.6, 131.6, 132.6, 133.5, 140.2, 144.1, 154.1; IR (KBr), ν: 1521 (NO_2), 1336 (NO_2) cm^{-1}; m/z (%)=318 (32), 317 (100) $[M]^+$, 316 (23), 287 (12), 286 (44), 271 (42), 270 (20), 209 (31), 207 (14), 142 (17), 135 (13), 129 (35), 128 (25), 127 (16), 102 (30), 101 (16), 89 (17), 81 (10), 77 (21), 76 (22), 75 (30), 73 (32), 59 (19), 57 (13), 51 (19), 50 (11), 45 (17), 43 (15).

4.4.5. 10-Bromo-8H-chromeno[2′,3′:4,5]imidazo[2,1-a]isoquinoline ***11***. **A**=7 mL, **B**=0.7 mL. Analytical sample was recrystallyzed from *i*-PrOH/DMF. Yield 100 mg (32%); as beige solid; mp 225–226 °C (dec); [Found: C, 61.61; H, 3.17; N, 8.04. $C_{18}H_{11}BrN_2O$ requires C, 61.56; H, 3.16; N, 7.98%]; δ_H (400 MHz, DMSO-d_6) 4.33 (s, 2H, H-8), 7.13 (d, J=8.7 Hz, 1H, H-12), 7.31 (d, J=7.3 Hz, 1H, H-5), 7.43 (dd, J=8.8, 2.1 Hz, 1H, H-11), 7.54–7.65 (m, 3H, H-2, H-3, H-9), 7.84 (d, J=7.3, 1H, H-6), 8.07 (d, J=6.9 Hz, 1H, H-4), 8.34 (d, J=7.8 Hz, 1H, H-1); δ_C (100 MHz, CF_3COOH+$CDCl_3$): 21.1, 102.3, 116.4, 118.0, 118.7, 119.2, 119.4, 119.8, 122.1, 128.6, 131.1, 131.9, 132.6, 132.9, 133.2, 133.4, 141.4, 149.0; LC/MS m/z (%)=353 (90), 351 (100) $[M]^+$.

4.4.6. 5-Bromo-8H-chromeno[2′,3′:4,5]imidazo[2,1-a]isoquinoline ***12***. **A**=10 mL, **B**=1 mL. Yield 30 mg (12%); as light-brown solid; mp 218 °C (dec); [Found: C, 61.64; H, 3.19; N, 7.95. $C_{18}H_{11}BrN_2O$ requires C, 61.56; H, 3.16; N, 7.98%]; δ_H (600 MHz, $CDCl_3$) 4.35 (s, 2H, H-8), 7.14 (td, J=7.5, 1.2 Hz, 1H, H-10), 7.22–7.24 (m, 1H, H-12), 7.28–7.33 (m, 2H, H-9, H-11), 7.69–7.78 (m, 2H, H-2, H-3), 8.07–8.11 (m, 2H, H-4, H-6), 8.87 (d, J=7.5 Hz, 1H, H-1); δ_C (100 MHz, DMSO-d_6): 23.2, 101.1, 107.0, 118.1, 118.9, 123.0, 123.1, 124.0, 124.2, 126.8, 127.6, 128.7, 129.2, 129.5, 131.1, 136.8, 150.3, 151.7; m/z (%)=353 (19), 352 (100), 351 (50), 350 (99) $[M]^+$, 349 (33), 271 (13), 209 (17), 207 (15), 129 (14), 128 (43), 127 (15), 79 (15).

4.4.7. 5,10-Dibromo-8H-chromeno[2′,3′:4,5]imidazo[2,1-a]isoquinoline ***13***. **A**=10 mL, **B**=1 mL. Yield 220 mg (56%); as beige solid; mp 231–232 °C (dec); [Found: C, 50.12; H, 2.35; N, 6.62. $C_{18}H_{10}Br_2N_2O$ requires C, 50.27; H, 2.34; N, 6.51%]; δ_H (400 MHz, DMSO-d_6) 4.40 (s, 2H, H-8), 7.18 (d, J=8.6 Hz, 1H, H-12), 7.47 (dd, J=8.6, 2.2 Hz, 1H, H-11), 7.56–7.60 (m, 1H, H-9), 7.73–7.78 (m, 2H, H-2, H-3), 8.04–8.07 (m, 1H, H-4), 8.44–8.49 (m, 1H, H-1), 8.56 (s, 1H, H-6); δ_C (100 MHz, CF_3COOH+$CDCl_3$): 20.8, 102.0, 115.2, 116.3, 117.5, 118.6, 119.2, 120.6, 122.5, 128.2, 130.7, 131.8, 132.5, 132.6, 132.9, 133.5, 141.5, 148.7; m/z (%)=429 (100), 428 (41) $[M]^+$, 427 (54), 350 (16), 348 (16), 176 (22), 174 (23), 135 (25), 127 (17).

