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Homophtalonitrile for Multicomponent Reactions: Syntheses and Optical Properties of *o*-Cyanophenyl- or Indol-3-yl-Substituted Chromeno[2,3-*c*]isoquinolin-5-Amines

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Malononitrile is a useful reagent for multicomponent reactions with hundreds of methods developed. In this paper, we suggest α-(cyano)-*o*-tolunitrile (homophtalonitrile) to work as a vinylogous malononitrile. Thus, a organocatalytic pseudo-three-component reaction of homopthalonitrile (2 equiv) and *o*-hydroxybenzaldehyde, leading to the diastereoselective formation of 5-amino-12*H*-chromeno[2,3-c]isoquinolin-12-yl)(cyano)-methyl)benzonitriles, was discovered. The possibility to employ other nucleophiles was demonstrated for indoles, and a sequential three-component reaction of homophtalonitrile, *o*-hydroxybenzaldehyde, and (aza)indole, giving 12-(1*H*-Indol-3-yl)-12*H*-chromeno[2,3-*c*]isoquinolin-5-amines, was developed. The photophysical properties of the synthesized compounds have been studied, revealing high fluorescence quantum yields (42–70%) for indol-3-yl substituted 12*H*-chromeno[2,3-*c*]isoquinolin-5-amines and reversible fluorescence quenching under acidic conditions.

1. Introduction

Multicomponent reactions emerged as a powerful tool for diversity-oriented synthesis and the discovery of the compounds with practically interesting properties.[1] Dinitriles are versatile reagents for organic synthesis[2] with malononitrile to be mostly known and studied in multicomponent reactions, usually employed for the preparation of 2-amino-4H-chromenes.[3] The pseudo-four-component reactions of *o*-hydroxybenzaldehydes, nucleophiles, and malononitrile (2 equiv) are vastly studied (Figure 1 a),[4] and malononitrile usually becomes a progenitor of an aminopyridine ring. The fragment of vinylogous malononitrile is found in α-(cyano)-*o*-tolunitrile (homophtalonitrile), which may be analogously used for annulation of an aminoisoquinoline ring, but its potential for the multicomponent reactions is yet underexplored. As far as the chromenes annulated with a pyridine ring represent a favored class of hetero-

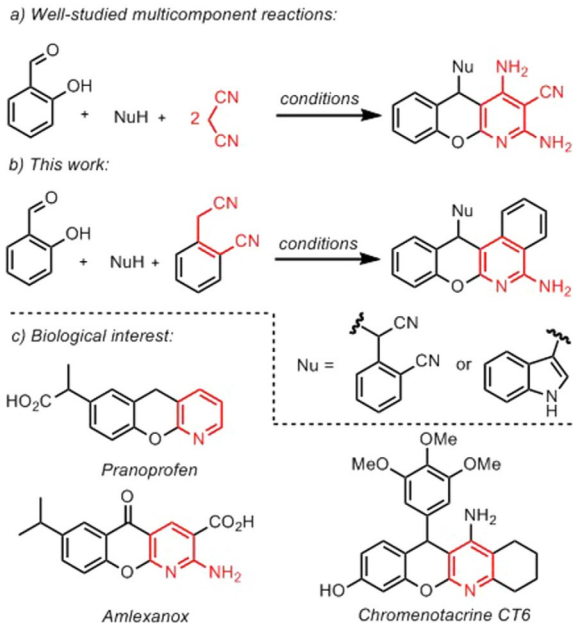

Figure 1. Representative examples of malononitrile multicomponent reactions and biologically active chromenopyridines.

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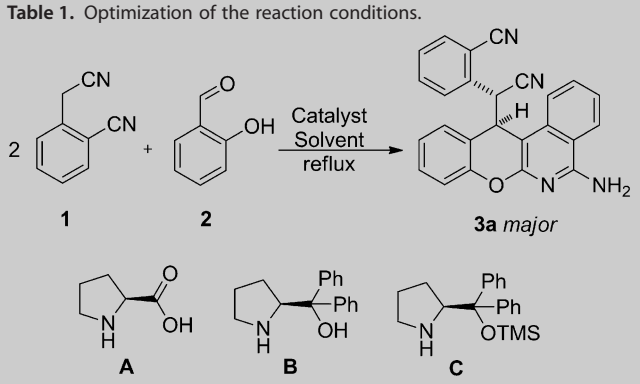
cyclic compounds for drug discovery (Figure 1 c),[5] we envisioned the use of homopthalonitrile to be of interest to significantly diversify the scope of the numerous malononitrile multicomponent reactions. Herein, we report a diastereoselective organocatalyzed pseudo-three-component reaction of homophtalonitrile (2 equiv) and *o*-hydroxybenzaldehyde, leading to the formation of 12-(*o*-cyanophenyl)chromenoisoquinolinamines. We also elaborated a sequential three-component reaction of homophtalonitrile, *o*-hydroxybenzaldehyde, and an indole, giving indol-3-yl substituted chromenoisoquinolinamines (Figure 1 b).

2. Results and Discussion

We recently reported that the treatment of homophtalonitrile **1** and *o*-hydroxybenzaldehyde **2** solution in ethanol with sodium carbonate resulted in the formation of diastereomeric mixture of chromenoisoquinolinamine **3** with a diastereomeric ratio (*d.r.*) of 69:31 (Table 1, entry 1).[6] Taking into account the potential importance of the chromenopyridine scaffold, we became interested in the possibility of a diastereoselective synthesis of these compounds. As far as the proline-catalyzed reactions are well established for performing stereoselective transformations,[7] we envisaged to carry out the considered reaction under organocatalytic conditions. Use of L-proline **A**, or L-proline-based catalysts **B** and **C** in 10 mol% amounts for the reaction of homophtalonitrile **1** and salicylaldehyde **2** in refluxing ethanol or dichloroethane resulted in the formation of the desired compound **3a** in only trace quantities (Table 1, entries 3–6). As L-proline is an inexpensive catalyst, we found it reasonable to use it in larger amounts. Thus, increasing the load of L-proline to 20 mol% resulted in the formation of **3a** with 68% yield and *d.r.* 95:5 (Table 1, entry 7). Taking an excess of aldehyde improved the yield of **3a** to 73% without changing the diastereoselectivity (Table 1, entry 8). When an excess of homophtalonitrile was used, the reaction yield decreased to 58% (Table 1, entry 9). The best yield of 88% was achieved with 30 mol% L-proline (Table 1, entry 10).

Table 1. Optimization of the reaction conditions.



