Synthesis of New Chromeno[4,3,2-*de*]quinazolin-2-ones, -quinazolines and -pyrrolo[2,1-*b*]quinazolines

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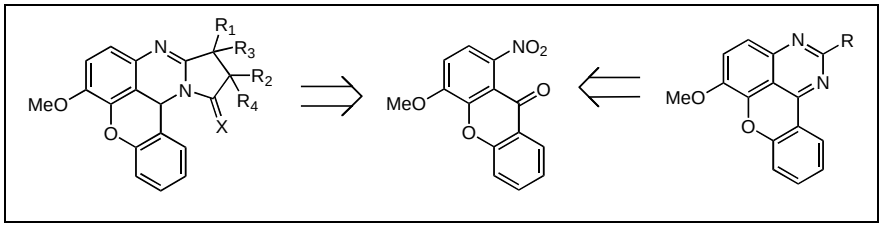

The total synthesis of chromeno[4,3,2-*de*]quinazolin-2-ones, -quinazolines and -pyrrolo[2,1-*b*]quinazolines from easily prepared 4-methoxy-1-nitro-9*H*-xanthen-9-one is reported. These compounds, in which a 1,3-diazine ring is fused to the xanthene scaffold, were obtained with good overall yields in very few steps.

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INTRODUCTION

Widespread interest in the synthesis of quinazolines [1] has been engendered by their sedative, CNS-depressant, neuroleptic, hypnotic, analgesic, diuretic, anthelminthic, antimicrobial, antitubercular, antibiotic, antihypertensive, antiinflammatory and antitumoral properties [2]. Many quinazolines have been found to inhibit kinases by competing with ATP for the kinase active site [2a]. Furthermore, as antagonists of melanin-concentrating hormone (MCH), they may be an effective treatment for obesity, reducing food intake and bodyweight [3].

Two subclasses of the quinazoline family are the quinazolinones and the pyrroloquinazolines. Large numbers of quinazolinones have been synthesized or isolated from plants, animals and microorganisms [4], and quinazolin-2(1*H*)-ones, in particular, can have anticonvulsant, antiinflammatory, cardiotonic and anticarcinogenic activities [5]. The pyrrolo[2,1-*b*]-quinazoline nucleus is present in batracylin [6], an anti-cancer DNA-binding agent, and related structures inhibit acetylcholinesterase and may therefore be effective for treatment of Alzheimer's disease [7].

Xanthenes, which include some of the first pigments to have been discovered, are used as linkers in solid phase peptide synthesis and as protectors of the 5'-OH group of nucleosides. Many have interesting biological effects such as inhibition of gastric secretion, and antitumoral, opiaceous or cytotoxic activities [8e].

In view of the above and as a part of a broader search for new structures with potential pharmacological activity [8] we have addressed the synthesis of new quinazolinones (**5**, **6**), quinazolines (**7**-**9**) and pyrrolo-[2,1-*b*]-quinazolines (**13**), resulting from the logical fusion of the xanthene and quinazoline pharmacophores.

RESULTS AND DISCUSSION

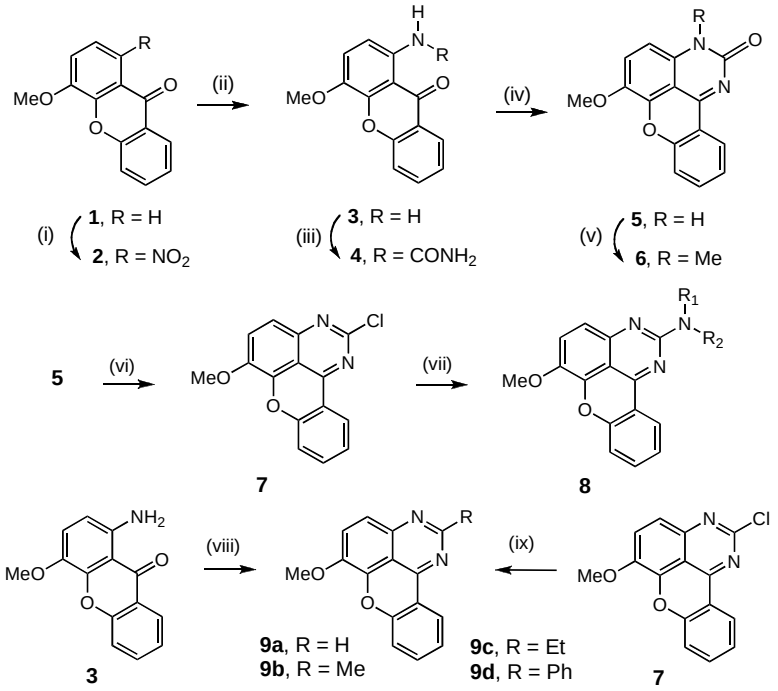
As our starting compound we choose 4-methoxyxanthone (**1**), which can easily be prepared from commercial guayacol and *o*-chlorobenzoic acid [9]. Regioselective nitration of **1** with concentrated nitric acid afforded nitroxanthone **2** [10], on which the dinitrogenated ring of the target molecules was assembled (Scheme 1).