4.4.8. 6-Methyl-8H-chromeno[2′,3′:4,5]imidazo[2,1-a]isoquinoline ***14***. **A**=4.5 mL, **B**=4.5 mL. Yield 30 mg (13%); as white solid; mp 176–177 °C (dec); [Found: C, 79.73; H, 4.90; N, 9.87. $C_{19}H_{14}N_2O$ requires C, 79.70; H, 4.93; N, 9.78%]; δ_H (400 MHz, DMSO-d_6) 2.87 (s, 3H, CH_3), 4.82 (s, 2H, H-8), 7.02 (s, 1H, H-5), 7.12–7.17 (m, 2H,

H-10, H-12), 7.28–7.32 (m, 1H, H-11), 7.35 (d, *J*=7.6 Hz, 1H, H-4), 7.52–7.58 (m, 2H, H-2, H-3), 7.71–7.73 (m, 1H, H-9), 8.30–8.32 (m, 1H, H-1); δ_C (100 MHz, DMSO-d_6): 18.7, 26.2, 100.9, 111.4, 117.2, 118.9, 121.3, 122.2, 123.5, 126.2, 127.1, 127.9, 128.1, 129.2, 130.5, 133.6, 133.9, 149.8, 150.6; *m*/*z* (%)=287 (11), 286 (60) $[M]^+$, 285 (100), 284 (11), 143 (14), 142 (12).

4.4.9. 14-Methyl-16H-benzo[5′,6′]chromeno[2′,3′:4,5]imidazo[2,1-a]-isoquinoline ***15***. **A**=7 mL, **B**=4.5 mL. Yield 60 mg (21%); as yellow solid; mp 200–202 °C (dec); [Found: C, 82.01; H, 4.84; N, 8.26. $C_{23}H_{16}N_2O$ requires C, 82.12; H, 4.79; N, 8.33%]; δ_H (400 MHz, DMSO-d_6) 2.92 (s, 3H, CH_3), 4.85 (s, 2H, H-8), 6.70 (s, 1H, H-5), 7.33 (d, *J*=8.7 Hz, 1H, H-14), 7.41–7.49 (m, 4H, H-9, H-10, H-11, H-12), 7.55–7.59 (m, 1H, H-4), 7.72 (d, *J*=8.7 Hz, 1H, H-13), 7.77–7.81 (m, 2H, H-2, H-3), 8.50 (d, *J*=7.8 Hz, 1H, H-1); δ_C (100 MHz, DMSO-d_6): 19.6, 25.4, 100.8, 110.5, 112.4, 118.8, 122.3, 123.2, 124.5, 125.9, 127.0, 127.3, 127.9, 128.6, 129.0, 129.6, 130.4, 130.8, 132.3, 132.9, 137.3, 139.5, 148.9; LC/MS *m*/*z* (%)=337 (100) $[M+H]^+$.

4.4.10. 12-Ethoxy-6-methyl-8H-chromeno[2′,3′:4,5]imidazo[2,1-a]-isoquinoline ***16***. **A**=4.5 mL, **B**=4.5 mL. Yield 80 mg (28%); as yellow solid; mp 168–169 °C (dec); [Found: C, 76.52; H, 5.20; N, 8.26. $C_{21}H_{18}N_2O_2$ requires C, 76.34; H, 5.49; N, 8.48%]; δ_H (400 MHz, $CDCl_3$) 1.50 (t, *J*=6.9 Hz, 3H, OCH_2CH_3), 2.83 (s, 3H, C_6-CH_3), 4.13 (q, *J*=6.9 Hz, 2H, OCH_2CH_3), 4.73 (s, 2H, H-8), 6.72 (s, 1H, H-5), 6.78–6.83 (m, 2H, H-9, H-10), 6.94–6.98 (m, 1H, H-11), 7.44–7.55 (m, 3H, H-2, H-3, H-4), 8.55 (d, *J*=7.8 Hz, 1H, H-1); δ_C (100 MHz, $CDCl_3$): 15.0, 19.4, 23.5, 65.4, 112.4, 114.1, 114.5, 115.7, 120.4, 120.8, 121.8, 124.1, 125.4, 125.7, 125.9, 127.0, 127.2, 127.7 (2C), 128.0, 131.0; *m*/*z* (%)=331 (16), 330 (73) $[M]^+$, 329 (100), 301 (40), 300 (14), 272 (15), 151 (11), 142 (10), 115 (12).