Entry	Catalyst	Solvent	Time [h]	Molar ratio **1:2**	Yield [%]	*d.r.*
1	Na_2CO_3 (3 equiv)	EtOH	3	2:1	96	61:39
2	**A** (10 mol%)	EtOH	>200	2:1	–	–
3	**B** (10 mol%)	EtOH	>200	2:1	–	–
4	**C** (10 mol%)	EtOH	>200	2:1	–	–
5	**A** (10 mol%)	$C_2H_4Cl_2$	>200	2:1	–	–
6	**A** (20 mol%)	EtOH	45	2:1	68	95:5
6	**A** (20 mol%)	EtOH	45	2:1.5	73	95:5
8	**A** (20 mol%)	EtOH	45	2.5:1	58	95:5
9	**A** (30 mol%)	EtOH	45	2:1.5	88	>95:5

To our satisfaction, the employment of ethoxy-, methoxy-, bromo-, chloro-, nitro-, or dichloro-containing salicylaldehydes led to the formation of corresponding compounds **1b–i** with good yields and excellent diastereoselectivity (Figure 2). Further examination of the reaction scope showed that the use of sterically hindered α-hydroxynaphtaldehyde, as far as 4-diethylamino-2-hydroxybenzaldehyde with a strongly electron-donating group in the *para* position to the carbaldehyde moiety, failed to give the target products. The reaction of benzylcyanide (1 equiv), homophtalonitrile (1 equiv), and salicylaldehyde

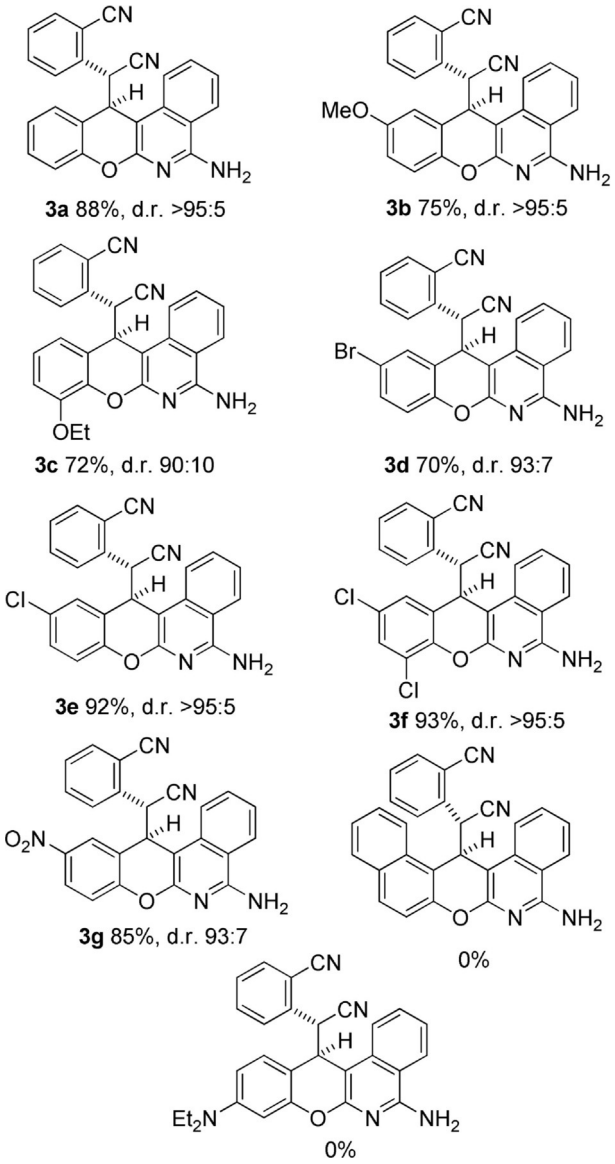


Figure 2. Scope of the pseudo-three-component reaction for the preparation of **3a–g**. Reaction conditions: homophtalonitrile (0.74 mmol), *o*-hydroxybenzaldehyde (0.53 mmol), L-proline (0.11 mmol), EtOH (3 mL), reflux, 45 h.

(1 equiv) furnished the product of the pseudo-three-component reaction as **1a**, demonstrating benzylcyanide to be unreactive as a third component. The use of more reactive *p*-nitrobenzylcyanide led to the formation of a complex mixture.

The structure of **3a** was meticulously determined by ^{1}H, ^{13}C, ^{1}H–^{1}H COSY, NOESY, ^{1}H–^{13}C HSQC, ^{1}H–^{13}C HMBC, ^{1}H–^{15}N HSQC, and ^{1}H–^{15}N HMBC NMR experiments. The relative stereochemistry was assigned for diastereomeric mixture with *d.r.* 69:31, based on NOESY experiments (see the Supporting Information for details). It is worth noting that compounds **3a**–**g** were prone to epimerization, and the quantity of the minor diastereomer increased when standing in DMSO solution.

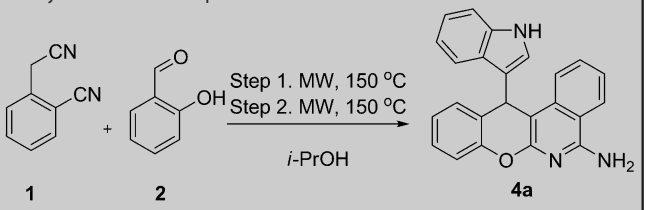
As we have recently shown the possibility to perform the sequential three-component reaction between homopthalonitrile, salicylaldehyde, and nitromethane,[6] we were interested in demonstrating the generality of the approach by using another nucleophile as a third component. Owing to the high abundance of the indole moiety in biologically active compounds and natural products, we chose to incorporate this heterocycle at the C12 position of the chromeno[3,2-*c*]isoquinolin-5-amine scaffold. Performing the one-pot reaction of homophtalonitrile, salicylaldehyde, and indole in refluxing ethanol with 20 mol% L-proline expectedly[8] gave trace amounts of the desired product. A previously established approach was used, and the synthesis was performed in two steps. First, homophtalonitrile (1 equiv), salicylaldehyde (1 equiv), and ammonium acetate (2 equiv) in *i*PrOH were heated to 150 °C in a microwave reactor for 10 min. Then, indole (3 equiv) and Et_3N (1 equiv) were added, and the reaction mixture was again heated to 150 °C for 10 min. This sequential protocol provided the desired indole-containing product **4a** in 34% yield (Table 2, entry 1). The employment of potassium carbonate did not increase the yields meaningfully (Table 2, entry 2), and increase of the reaction time had no effect (Table 2, entry 3), whereas taking aldehyde in excess (3 equiv) improved the yield to 65% (Table 2, entry 4). Further screening of the reagents quantities (Table 2, entries 5–8) revealed the best ratio to be 1:2:2 (homophtalonitrile/aldehyde/indole), giving **4a** in 71% yield (table 2, entry 7).