4.4.11. 6-Methyl-10-nitro-8H-chromeno[2′,3′:4,5]imidazo[2,1-a]isoquinoline ***17***. **A**=7 mL, **B**=4.5 mL. Yield 80 mg (25%); as orange solid; mp 236–237 °C (dec); [Found: C, 68.93; H, 3.99; N, 12.72. $C_{19}H_{13}N_3O_3$ requires C, 68.88; H, 3.95; N, 12.68%]; δ_H (400 MHz, DMSO-d_6) 2.80 (s, 3H, CH_3), 4.82 (s, 2H, H-8), 6.93 (s, 1H, H-5), 7.28 (d, *J*=9.5 Hz, 1H, H-12), 7.46–7.52 (m, 2H, H-3, H-4), 7.63 (d, *J*=7.6 Hz, 1H, H-2), 8.04 (dd, *J*=9.5, 2.2 Hz, 1H, H-11), 8.18 (s, 1H, H-9), 8.24 (d, *J*=7.6 Hz, 1H, H-1); δ_C (100 MHz, CF_3COOD+$CDCl_3$): 17.4, 25.4, 102.2, 114.6, 118.1, 118.3, 121.4, 124.6, 126.0, 126.9 (2C), 129.7, 131.9, 132.8, 133.0, 134.8, 140.5, 144.0, 153.3; IR (KBr), *ν*: 1526 (NO_2), 1342 (NO_2) cm^{-1}; *m*/*z* (%)=332 (17), 331 (83) $[M]^+$, 330 (100), 285 (19), 284 (72), 283 (11), 142 (20), 115 (14).

4.4.12. 10-Bromo-6-methyl-8H-chromeno[2′,3′:4,5]imidazo[2,1-a]-isoquinoline ***18***. **A**=7 mL, **B**=4.5 mL. Yield 100 mg (29%); as white solid; mp 208 °C (dec); [Found: C, 62.55; H, 3.65; N, 7.81. $C_{19}H_{13}BrN_2O$ requires C, 62.48; H, 3.59; N, 7.67%]; δ_H (400 MHz, DMSO-d_6) 2.82 (s, 3H, CH_3), 4.71 (s, 2H, H-8), 6.74 (s, 1H, H-5), 7.05 (d, *J*=8.5 Hz, 1H, H-12), 7.32–7.36 (m, 2H, H-3, H-4), 7.47–7.56 (m, 3H, H-1, H-2, H-9), 8.50 (d, *J*=8.5 Hz, 1H, H-11); δ_C (100 MHz, DMSO-d_6): 19.5, 27.4, 99.5, 112.5, 114.4, 115.5, 119.6, 120.5, 122.2, 123.2, 126.0, 129.6, 129.8, 127.4, 127.9, 128.1, 131.1, 132.6, 150.5; *m*/*z* (%)=367 (15), 366 (64), 365 (95), 364 (61) $[M]^+$, 363 (100), 285 (24), 202 (13), 142 (27), 115 (28), 79 (14), 43 (22).

4.4.13. 12-Chloro-6-methyl-8H-chromeno[2′,3′:4,5]imidazo[2,1-a]-isoquinoline ***19***. **A**=7 mL, **B**=4.5 mL. Yield 150 mg (52%); as white solid; mp 229–230 °C (dec); [Found: C, 71.01; H, 4.14; N, 8.64. $C_{19}H_{13}ClN_2O$ requires C, 71.14; H, 4.08; N, 8.73%]; δ_H (400 MHz, HMPA-d_{18}) 2.99 (s, 3H, CH_3), 5.04 (s, 2H, H-8), 7.15–7.19 (m, 1H, H-10), 7.25 (s, 1H, H-5), 7.37–7.44 (m, 2H, H-4, H-9), 7.52–7.64 (m, 2H, H-2, H-3), 7.77–7.79 (m, 1H, H-11), 8.30–8.32 (m, 1H, H-1); δ_C (100 MHz, CF_3COOH+$CDCl_3$): 18.0, 25.6, 102.9, 114.6, 117.6, 117.8, 117.9, 121.1, 122.7, 125.4, 127.0, 127.9, 129.7, 131.6, 132.6, 133.0, 134.1, 140.9, 144.4; *m*/*z* (%)=322 (20), 321 (43), 320 (63) $[M]^+$, 319 (100), 142 (27).

4.4.14. 10,12-Dichloro-6-Methyl-8H-chromeno[2′,3′:4,5]imidazo[2,1-a]isoquinoline ***20***. **A**=7 mL, **B**=4.5 mL. Yield 210 mg (65%); as white solid; mp 252–253 °C (dec); [Found: C, 64.15; H, 3.35; N, 7.97. $C_{19}H_{12}Cl_2N_2O$ requires C, 64.24; H, 3.41; N, 7.89%]; δ_H (400 MHz, CF_3COOH+$CDCl_3$) 2.87 (s, 3H, Me), 4.66 (s, 2H, H-8), 7.09 (d, *J*=2.3 Hz, 1H, H-9), 7.20 (d, *J*=2.3 Hz, 1H, H-11), 7.63–7.77 (m, 4H, H-2, H-3, H-4, H-5), 8.18 (d, *J*=8.2 Hz, 1H, H-1); δ_C (100 MHz, CF_3COOH+$CDCl_3$): 17.6, 21.6, 102.8, 114.7, 118.0, 119.1, 121.5, 123.8, 127.0, 127.7, 129.6, 129.8, 130.9, 131.9, 132.8, 133.1, 134.6, 140.9, 143.5; *m*/*z* (%)=357 (16), 356 (39), 355 (71), 354 (65) $[M]^+$, 353 (100), 159 (15).

4.4.15. 3-Hydroxy-8H-chromeno[2′,3′:4,5]imidazo[2,1-a]isoquinoline ***21***. **A**=10 mL, **B**=1 mL. Yield 150 mg (59%); as light-yellow solid; mp 231–232 °C (dec); [Found: C, 74.94; H, 4.16; N, 9.80. $C_{18}H_{12}N_2O_2$ requires C, 74.99; H, 4.20; N, 9.72%]; δ_H (400 MHz, DMSO-d_6) 4.29 (s, 2H, H-8), 7.10–7.18 (m, 5H, H-2, H-4, H-5, H-11, H-12), 7.28 (t, *J*=8.5 Hz, 1H, H-10), 7.35 (d, *J*=8.5 Hz, 1H, H-9), 8.03 (d, *J*=6.2 Hz, 1H, H-6), 8.17–8.19 (m, 1H, H-1), 10.00 (s, 1H, OH); δ_C (100 MHz, DMSO-d_6): 23.1, 99.1, 111.1, 112.0, 116.2, 118.0, 118.9, 119.1, 122.6, 124.0, 124.5, 128.5, 131.2, 131.4, 138.2, 150.1, 152.0, 157.8; *m*/*z* (%)=289 (16), 288 (100) $[M]^+$, 287 (64), 144 (10), 43 (11).

4.4.16. 11-Hydroxy-16H-benzo[5′,6′]chromeno[2′,3′:4,5]imidazo[2,1-a]isoquinoline ***22***. **A**=10 mL, **B**=1 mL. Yield 150 mg (48%); as light-brown solid; mp 248–250 °C (dec); [Found: C, 77.91; H, 4.25; N, 8.04. $C_{22}H_{14}N_2O_2$ requires C, 78.09; H, 4.17; N, 8.28%]; δ_H (400 MHz, DMSO-d_6) 4.63 (s, 2H, H-16), 7.17–7.23 (m, 2H, H-10, H-12), 7.28 (d, *J*=7.2 Hz, 1H, H-13), 7.45 (d, *J*=8.8 Hz, 1H, H-5), 7.54–7.58 (m, 1H, H-3), 7.69–7.78 (m, 1H, H-2), 7.95–8.04 (m, 3H, H-4, H-6, H-9), 8.25–8.27 (m, 2H, H-1, H-14), 10.09 (s, 1H, OH); δ_C (100 MHz, DMSO-d_6): 21.2, 99.8, 111.1, 111.7, 112.2, 116.2, 119.0, 119.1, 122.8, 123.5, 124.6, 125.3, 127.6, 128.8, 129.3, 130.5, 131.5, 132.8, 138.3, 149.4, 149.6, 157.8; *m*/*z* (%)=338 (100) $[M]^+$, 337 (57), 144 (18), 115 (11), 43 (32).

4.4.17. 12-Ethoxy-3-hydroxy-8-H-chromeno[2′,3′:4,5]imidazo[2,1-a]-isoquinoline ***23***. **A**=10 mL, **B**=1 mL. Yield 110 mg (37%); as light-yellow solid; mp 232–233 °C (dec); [Found: C, 72.14; H, 4.92; N, 8.21. $C_{20}H_{16}N_2O_3$ requires C, 72.28; H, 4.85; N, 8.43%]; δ_H (400 MHz, DMSO-d_6) 1.20 (t, *J*=6.7 Hz, 3H, OCH_2CH_3), 3.87 (q, *J*=6.7 Hz, 2H, OCH_2CH_3), 4.02 (s, 2H, H-8), 6.60 (m, 2H, H-5, H-11), 6.73 (m, 2H, H-9, H-10), 6.83 (s, 1H, H-4), 6.90 (d, *J*=8.9 Hz, 1H, H-2), 7.42 (d, *J*=6.9 Hz, 1H, H-1), 8.09 (d, *J*=8.9 Hz, 1H, H-1), 9.12 (s, 1H, OH); δ_C (100 MHz, DMSO-d_6): 15.3, 23.3, 65.0, 99.1, 111.1, 112.0, 112.9, 116.3, 118.9, 119.8, 122.4, 122.6, 123.6, 124.5, 131.3, 138.2, 142.1, 148.4, 150.0, 157.8; *m*/*z* (%)=333 (9), 332 (100) $[M]^+$, 331 (43), 303 (19), 288 (30), 287 (28), 151 (22), 144 (13), 43 (28).