Investigating the scope of this sequential transformation, we were pleased to find that different aldehydes worked appropriately, and products **4b**–**e** were synthesized in 76–82% yields (Scheme 1). We also showed, that 6- and 7-azaindoles could be involved in the reaction, producing compounds **4f** and **4g** with 74 and 69% yields, respectively.

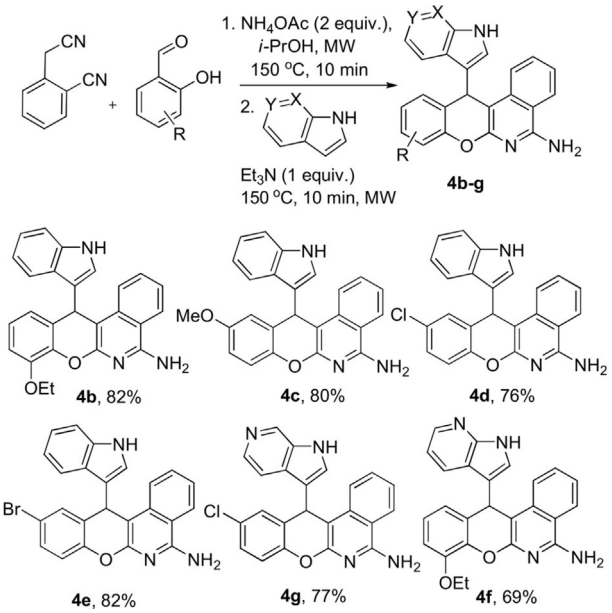
The structure of compound **4a** was unambiguously determined by using single-crystal X-ray diffraction study (Figure 3).

Based on the literature[9] and our experimental observations,[6] we believe that the interaction of homophtalonitrile **1** with salicylaldehyde **2** starts with Knoevenagel condensation, giving a styryl derivative that may undergo two consecutive intramolecular cyclizations to form intermediate **5** (*m/z* 246, MALDI MS 249 [$M^+ + 2H + H$], 307 [$M^+ + i$PrOH]). The formation of product **3a** may be explained by the L-proline-directed Michael addition of another equivalent of homophtalonitrile to the intermediate **5**. The formation of product **4a** may be interpreted through analogous Michael addition of an indole to this intermediate (Scheme 2). Taking into account the reversibility of the Michael addition reaction, we envisaged that prod-

Table 2. Optimization of the reaction conditions for the preparation of indolyl-substituted compound **4a**.



Entry	Ratio **1**:**2**:indole	Step 1	Step 2	Yield [%]
1	1:1:3	NH_4OAc (2 equiv) 10 min	indole (3 equiv) Et_3N (1 equiv) 10 min	34
2	1:1:3	K_2CO_3 (2 equiv) 10 min	indole (3 equiv) 10 min	40
3	1:1:3	NH_4OAc (2 equiv) 20 min	indole (3 equiv) Et_3N (1 equiv) 20 min	40
4	1:3:3	NH_4OAc (2 equiv) 10 min	indole (3 equiv) Et_3N (1 equiv) 10 min	65
5	1:1:1.2	NH_4OAc (2 equiv), 20 min	indole (1.2 equiv) Et_3N (1 equiv) 20 min	40
6	1:1.5:1.2	NH_4OAc (2 equiv) 10 min	indole (1.2 equiv) Et_3N (1 equiv) 10 min	57
7	1:2:2	NH_4OAc (2 equiv) 10 min	indole (2 equiv) Et_3N (1 equiv) 10 min	71
8	2:1:1.2	NH_4OAc (2 equiv), 10 min	indole (1.2 equiv) Et_3N (1 equiv) 10 min	48



Scheme 1. Scope of the sequential three-component reaction towards the preparation of compounds **4b**–**g**.

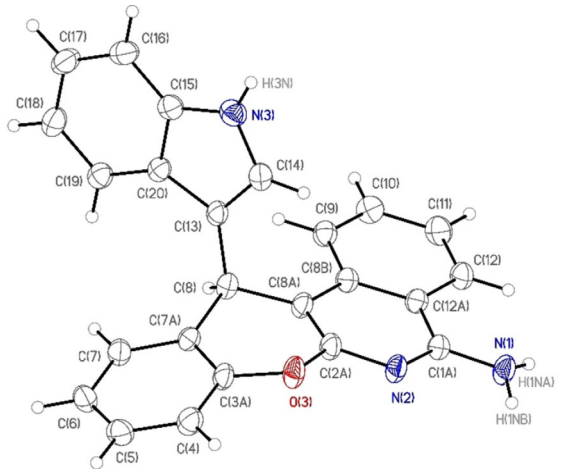
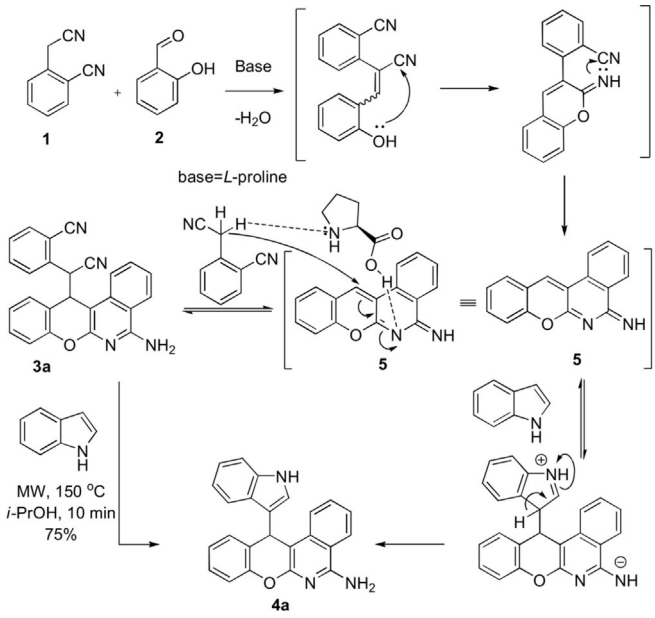


Figure 3. General view of the one of two symmetrically independent molecules in the crystal **4a**. Anisotropic displacement parameters are drawn at 50% probability. The disordered solvating ethyl acetate molecule was removed with the SQUEEZE method and are not shown.



Scheme 2. Likely mechanism of formation for **3a** and **4a**.

uct **3a** may be converted to **4a** under the action of an indole, which looks less reversible owing to aromatization of an indole moiety. This hypothesis, and the reaction pathway itself, was supported by heating product **3a** with an excess indole in a microwave reactor for 10 min at 150 °C and isolation of product **4a** in 75% yield.