4.4.18. 3-Hydroxy-11-methoxy-8H-chromeno[2′,3′:4,5]imidazo[2,1-a]isoquinoline ***24***. **A**=10 mL, **B**=1 mL. Yield 10.0 mg (3%); as brown solid; mp>300 °C (dec); [Found: C, 71.55; H, 4.61; N, 8.69. $C_{19}H_{14}N_2O_3$ requires C, 71.69; H, 4.43; N, 8.80%]; δ_H (400 MHz, DMSO-d_6) 3.75 (s, 3H, OCH_3), 4.20 (s, 2H, H-8), 6.71–6.74 (m, 2H, H-10, H-12), 7.10–7.13 (m, 2H, H-4, H-9), 7.16 (d, *J*=7.1, 1H, H-5), 7.25 (m, 1H, H-2), 8.02 (d, *J*=7.1 Hz, 1H, H-6), 8.15–8.20 (m, 1H, H-1), 9.96 (s, 1H, OH); δ_C (100 MHz, DMSO-d_6): 21.6, 55.2, 98.6, 102.2, 110.0, 110.1, 110.3, 111.2, 115.4, 118.1, 121.7, 123.7, 130.6, 130.8, 137.3, 149.2, 151.9, 157.0, 158.8; *m*/*z* (%)=319 (10), 318 (46) $[M]^+$, 317 (100), 274 (12).

4.4.19. 3-Hydroxy-10-nitro-8H-chromeno[2′,3′:4,5]imidazo[2,1-a]-isoquinoline ***25***. **A**=10 mL, **B**=1 mL. Yield 140 mg (49%); as green-yellow solid; mp 209–211 °C (dec); [Found: C, 64.74; H, 3.19; N,

12.51. $C_{18}H_{11}N_3O_4$ requires C, 64.86; H, 3.33; N, 12.61%]; δ_H (400 MHz, DMSO-d_6): 4.46 (s, 2H, H-8), 7.14–7.21 (m, 2H, H-4, H-12), 7.25 (d, J=7.3 Hz, 1H, H-5), 7.43 (d, J=8.7 Hz, 1H, H-2), 8.07 (d, J=7.3 Hz, 1H, H-6), 8.16–8.22 (m, 2H, H-1, H-11), 8.33 (d, J=2.3 Hz, 1H, H-9), 10.09 (s, 1H, OH); δ_C (100 MHz, CF_3COOH+$CDCl_3$): 21.7, 103.0, 115.6, 118.2, 119.9, 120.3, 120.6, 122.2, 124.0, 124.8, 125.5, 126.1, 127.6, 133.4, 133.6, 141.5, 145.1, 152.4; IR (KBr), ν: 1520 (NO_2), 1334 (NO_2) cm^{-1}; m/z (%)=333 (4) $[M]^+$, 101 (30), 43 (100).

4.4.20. 10-Bromo-3-hydroxy-8H-chromeno[2′,3′:4,5]imidazo[2,1-a]-isoquinoline ***26***. **A**=10 mL, **B**=1 mL. Yield 170 mg (51%); as light-yellow solid; mp>300 °C (dec); [Found: C, 58.93; H, 3.16; N, 7.70. $C_{18}H_{11}BrN_2O_2$ requires C, 58.88; H, 3.02; N, 7.63%]; δ_H (400 MHz, DMSO-d_6): 4.31 (s, 2H, H-8), 7.11–7.20 (m, 4H, H-2, H-4, H-5, H-12), 7.45 (dd, J=8.7, 2.3 Hz, 1H, H-11), 7.57 (d, J=2.3 Hz, 1H, H-9), 8.02 (d, J=6.9 Hz, 1H, H-1), 8.16–8.20 (m, 1H, H-6), 10.00 (s, 1H, OH); δ_C (100 MHz, DMSO-d_6): 22.2, 98.0, 110.3, 111.4, 114.5, 115.4, 118.1, 119.3, 121.0, 121.7, 123.7, 130.5, 130.6, 132.7, 137.6, 149.0, 150.6, 157.0; m/z (%)=369 (19), 368 (99), 367 (58), 366 (100) $[M]^+$, 365 (46), 286 (10), 144 (23), 143 (39), 43 (12).

4.4.21. 12-Chloro-3-hydroxy-8H-chromeno[2′,3′:4,5]imidazo[2,1-a]-isoquinoline ***27***. **A**=10 mL, **B**=1 mL. Yield 220 mg (76%); as brown solid; mp 215–216 °C (dec); [Found: C, 66.64; H, 3.51; N, 8.59. $C_{18}H_{11}ClN_2O_2$ requires C, 66.99; H, 3.44; N, 8.68%]; δ_H (400 MHz, DMSO-d_6): 4.36 (s, 2H, H-8), 7.09–7.46 (m, 4H, H-2, H-4, H-5, H-10), 7.34 (d, J=8.2 Hz, 1H, H-11), 7.44 (d, J=8.2 Hz, 1H, H-9), 8.05 (d, J=7.3 Hz, 1H, H-1), 8.20 (d, J=9.2 Hz, 1H, H-6), 10.03 (s, 1H, OH); δ_C (100 MHz, CF_3COOH+DMSO-d_6): 20.6, 102.3, 113.1, 113.2, 116.0, 116.7, 117.4, 118.3, 121.6, 122.7, 125.3, 128.2, 129.5, 131.3, 132.5, 140.5, 145.2, 152.3; m/z (%)=324 (42), 322 (100) $[M]^+$, 161 (10), 144 (15), 143 (12), 116 (12), 89 (16), 73 (38), 43 (22).

4.4.22. 10,12-Dichloro-3-hydroxy-8H-chromeno[2′,3′:4,5]imidazo [2,1-a]isoquinoline ***28***. **A**=10 mL, **B**=1 mL. Yield 150 mg (48%); as yellow solid; mp 221–223 °C (dec); [Found: C, 60.32; H, 2.71; N, 7.61. $C_{18}H_{10}Cl_2N_2O_2$ requires C, 60.53; H, 2.82; N, 7.84%]; δ_H (400 MHz, DMSO-d_6) 4.40 (s, 2H, H-8), 7.16–7.26 (m, 3H, H-2, H-4, H-5), 7.50 (d, J=2.3 Hz, 1H, H-11), 7.66 (d, J=2.3 Hz, 1H, H-9), 8.07 (d, J=6.9 Hz, 1H, H-6), 8.21–8.24 (m, 1H, H-1), 10.09 (s, 1H, OH); δ_C (100 MHz, CF_3COOH+DMSO-d_6): 20.8, 101.3, 111.6, 111.8, 114.9, 116.0, 117.7, 119.8, 120.9, 121.9, 123.9, 127.9, 129.4, 133.6, 134.1, 140.1, 144.3, 158.8; m/z (%)=358 (13), 357 (5), 356 (21) $[M]^+$, 160 (10), 64 (12), 58 (23), 43 (100), 42 (21).

4.4.23. 4-Hydroxy-8H-chromeno[2′,3′:4,5]imidazo[2,1-a]isoquinoline ***29***. **A**=7.5 mL, **B**=0.75 mL. Yield 90 mg (34%); as brown solid; mp 170–171 °C (dec); [Found: C, 74.85; H, 4.13; N, 9.67. $C_{18}H_{12}N_2O_2$ requires C, 74.99; H, 4.20; N, 9.72%]; δ_H (400 MHz, DMSO-d_6) 4.33 (s, 2H, H-8), 6.99 (d, J=8.0 Hz, 1H, H-12), 7.11–7.19 (m, 2H, H-2, H-3), 7.27–7.31 (m, 1H, H-1), 7.36–7.47 (m, 3H, H-9, H-10, H-11), 7.79 (d, J=7.7 Hz, 1H, H-5), 8.06 (d, J=7.7 Hz, 1H, H-6), 10.36 (s, 1H, OH); δ_C (100 MHz, CF_3COOH+$CDCl_3$): 20.8, 102.5, 113.4, 113.8, 115.4, 116.4, 117.2, 117.5, 118.5, 121.8, 125.8, 129.2, 130.1, 131.7, 132.5, 141.4, 149.6, 152.5; m/z (%)=289 (11), 288 (61) $[M]^+$, 287 (100), 258 (12), 143 (12), 89 (12).

4.4.24. 12-Hydroxy-16H-benzo[5′,6′]chromeno[2′,3′:4,5]imidazo[2,1-a]isoquinoline ***30***. **A**=7.5 mL, **B**=0.75 mL. Yield 160 mg (51%); as brown solid; mp 214–215 °C (dec); [Found: C, 78.16; H, 4.13; N, 8.37. $C_{22}H_{14}N_2O_2$ requires C, 78.09; H, 4.17; N, 8.28%]; δ_H (400 MHz, DMSO-d_6) 4.68 (s, 2H, H-16), 7.04 (d, J=7.8 Hz, 1H, H-6), 7.46–7.50 (m, 2H, H-10, H-11), 7.55–7.59 (m, 2H, H-2, H-3), 7.70–7.74 (m, 1H, H-4), 7.86 (d, J=7.8 Hz, 1H, H-5), 7.96–8.06 (m, 3H, H-1, H-9, H-13), 8.29 (d, J=7.3 Hz, 1H, H-14), 10.41 (s, 1H, OH); δ_C (100 MHz, DMSO-d_6): 20.7, 100.5, 106.6, 111.0, 111.6, 112.7, 118.5, 118.7, 120.6, 123.0, 123.6, 124.8, 127.1, 128.2, 128.7, 128.8, 129.9, 132.2, 136.9, 148.7, 149.1, 153.3; m/z (%)=339 (12), 338 (54) $[M]^+$, 337 (100), 225 (17), 224 (22), 187 (12), 169 (21), 167 (18), 146 (11), 144 (16), 143 (20), 142 (33), 128 (20), 127 (30), 115 (27), 106 (14), 105 (18), 103 (11), 101 (16), 98 (17), 92 (12), 91 (30), 84 (12), 83 (18), 82 (10), 80 (12), 79 (13), 78 (11), 73 (29), 72 (12), 69 (12), 64 (70), 63 (14), 59 (19), 56 (36), 55 (44), 53 (13), 52 (18), 48 (69), 45 (40), 43 (19).