The synthesized compounds were noticed to be fluorescent, that is, emitting blue light when exposed to UV radiation (Figure 4). As the preparation of fluorescent compounds with emission bands in blue region are of value,[8] and to better understand the potential of these molecules to be employed in organoelectronics, the optical properties of compounds **3a**, **4a**, **4b**, **4d**, **4f**, and **4g** were studied and are summarized in Table 3. Firstly, absorbance and emission spectra for com-

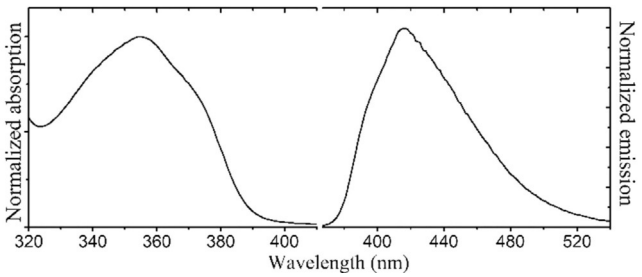


Figure 4. Absorption and emission spectra of the compound **4a**.

Table 3. Photophysical properties of synthesized chromenoisoquinolinamines **3a**, **4a**, **4b**, **4d**, **4f**, and **4g** (in methanol).

Compound	Abs[a] [nm]	ε[b] [(M cm)$^{-1}$]	Em[a] [nm]	FQY [%]
3a	354	7000	416	2.1
4a	355	4500	415	48
4b	354	6000	416	58
4d	354	4500	416	42
4f	354	4500	415	70
4g	354	4500	415	57

[a] Peak maximum. [b] Molar extinction coefficient.

pounds **3a**, **4a**, **4b**, **4d**, **4f**, and **4g** exhibited similar maximum wavelengths at 354–355 nm and 415–416 nm, respectively. Secondly, the fluorescence quantum yield (FQY) of compounds **3a**, **4a**, **4b**, **4d**, **4f**, and **4g** were highest in polar and protic solvents (e.g. methanol) and changed drastically with the transition from **3a** (FQY 2.1%) to indol-3-yl-substituted compounds **4** (FQY 42–70%).

It was also noticed that the fluorescence of compounds **4** was quenched in the presence of acids. Thus, the emission spectra of compound **4a** with different concentrations of trifluoroacetic acid was performed, showing complete loss of fluorescence with a tenfold excess of the acid (Figure 5a). The quenching was found to be reversible, and the addition of triethylamine in a sufficient quantity returned the fluorescence emission to the initial intensity (Figure 5b).

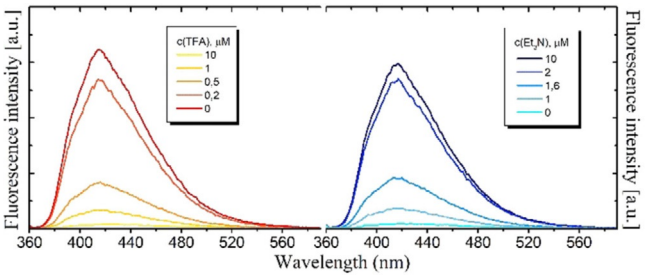


Figure 5. Fluorescence quenching experiments for the compound **4a**.

The optical behavior of compounds **3a** and **4a**, **4b**, **4d**, **4f**, and **4g** correlates well with the results of DFT calculations (Table 4). The electron density for frontier orbitals of all com-

Table 4. Energies of HOMO and LUMO derived from DFT method [eV].

Entry	Cmpd	HOMO energy	LUMO energy	Band gap
1	**3a**	−5662	−2028	3.633
2	**4a**	−5453	−1325	4.128
3	**4b**	−5320	−1245	4.075
4	**4d**	−5583	−1444	4.139
5	**4f**	−5413	−1328	4.085
6	**4g**	−5713	−1556	4.157

pounds **4** are localized on isoquinolinamine moieties, and the gaps between these orbitals are equal, explaining the similarity of the absorption and emission maxima positions and fluorescence quenching in acidic media. We also demonstrate that compound **3a** possesses an additional lowest excited state with electron density localized on benzonitrile moiety (for details, see the Supporting Information). Probably, the excited state is dark, which, by the virtue of Kasha's rule, leads to a low FQY.

3. Conclusions

In summary, we have developed an organocatalytic pseudo-three-component reaction of homopthalonitrile (2 equiv) and *o*-hydroxybenzaldehyde, leading to the diastereoselective formation of 5-amino-12*H*-chromeno[2,3-c]isoquinolin-12-yl)(cyano)methyl)benzonitriles **3a–g**. We have also demonstrated the possibility to employ other nucleophiles by elaborating sequential three-component reaction of homophtalonitrile, *o*-hydroxybenzaldehyde, and (aza)indole, giving 12-(1*H*-Indol-3-yl)-12*H*-chromeno[2,3-*c*]isoquinolin-5-amines **4a–f**. The synthesized compounds exhibited interesting photophysical properties, with indol-3-yl substituted 12*H*-chromeno[2,3-*c*]isoquinolin-5-amines having high fluorescence quantum yields (42–70%) and exhibiting reversible fluorescence quenching under acidic conditions. We believe that our work shows the high potential of homophtalonitrile to be used as a vinylogous malononitrile and that many applications of this reagent to the field of multicomponent reaction will follow.

Experimental Section

General Remarks

IR spectra were recorded on an Infralum-ft-801 (FTIR) spectrophotometer. ^{1}H NMR spectra were recorded on Bruker Avance 400 (400 MHz) spectrometer and JEOL ECA 600 (600 MHz) spectrometer; chemical shifts (δ ppm) and coupling constants (Hz) are reported in the standard fashion with reference to residual signals of DMSO (δH = 2.50 ppm). ^{13}C NMR spectra were recorded on Bruker Avance 400 (100 MHz) and JEOL ECA 600 (150 MHz) spectrometers at RT; chemical shifts (δ ppm) are reported relative to DMSO [δC = 39.51 ppm (central line of septet)]. In the ^{1}H-NMR sprecta, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, sept = septet, dd = doublet of doublet, m = multiplet and br. s = broad singlet. High-resolution mass spectra (HRMS) were recorded on a Bruker MicrOTOF-Q II with electron spray ionization (ESI) mode. The microwave irradiation experiments were carried out in an Anton Paar 300 microwave apparatus. The reactions were carried out in 10 mL glass tubes, sealed with silicon septum and placed in the microwave cavity. The reactions were irradiated at the required set temperature for the stipulated time and then cooled to 55 °C with air jet cooling. Reactions were monitored by TLC on silica gel using a combination of hexane and ethyl acetate (1:1) as eluents. Solvents were distilled prior to use; homophthalonitrile (90% tech), 7-azaindole, 6-azaindole, 2-hydroxy-5-methoxybenzaldehyde, 5-chlorosalicylaldehyde, 3,5-dichlorosalicylaldehyde, 2-hydroxy-5-nitrobenzaldehyde were purchased from Alfa Aesar; 3-ethoxysalicylaldehyde was purchased from Sigma–Aldrich; 5-bromosalicylaldehyde, 2-hydroxy-1-naphthaldehyde and salicylaldehyde were purchased from ACROS Organics and used as received. Silica gel 60 (0.04–0.063 mm) from Macherey–Nagel was used for column chromatography. Melting points were measured on SMP-10 apparatus in capillary tubes. UV/VIS spectra were recorded with a Varian Cary 100 spectrophotometer. Fluorescence excitation and emission spectra were recorded with Agilent Cary Eclipse fluorescence spectrophotometer, quantum yields were determined according to literature procedure[10] and employing quinine sulfate (QS) as a standard.