4.4.25. 12-Ethoxy-4-hydroxy-8H-chromeno[2′,3′:4,5]imidazo[2,1-a]-isoquinoline ***31***. **A**=7.5 mL, **B**=0.75 mL. Yield 40 mg (12%); as beige solid; mp 189–191 °C (dec); [Found: C, 72.16; H, 4.89; N, 8.32. $C_{20}H_{16}N_2O_3$ requires C, 72.28; H, 4.85; N, 8.43%]; δ_H (400 MHz, DMSO-d_6) 1.42 (t, J=6.9 Hz, 3H, OCH_2CH_3), 4.12 (q, J=6.9 Hz, 2H, OCH_2CH_3), 4.36 (s, 2H, H-8), 6.93 (d, J=7.8 Hz, 1H, H-3), 6.98–7.09 (m, 3H, H-9, H-10, H-11), 7.44–7.50 (m, 2H, H-1, H-2), 7.82 (d, J=7.8 Hz, 1H, H-5), 8.09 (d, J=7.8 Hz, 1H, H-6), 10.38 (s, 1H, OH); δ_C (100 MHz, DMSO-d_6): 15.3, 23.3, 64.8, 100.3, 107.0, 112.2, 112.7, 113.2, 119.3, 119.7, 121.0, 122.4, 123.7, 124.2, 129.2, 137.4, 142.0, 148.3, 150.2, 154.0; m/z (%)=333 (16), 332 (78) $[M]^+$, 331 (100), 303 (45), 302 (15), 274 (21), 152 (16), 116 (12), 89 (13).

4.4.26. 4-Hydroxy-10-nitro-8H-chromeno[2′,3′:4,5]imidazo[2,1-a]-isoquinoline ***32***. **A**=7.5 mL, **B**=0.75 mL. Yield 90 mg (31%); as light-grey solid; mp 186–187 °C (dec); [Found: C, 64.70; H, 3.42; N, 12.49. $C_{18}H_{11}N_3O_4$ requires C, 64.86; H, 3.33; N, 12.61%]; δ_H (400 MHz, DMSO-d_6) 4.46 (s, 2H, H-8), 6.99 (d, J=8.9 Hz, 1H, H-12), 7.39–7.43 (m, 1H, H-3), 7.49 (d, J=7.3 Hz, 1H, H-5), 7.78 (d, J=8.9 Hz, 1H, H-11), 8.05 (d, J=7.3 Hz, 1H, H-6), 8.13–8.19 (m, 2H, H-1, H-2), 8.30 (d, J=2.7 Hz, 1H, H-9), 10.38 (s, 1H, OH); δ_C (100 MHz, CF_3COOH+$CDCl_3$): 21.2, 102.2, 113.8, 113.9, 116.8, 117.1, 118.2, 118.4, 119.0, 122.2, 124.9, 126.6, 132.0, 133.5, 140.6, 144.5, 152.7, 154.5; IR (KBr), ν: 1516 (NO_2), 1332 (NO_2) cm^{-1}; m/z (%)= 334 (18), 333 (91) $[M]^+$, 332 (100), 287 (23), 286 (87), 116 (12), 89 (13).

4.4.27. 10-Bromo-4-hydroxy-8H-chromeno[2′,3′:4,5]imidazo[2,1-a]-isoquinoline ***33***. **A**=7.5 mL, **B**=0.75 mL. Yield 170 mg (51%); as brown solid; mp 208–210 °C (dec); [Found: C, 58.96; H, 3.12; N, 7.80. $C_{18}H_{11}BrN_2O_2$ requires C, 58.88; H, 3.02; N, 7.63%]; δ_H (400 MHz, DMSO-d_6) 4.36 (s, 2H, H-8), 7.01 (d, J=7.8 Hz, 1H, H-3), 7.18 (d, J=8.7 Hz, 1H, H-12), 7.43–7.50 (m, 3H, H-1, H-2, H-5), 7.60 (bs, 1H, H-9), 7.81 (d, J=8.3 Hz, 1H, H-11), 8.05 (d, J=7.3 Hz, 1H, H-6), 10.38 (s, 1H, OH); δ_C (100 MHz, DMSO-d_6): 22.4, 99.4, 106.6, 111.6, 112.6, 114.9, 118.7, 119.6, 120.4, 121.1, 123.5, 128.7, 130.8, 133.0, 136.9, 149.3, 150.6, 153.3; m/z (%)=369 (12), 368 (64), 367 (100), 366 (70) $[M]^+$, 365 (96), 287 (10), 286 (28), 145 (10), 143 (33), 116 (13), 115 (15), 89 (14).

4.4.28. 12-Chloro-4-hydroxy-8H-chromeno[2′,3′:4,5]imidazo[2,1-a]-isoquinoline ***34***. **A**=7.5 mL, **B**=0.75 mL. Yield 120 mg (41%); as light beige solid; mp 228–230 °C (dec); [Found: C, 66.85; H, 3.51; N, 8.53. $C_{18}H_{11}ClN_2O_2$ requires C, 66.99; H, 3.44; N, 8.68%]; δ_H (400 MHz, DMSO-d_6) 4.43 (s, 2H, H-8), 7.03 (d, J=7.8 Hz, 1H, H-3), 7.15–7.19 (m, 1H, H-2), 7.39 (d, J=7.8 Hz, 1H, H-1), 7.46–7.52 (m, 3H, H-5, H-9, H-10), 7.84 (d, J=8.2 Hz, 1H, H-11), 8.11 (d, J=7.3 Hz, 1H, H-6), 10.38 (s, 1H, OH); δ_C (100 MHz, DMSO-d_6): 69.7, 99.9, 106.7, 109.6, 111.7, 112.6, 114.5, 118.7, 120.6, 120.8, 123.5, 123.9, 128.7, 128.8, 129.6, 129.9, 133.5, 153.3; m/z (%)=324 (20), 323 (41), 322 (63) $[M]^+$, 321 (100), 144 (18), 73 (13), 44 (12).

4.4.29. 10,12-Dichloro-4-Hydroxy-8H-chromeno[2′,3′:4,5]imidazo [2,1-a]isoquinoline ***35***. **A**=7.5 mL, **B**=0.75 mL. Yield 220 mg (67%); as light beige solid; mp>300 °C (dec); [Found: C, 60.41; H, 2.74; N, 7.81. $C_{18}H_{10}Cl_2N_2O_2$ requires C, 60.53; H, 2.82; N, 7.84%]; δ_H

(400 MHz, DMSO-d_6): 4.57 (s, 2H, H-8), 7.10 (d, J=7.8 Hz, 1H, H-3), 7.40–7.47 (m, 2H, H-9, H-5), 7.52 (d, J=7.3 Hz, 1H, H-6), 7.62 (d, J=2.2 Hz, 1H, H-11), 7.76 (d, J=7.8 Hz, 1H, H-2), 8.29 (d, J=7.8 Hz, 1H, H-1), 11.50 (s, 1H, OH); δ_C (100 MHz, CF_3COOH+DMSO-d_6): 20.5, 101.8, 113.2, 113.3, 116.2, 116.6, 117.9, 118.4, 121.6, 123.8, 127.7, 129.3, 130.9, 131.3, 132.8, 140.4, 144.0, 152.1; m/z (%)=359 (18), 358 (41), 357 (71), 356 (63) $[M]^+$, 355 (100), 160 (33), 143 (35), 85 (15), 84 (32), 43 (25).

4.5. Multi component synthesis of 8*H*-Chromeno[2′,3′:4,5]imidazo[2,1-*a*]isoquinoline 7

A solution of isoquinoline (715 mg, 5.55 mmol), *o*-hydroxybenzaldehyde (610 mg, 5 mmol), chloroacetonitrile (0.88 mL, 13.9 mmol) and *i*-Pr_2NEt (1.65 mL, 10 mmol) in methanol (10 mL) was heated at reflux for 9 h. The precipitate was filtered, washed with ethanol. The crude product was recrystallysed from ethanol to give 80 mg (6%) compound **7** as light beige solid.

4.6. 8,8-Dimethyl-8,16-dihydro-13*H*-[1]benzosilano[2,3-*d*]chromeno[2′,3′:4,5]imidazo[1,2-*a*]-pyridin-13-on 36

The procedure was the same as for preparation of compounds **7**–**35** (**A**=8 mL, **B**=1.5 mL). Yield 30 mg (10%); as light-brown solid; mp 250–251 °C (dec); [Found: C, 72.32; H, 4.66; N, 7.28. $C_{23}H_{18}N_2O_2Si$ requires C, 72.22; H, 4.74; N, 7.32%]; δ_H (400 MHz, DMSO-d_6) 0.56 (s, 6H, Si(CH_3)$_2$), 4.35 (s, 2H, H-16), 7.14 (td, J=7.5, 1.4 Hz, 1H, H-2), 7.22–7.31 (m, 2H, H-3, H-4), 7.35 (d, J=7.5 Hz, 1H, H-1), 7.58–7.66 (m, 2H, H-10, H-11), 7.72 (dd, J=6.9, 1.8 Hz, 1H, H-12), 7.84 (d, 1H, H-7), 8.45 (dd, J=7.8, 1.4 Hz, 1H, H-9), 8.99 (s, 1H, H-14); δ_C (100 MHz, DMSO-d_6): −0.9(2C), 22.8, 100.7, 118.1, 118.9, 120.6, 124.5, 125.0, 127.9, 128.8, 129.3, 130.8, 131.3, 132.1, 133.0, 134.5, 139.6, 140.3, 140.6, 151.5, 153.3, 186.1; IR (KBr), ν: 1656 (C=O) cm^{-1}; m/z (%)=383 (19), 382 (64) $[M]^+$, 381 (100), 323 (10), 183 (22).

Acknowledgements

The financial support of the Russian Foundation for Basic Research (grant # 12-03-93000-Viet_a) is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2012.04.087. These data include MOL files and InChiKeys of the most important compounds described in this article.

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