General Procedure for the Synthesis of Isoquinolineamines (3a–g)

o-Hydroxybenzaldehyde (0.53 mmol, 1.43 equiv) were added to a solution of homopthalonitrile (117 mg, 0.74 mmol, 2 equiv) in ethanol (3 mL), and L-proline (12.7 mg, 0.11 mmol, 0.3 equiv) was subsequently added. The resultant mixture was refluxed for 45 h. Upon completion, the mixture was cooled to room temperature, the precipitate was filtered off, and washed with minimal quantity of cold EtOH, followed by water (5×5 mL), and then dried in air to give isoquinolineamines **3a–g** (69–82%) as solids.

2-((R)-((R*)-5-Amino-12H-chromeno[2,3-c]isoquinolin-12-yl)-(cyano)methyl)benzonitrile (3a)*

Yield: 126 mg (88%), *d.r.* >95:5 as a white solid. MP = 233–234 °C with decomposition. IR (KBr): ν_{max} = 3485, 3373, 3236–3212, 3073-3018, 2238, 2229, 1632, 1556, 1514, 1493, 1458, 1439, 1409, 1394, 1343, 1243, 1198, 1165, 763 cm^{-1}. ^{1}H NMR ([*D6*]DMSO, 600 MHz): δ = 4.83 (d, *J* = 5.1 Hz, 1H), 5.23 (d, *J* = 5.1 Hz, 1H), 6.59 (d, *J* = 7.1 Hz, 1H), 6.93 (t, *J* = 7.1 Hz, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.27 (s, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.37 (t, *J* = 7.3 Hz, 1H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.57–7.62 (m, 2H), 7.82 (d, *J* = 7.1 Hz, 1H), 8.10 (d, *J* = 8.1 Hz, 1H), 8.23 ppm (d, *J* = 8.1 Hz, 1H). ^{13}C NMR ([*D6*]DMSO, 150 MHz): δ = 39.3, 43.6, 91.8, 111.5, 115.7, 116.3, 117.2, 118.3, 119.1, 121.4, 122.6, 123.4, 124.8, 129.0, 129.2, 130.1, 130.3, 130.5, 133.1, 133.5, 136.3, 136.5, 152.5, 155.3, 157.3 ppm. HRMS (ESI$^+$) calculated for $[C_{25}H_{17}N_4O]^+ = [M+H]^+$: 389.1396; found 389.1398.

2-((R)-((R*)-5-Amino-10-methoxy-12H-chromeno[2,3-c]isoquinolin-12-yl)(cyano)methyl)benzonitrile (3b)*

Yield: 116 mg (75%), *d.r.* >95:5 as a white solid. MP = 225–226 °C with decomposition. IR (KBr): ν_{max} = 3449, 3301, 3156, 3082-3068, 3003, 2950–2915, 2830, 2241, 2219, 1645, 1620, 1594, 1562, 1501, 1413, 1343, 1227, 763 cm^{-1}. ^{1}H NMR ([*D6*]DMSO, 600 MHz): δ = 3.47 (s, 3H), 4.89 (d, *J* = 5.8 Hz, 1H), 5.21 (d, *J* = 5.8 Hz, 1H), 6.11 (d, *J* = 3.2 Hz, 1H), 6.89 (dd, *J* = 8.0, 2.7 Hz, 1H), 7.08 (d, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 9.1 Hz, 1H), 7.24 (s, 2H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.55 (t,

J=8.0 Hz, 1H), 7.57–7.67 (m, 2H), 7.86 (dd, J=7.4, 1.5, 1H), 8.14 (d, J=8.3 Hz, 1H), 8.24 ppm (d, J=8.3 Hz, 1H). ^{13}C NMR ([*D6*]DMSO, 150 MHz): δ=39.7, 43.5, 55.2, 91.3, 111.5, 113.7, 115.6, 115.7, 117.1, 117.4, 118.4, 119.5, 121.4, 123.4, 124.9, 129.2, 130.4, 130.6, 133.2, 133.6, 136.5, 136.6, 146.4, 154.2, 155.6, 157.3 ppm. HRMS (ESI$^+$) calculated for $[C_{26}H_{19}N_4O_2]^+$=$[M+H]^+$: 419.1502; found 419.1506.

2-((R)-((R*)-5-Amino-8-ethoxy-12H-chromeno[2,3-c]isoquinolin-12-yl)(cyano)methyl)benzonitrile (3c)*

Yield: 115 mg (72%), *d.r.*=90:10 as a white solid. MP=248–249 °C with decomposition. IR (KBr): ν_{max}=3512, 3276, 3160, 3077, 2979, 2934, 2884, 2242, 2222, 1623, 1606, 1585, 1469, 1270, 1231, 1084, 752 cm^{-1}. ^{1}H NMR ([*D6*]DMSO, 600 MHz): δ=1.41 (t, J=6.7 Hz, 3H), 4.05–4.14 (m, 2H), 4.81 (d, J=5.5 Hz, 1H), 5.18 (d, J=5.5 Hz, 1H), 6.14 (d, J=7.5 Hz, 1H), 6.82 (t, J=7.8 Hz, 1H), 6.98 (d, J=7.8 Hz, 1H), 7.14 (d, J=7.5 Hz, 1H), 7.30 (m, 2H), 7.36 (t, J=7.3 Hz, 1H), 7.51 (t, J=7.5 Hz, 1H), 7.56 (t, J=7.6 Hz, 1H), 7.60 (t, J=7.6 Hz, 1H), 7.80 (d, J=7.6 Hz, 1H), 8.05 (d, J=8.2 Hz, 1H), 8.22 ppm (d, J=8.2 Hz, 1H). ^{13}C NMR ([*D6*]DMSO, 150 MHz): δ=14.8, 39.8, 43.6, 64.1, 91.7, 111.4, 112.8, 115.7, 117.3, 118.4, 120.0, 121.3 (2C), 122.4, 123.4, 124.8, 129.2, 130.3, 130.5, 133.1, 133.4, 136.5 (2C), 142.1, 146.8, 155.4, 157.3 ppm. HRMS (ESI$^+$) calculated for $[C_{27}H_{21}N_4O_2]^+$=$[M+H]^+$: 433.1659; found 433.1655.

2-((R)-((R*)-5-Amino-10-bromo-12H-chromeno[2,3-c]isoquinolin-12-yl)(cyano)methyl)benzonitrile (3d)*

Yield: 121 mg (70%), *d.r.*=93:7 as a beige solid. MP=271–273 °C with decomposition. IR (KBr): ν_{max}=3448, 3310, 3150, 3071, 2923, 2242, 2223, 1649, 1618, 1559, 1518, 1482, 1413, 1344, 1244, 1195, 762 cm^{-1}. ^{1}H NMR ([*D6*]DMSO, 600 MHz): δ=4.86 (d, J=5.6 Hz, 1H), 5.27 (d, J=5.6, 1H), 6.71 (d, J=2.0 Hz, 1H), 7.05 (d, J=8.1 Hz, 1H), 7.16 (d, J=8.6 Hz, 1H), 7.31 (s, 2H), 7.40 (t, J=7.5 Hz, 1H), 7.49 (dd, J=2.0, 8.6 Hz, 1H), 7.57 (t, J=7.6, 1H), 7.61 (t, J=7.5 Hz, 1H), 7.66 (t, J=7.7 Hz, 1H), 7.85 (d, J=7.6 Hz, 1H), 8.10 (d, J=8.6 Hz, 1H), 8.24 ppm (d, J=8.3 Hz, 1H). ^{13}C NMR ([*D6*]DMSO, 150 MHz): δ=39.1, 43.4, 91.2, 111.7, 115.8, 117.2, 118.0, 118.3, 121.0, 121.5, 123.7, 124.7, 126.3, 128.9, 129.4, 129.8, 130.3, 130.7, 133.0, 133.6, 136.0, 136.4, 151.4, 155.0, 157.5 ppm. HRMS (ESI+) calculated for $[C_{25}H_{16}N_4OBr]^+$=$[M+H]^+$: 467.0502; found 467.0505.

2-((R)-((R*)-5-Amino-10-chloro-12H-chromeno[2,3-c]isoquinolin-12-yl)(cyano)methyl)benzonitrile (3e)*

Yield: 144 mg (92%), *d.r.* >95:5 as a grey solid. MP=268–269 °C with decomposition. IR (KBr): ν_{max}=3450, 3309, 3150, 2928, 2241, 2223, 1649, 1619, 1561, 1518, 1483, 1445, 1414, 1344, 1244, 1195, 762 cm^{-1}. ^{1}H NMR ([*D6*]DMSO, 600 MHz): δ=4.87 (d, J=5.2 Hz, 1H), 5.29 (d, J=5.2 Hz, 1H), 6.61 (s, 1H), 7.06 (d, J=7.7 Hz, 1H), 7.22 (d, J=8.7 Hz, 1H), 7.32 (s, 2H), 7.37–7.41 (m, 2H), 7.57 (t, J=7.6 Hz, 1H), 7.61 (t, J=7.7 Hz, 1H), 7.65 (t, J=7.5 Hz, 1H), 7.85 (d, J=7.6 Hz, 1H), 8.10 (d, J=8.5 Hz, 1H), 8.25 ppm (d, J=8.0 Hz, 1H). ^{13}C NMR ([*D6*]DMSO, 150 MHz): δ=39.7, 43.4, 91.1, 111.6, 115.8, 117.1, 118.0, 118.2, 120.9, 121.5, 123.7, 124.8, 126.2, 128.8, 129.4, 129.8, 130.3, 130.6, 133.0, 133.6, 136.0, 136.4, 151.4, 155.0, 157.4 ppm. HRMS (ESI$^+$) calculated for $[C_{25}H_{16}N_4OCl]^+$=$[M+H]^+$: 423.1007; found 423.1017.

2-((R)-((R*)-5-Amino-8,10-dichloro-12H-chromeno[2,3-c]isoquinolin-12-yl)(cyano)methyl)benzonitrile (3f)*

Yield: 157 mg (93%), *d.r.* >95:5 as a light brown solid. MP=256–257 °C with decomposition. IR (KBr): ν_{max}=3500, 3398, 3299, 3142, 2935, 2245, 2223, 1643, 1618, 1575, 1559, 1516, 1463, 1412, 1394, 1343, 1254, 1206, 1161, 992, 755 cm^{-1}. ^{1}H NMR ([*D6*]DMSO, 600 MHz): δ=4.89 (d, J=5.2 Hz, 1H), 5.26 (d, J=5.2 Hz, 1H), 6.68 (s, 1H), 7.11 (d, J=7.7 Hz, 1H), 7.41 −7.45 (m, 3H), 7.56 (t, J=7.4 Hz, 1H), 7.61 (t, J=7.4 Hz, 1H), 7.65 −7.68 (m, 2H), 7.82 (d, J=7.4 Hz, 1H), 8.06 (d, J=8.2 Hz, 1H), 8.25 ppm (d, J=8.0 Hz, 1H). ^{13}C NMR ([*D6*]DMSO, 150 MHz): δ=39.3, 43.3, 91.0, 111.7, 116.1, 117.1, 118.2, 121.3, 121.7, 122.6, 124.0, 124.9, 126.4, 128.8 (2C), 129.5, 130.3, 130.7, 133.1, 133.6, 135.7, 136.3, 147.5, 154.7, 157.6 ppm. HRMS (ESI$^+$) calculated for $[C_{25}H_{15}N_4OCl_2]^+$=$[M+H]^+$: 457.0617; found 457.0631.

2-((R)-((R*)-5-Amino-10-nitro-12H-chromeno[2,3-c]isoquinolin-12-yl)(cyano)methyl)benzonitrile (3g)*

Yield: 136 mg (85%), *d.r.*=93:7 as a light brown solid. MP=279–280 °C with decomposition. IR (KBr): ν_{max}=3455, 3393-3363, 3307, 3156, 3087, 2931, 2241, 2220, 1645, 1620, 1517, 1339, 1253, 760 cm^{-1}. ^{1}H NMR ([*D6*]DMSO, 600 MHz): δ=4.95 (d, J=5.1 Hz, 1H), 5.51 (d, J=5.1 Hz, 1H), 7.00 (d, J=7.6 Hz, 1H), 7.41–7.46 (m, 4H), 7.55 −7.62 (m, 3H), 7.66 (t, J=7.6 Hz, 1H), 7.88 (d, J=7.4 Hz, 1H), 8.17 (d, J=8.4 Hz, 1H), 8.24 (dd, J=2.6, 9.0 Hz, 1H), 8.28 ppm (d, J=8.2 Hz, 1H). ^{13}C NMR ([*D6*]DMSO, 150 MHz): δ=38.8, 43.4, 90.8, 111.7, 116.2, 117.1, 117.5, 118.2, 120.0, 121.8, 124.1, 124.86, 124.9, 126.6, 129.5, 130.2, 130.8, 133.2, 133.7, 135.5, 136.2, 142.1, 154.3, 157.4, 157.6 ppm. HRMS (ESI$^+$) calculated for $[C_{25}H_{16}N_5O_3]^+$=$[M+H]^+$: 434.1247; found 434.1247.

General Procedure for the Synthesis of Indolyl- or Azaindolyl-Substituted Isoquinolineamines (4a–f)

Homophthalonitrile **1** (129 mg, 0.818 mmol, 1 equiv) and *o*-hydroxybenzaldehyde **2** (1.64 mmol, 2 equiv) were added to a 10 mL glass tube equipped with a magnetic stir bar sealed with silicon septum, followed by NH_4OAc (142 mg, 1.64 mmol, 2 equiv) and isopropanol (2 mL). The resultant mixture was subjected to microwave irradiation at 150 °C for 10 min. Then, the indole (192 mg, 1.64 mmol, 2 equiv) or azaindole (6-azaindole/7-azaindole) (193 mg, 1.64 mmol, 2 equiv) and Et_3N (114 µL, 1 equiv) were added to the reaction mixture and heated again under microwave irradiation at 150 °C for 10 min. Upon completion, the mixture was cooled to room temperature and the solvent was then evaporated under reduced pressure. Silica gel column chromatography (hexane/ethyl acetate in different proportions of 3:1 or 1:1) was performed for purification; the resulting compounds formed co-crystals with ethyl acetate and evaporation with methanol or ethanol was needed to give the isoquinolineamines **4a–f** (69–82%) as pure solids.

12-(1H-Indol-3-yl)-12H-chromeno[2,3-c]isoquinolin-5-amine (4a)

Yield: 212 mg (71%) as a beige amorphous solid. R_f=0.22 (hexane/ethyl acetate 1:1, silica). IR (KBr): ν_{max}=3486, 3444, 3388, 3192, 3062, 2973–2855, 1622, 1514, 1454, 1397, 1344, 1233, 743 cm^{-1}. ^{1}H NMR ([*D6*]DMSO, 600 MHz): δ=5.96 (s, 1H), 6.83 (t, J=7.5 Hz, 1H), 6.95 (t, J=7.5 Hz, 1H), 7.00 (t, J=6.6 Hz, 1H), 7.08 (s, 2H),

7.16–7.19 (m, 2H), 7.25 (d, J=7.6, 1H), 7.27 (d, J=7.6 Hz, 1H), 7.39 (d, J=7.6 Hz, 1H), 7.44 (d, J=8.1 Hz, 1H), 7.46 (d, J=2.3 Hz, 1H), 7.50 (t, J=7.7 Hz, 1H), 7.93 (d, J=8.5 Hz, 1H), 8.17 (d, J=8.5 Hz, 1H), 10.85 ppm (s, 1H). ^{13}C NMR ([*D6*]DMSO, 150 MHz): δ=32.4, 95.5, 111.6, 116.0, 116.1, 118.4, 118.5, 120.5, 120.8, 122.4, 122.5, 123.0, 123.3, 124.5, 125.27, 125.33, 127.2, 129.6, 130.1, 136.5, 137.4, 150.2, 152.6, 156.6 ppm. HRMS (ESI$^+$) calculated for $[C_{24}H_{18}N_3O]^+$ = $[M+H]^+$: 364.1444; found 364.1444.

8-Ethoxy-12-(1H-indol-3-yl)-12H-chromeno[2,3-c]isoquinolin-5-amine (4b)

Yield: 274 mg (82%) as an orange solid. MP=230–232 °C with decomposition. IR (KBr): ν_{max}=3488, 3431, 3280, 3187, 3162, 3062, 2976–2864, 1625, 1608, 1584, 1561, 1471-1441, 1392, 1343, 1270, 1223, 1083, 740 cm^{-1}. ^{1}H NMR ([*D6*]DMSO, 600 MHz): δ=1.42 (t, J=7.1 Hz, 3H), 4.07 (q, J=7.1 Hz, 2H), 5.94 (s, 1H), 6.80–6.83 (m, 2H), 6.88 (t, J=7.8 Hz, 1H), 6.92–6.95 (m, 2H), 7.06 (s, 2H), 7.22–7.27 (m, 2H), 7.40–7.42 (m, 2H), 7.48 (t, J=7.7 Hz, 1H), 7.90 (d, J=8.6 Hz, 1H), 8.14 (d, J=8.2 Hz, 1H), 10.82 ppm (s, 1H). ^{13}C NMR ([*D6*]DMSO, 150 MHz): δ=14.8, 32.5, 63.9, 95.0, 110.7, 111.5, 116.1, 118.4, 118.5, 120.5, 120.8, 120.9, 122.46, 122.5, 122.8, 122.9, 124.5, 125.3, 126.0, 130.0, 136.5, 137.4, 139.8, 146.7, 152.6, 156.5 ppm. HRMS (ESI$^+$) calculated for $[C_{26}H_{22}N_3O_2]^+$ = $[M+H]^+$: 408.1706; found 408.1705.

12-(1H-Indol-3-yl)-10-methoxy-12H-chromeno[2,3-c]isoquinolin-5-amine (4c)

Yield: 256 mg (80%) as a light orange amorphous compound. R_f= 0.15 (hexane/ethyl acetate 1:1, silica). IR (KBr): ν_{max}=3485–2834, 1620, 1495, 1448, 1398, 1344, 1215, 742 cm^{-1}. ^{1}H NMR ([*D6*]DMSO, 600 MHz): δ=3.64 (s, 3H), 5.93 (s, 1H), 6.77 (dd, J=8.8, 2.8 Hz, 1H), 6.81 (t, J=7.5 Hz, 1H), 6.91 (d, J=2.7 Hz, 1H), 6.92–6.95 (m, 1H), 7.03 (s, 2H), 7.10 (d, J=8.9 Hz, 1H), 7.23–7.26 (m, 2H), 7.41 (d, J= 8.1 Hz, 1H), 7.46 (br s, 1H), 7.49 (t, J=8.1 Hz, 1H), 7.90 (d, J= 8.6 Hz, 1H), 8.14 (d, J=8.23 Hz, 1H), 10.84 ppm (s, 1H). ^{13}C NMR ([*D6*]DMSO, 150 MHz): δ=32.8, 55.3, 94.6, 111.6, 112.9, 114.0, 115.0, 116.9, 118.45, 118.48, 120.3, 120.9, 122.4, 122.5, 122.8, 124.5, 125.3, 126.1, 130.1, 136.6, 137.4, 144.2, 152.8, 155.0, 156.5 ppm. HRMS (ESI$^+$) calculated for $[C_{25}H_{20}N_3O_2]^+$ = $[M+H]^+$: 394.1550; found 394.1553.

10-Chloro-12-(1H-indol-3-yl)-12H-chromeno[2,3-c]isoquinolin-5-amine (4d)

Yield: 246 mg (76%) as a colorless amorphous solid. R_f=0.19 (hexane/ethyl acetate 1:1, silica). IR (KBr): ν_{max}=3636, 3478–3028, 2952, 2891, 2841, 2780–2718, 1621, 1566, 1482, 1461, 1396, 1343, 1252, 815 cm^{-1}. ^{1}H NMR ([*D6*]DMSO, 600 MHz): δ=5.96 (s, 1H), 6.79 (t, J=7.5 Hz, 1H), 6.91 (t, J=7.5 Hz, 1H), 7.07 (s, 2H), 7.16–7.25 (m, 4H), 7.34–7.37 (m, 2H), 7.46–7.48 (m, 2H), 7.85 (d, J= 8.4 Hz, 1H), 8.12 (d, J=8.2 Hz, 1H), 10.88 ppm (s, 1H). ^{13}C NMR ([*D6*]DMSO, 150 MHz): δ=32.3, 94.5, 111.7, 116.2, 118.2, 118.6 (2C), 120.0, 121.0, 122.5, 122.7, 123.2, 124.5, 125.1, 126.6, 127.2, 127.4, 129.0, 130.2, 136.5, 137.2, 149.0, 152.3, 156.7 ppm. HRMS (ESI$^+$) calculated for $[C_{24}H_{17}N_3OCl]^+$ = $[M+H]^+$: 398.1054; found 398.1057.

10-Bromo-12-(1H-indol-3-yl)-12H-chromeno[2,3-c]isoquinolin-5-amine (4e)

Yield: 297 mg (82%) as an orange amorphous compound. R_f=0.19 (hexane/ethyl acetate 1:1, silica). IR (KBr): ν_{max}=3495, 3395, 3178, 3069, 2981, 2926–2880, 1620, 1454, 1403, 1343, 1252, 743 cm^{-1}. ^{1}H NMR ([*D6*]DMSO, 600 MHz): δ=6.00 (s, 1H), 6.82 (t, J=7.5 Hz, 1H), 6.94 (t, J=7.5, 1H), 7.10 (s, 2H), 7.14 (d, J=8.5 Hz, 1H), 7.24–7.28 (m, 2H), 7.33–7.37 (m, 2H), 7.50–7.52 (m, 3H), 7.88 (d, J= 8.6 Hz, 1H), 8.14 (d, J=8.3 Hz, 1H), 10.91 ppm (s, 1H). ^{13}C NMR ([*D6*]DMSO, 150 MHz): δ=32.2, 94.5, 111.7, 114.6, 116.2, 118.2, 118.6, 118.7, 120.0, 121.0, 122.5, 122.7, 123.2, 124.6, 125.1, 127.9, 130.1, 130.2, 132.0, 136.5, 137.2, 149.5, 152.3, 156.7 ppm. HRMS (ESI$^+$) calculated for $[C_{24}H_{17}N_3OBr]^+$ = $[M+H]^+$: 442.0549; found 442.0549.

8-Ethoxy-12-(1H-pyrrolo[2,3-b]pyridin-3-yl)-12H-chromeno[2,3-c]isoquinolin-5-amine (4f)

Yield: 230 mg (69%) as a yellow solid. MP=224–225 °C with decomposition. IR (KBr): ν_{max}=3400, 3325, 3156, 3030, 2979, 2926–2880, 1617, 1586, 1563, 1474, 1445, 1396, 1343, 1272, 1219, 1087, 773 cm^{-1}. ^{1}H NMR ([*D6*]DMSO, 600 MHz): δ=1.41 (t, J=6.9 Hz, 3H), 4.07 (dd, J=6.9, 2.2 Hz, 2H), 5.94 (s, 1H), 6.84 (d, J=7.8 Hz, 1H), 6.87 (dd, J=4.9, 7.9 Hz, 1H), 6.90–6.95 (m, 2H), 7.10 (s, 2H), 7.27 (t, J=7.6 Hz, 1H), 7.51 (t, J=7.6 Hz, 1H), 7.59 (d, J=2.3 Hz, 1H), 7.65 (d, J=7.8 Hz, 1H), 7.90 (d, J=8.5 Hz, 1H), 8.04 (d, J=4.9 Hz, 1H), 8.14 (d, J=8.3 Hz, 1H), 11.39 ppm (s, 1H). ^{13}C NMR ([*D6*]DMSO, 150 MHz): δ=14.8, 32.6, 63.9, 94.6, 110.9, 115.0, 116.0, 117.6, 119.2, 120.8, 122.4, 122.7, 123.0, 123.1, 124.5, 125.6, 126.4, 130.2, 137.2, 139.8, 142.3, 146.7, 148.6, 152.6, 156.7 ppm. HRMS (ESI$^+$) calculated for $[C_{25}H_{21}N_4O_2]^+$ = $[M+H]^+$: 409.1659; found 409.1665.

10-Chloro-12-(1H-pyrrolo[2,3-c]pyridin-3-yl)-12H-chromeno[2,3-c]isoquinolin-5-amine (4g)

Yield: 251 mg (77%) as a light yellow solid. MP=209–211 °C. IR (KBr): ν_{max}=3500, 3398, 3229, 3063, 2971, 2923, 2873, 1620, 1563, 1481, 1449, 1397, 1343, 1253, 1186, 743 cm^{-1}. ^{1}H NMR ([*D6*]DMSO, 600 MHz): δ=6.05 (s, 1H), 7.16 (s, 2H), 7.23–7.27 (m, 4H), 7.42 (s, 1H), 7.52 (t, J=7.5, 1H), 7.77 (s, 1H), 7.84 (d, J=8.6 Hz, 1H), 7.92 (d, J=5.5 Hz, 1H),8.17 (d, J=8.1 Hz, 1H), 8.61 (s, 1H), 11.53 ppm (s, 1H). ^{13}C NMR ([*D6*]DMSO, 150 MHz): δ=31.9, 94.1, 112.8, 116.2, 118.3, 119.8, 122.3, 123.4, 124.7, 126.7, 126.9, 127.0, 127.5, 129.0, 129.2, 130.4, 133.7, 134.8, 137.1, 137.5, 149.1, 152.4, 156.9 ppm. HRMS (ESI$^+$) calculated for $[C_{23}H_{16}N_4OCl]^+$ = $[M+H]^+$: 399.1007; found 399.1011.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: chromeno[2,3-*c*]isoquinoline · fluorescence · multicomponent reactions · organocatalysis · sequential reactions

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