We first tried to synthesize quinazolinone **5** by direct cyclocondensation of aminoxanthenone **3**, which was straightforwardly prepared from **2** in 95% yield by Pd-catalysed hydrogen transfer. However, attempts to condense aminoxanthenone **3** with aminoacylating agents by means of procedures reported for simple quinazolinones [11] met with limited success at best. Refluxing **3** with urea in acetic acid for 1 day afforded **5** only as one component of a complex mixture that we could not resolve, the other compounds being the starting material, its *N*-acetyl derivative and urea **4**. Heating **3** with urea or with ethyl carbamate and $ZnCl_2$ at 190 °C allowed isolation of **5**, but only in 20% yield. In another attempt we prepared the *N*-trichloroacetamido derivative of **3** and heated it with ammonium acetate in DMSO for 30 h, but the product was again a complex mixture. In view of these results we then addressed the stepwise synthesis of quinazolinone **5** *via* urea **4**, which was obtained in 63% yield by treating **3** with potassium cyanate in acetic acid (conditions which normally afford quinazolinones directly) [11b]; the main sideproduct was the *N*-acetyl derivative of **3**. Boiling **4** in a solution of potassium hydroxide in ethanol led to its cyclodehydration, affording quinazolinone **5** in 92% yield. We then converted **5** to the *N*-methylated

compound **6** by treatment with MeI in the presence of NaH.

Quinazolinone **5** provided access to a number of 2-substituted quinazolines *via* its 2-chloro derivative **7**, which was obtained by reaction with $POCl_3$. The first of this series were guanidines **8a**-**8d**, which were obtained by refluxing an alcoholic solution of **7** with hydrazine and primary amines (Table 1, entries 1-4). However, attempts to prepare 2-aminoquinazoline **8e** by direct amination of **7** with solutions of ammonia in water, ethanol or THF led only to recovery of the starting material. Interestingly, when a DMF solution of compound **7** and ammonia in ethanol was refluxed for 6 hours afforded the dimethylamino derivative **8f**, probably as the result of decomposition of the DMF into CO and Me_2NH [12], yield by direct cyclocondensation of aminoxanthenone **3** with formamide, by heating at high temperature under Leuckart conditions. However, this approach was much less efficient for **9b**, which was obtained nevertheless in 47% yield, by refluxing aminoxanthenone **3** and acetamide in CH_3CN for 3 hours in the presence of $POCl_3$, and failed completely when tried with other amides (trimethylacetamide, nicotinamide) under various conditions and with various catalysts.

As the key ring-forming step in the syntheses of pyrrolo-fused systems **13** we envisaged cyclodehydration of aminoamides **12**, which were obtained from nitroxanthone **2** as shown in Scheme 2. Briefly, reduction of **2** with sodium borohydride led quantitatively to nitroxanthenol **10**, which was used to alkylate



Scheme 1. Reagents and conditions. (i) HNO_3, 85 ºC, 45 min., 86%. (ii) HCO_2NH_4, 10% Pd/C, EtOH, reflux, 1 h, 95%. (iii) KOCN, AcOH, r.t., 3 h, 63%. (iv) KOH, EtOH, reflux, 30 min., 92%. (v) NaH, MeI, DMF, 0 ºC, 2 h, 95%. (vi) $POCl_3$, 85 ºC, 3.5 h, 98%. (vii) R_1R_2NH, ROH, reflux (see Table 1 for yields). (viii) For **9a**, $HCONH_2/H_2O$, 175 ºC, 4 h, 95%; for **9b**, CH_3CONH_2, $POCl_3$, CH_3CN, reflux, 3 h, 47%. (ix) For **9c**, EtMgBr, $Fe(acac)_3$, THF, r.t. , 1 h, 41%; for **9d**, PhMgBr, $Fe(acac)_3$, THF, r.t. , 0.2 h, 57%.

followed by nucleophilic attack by the latter (entry 6). Eventually, **8e** was conveniently obtained by hydrogenolysis of the *N*-benzyl derivative **8d** (entry 5). Also, different acyclic and cyclic secondary amines were introduced with the same methodology used before (entries 7-11). Finally, the possibility of introducing carbon nucleophiles was verified by preparation of ethyl and phenyl quinazolines **9c** and **9d**, which were obtained by treatment of **7** with the corresponding Grignard reagents under Fe(III) catalysis (Scheme 1).

In a much shorter but less general approach, quinazoline **9a**, which has no 2-substituent, was obtained in 95% succinimide, phthalimide or pyrrolidin-2-one under acidic conditions to obtain compounds **11a-c** (Table 2). Pd-catalysed hydrogenation in MeOH then afforded amino derivatives **12a-c** in the yields indicated in Table 2. Cyclodehydration of **12a** and **12b** was successfully achieved by acid treatment with $BF_3.Et_2O$ in THF, giving compounds **13a** and **13b**, but the pyrrolidinone derivative **12c** gave an unstable product that we were unable to isolate and purify.

In the case of **13b**, it was found that the last two steps could be carried out in one pot: when **11b** was treated with $SnCl_2$ in DMF at room temperature, or with

Table 1

Quinazolines **8** prepared from chloride **7**.

Entry	Nucleophile	Solvent	Quinazoline	R_1	R_2	Yield (%) [a]
1	H_2N-NH_2	EtOH	**8a**	H	NH_2	85
2	$^{n}PrNH_2$	^{i}PrOH	**8b**	H	^{n}Pr	100
3	$^{n}BuNH_2$	^{i}PrOH	**8c**	H	^{n}Bu	100
4	$BnNH_2$	^{i}PrOH	**8d**	H	Bn	82
5	-	EtOH	**8e** [b]	H	H	51
6	Me_2NH [c]	DMF	**8f**	Me	Me	90
7	Et_2NH	^{i}PrOH	**8g**	Et	Et	90
8	Pyrrolidine	^{i}PrOH	**8h**	-$(CH_2)_4$-		81
9	Piperidine	^{i}PrOH	**8i**	-$(CH_2)_5$-		65
10	Morpholine	^{i}PrOH	**8j**	-$(CH_2)_2O(CH_2)_2$-		95
11	*N*-Methylpiperazine	^{i}PrOH	**8k**	-$(CH_2)_2N(Me)(CH_2)_2$-		63

[a] Yields of chromatographically pure products. [b] Prepared by hydrogenolysis of **8d**. [c] Result of decomposition of DMF at high temperatures.

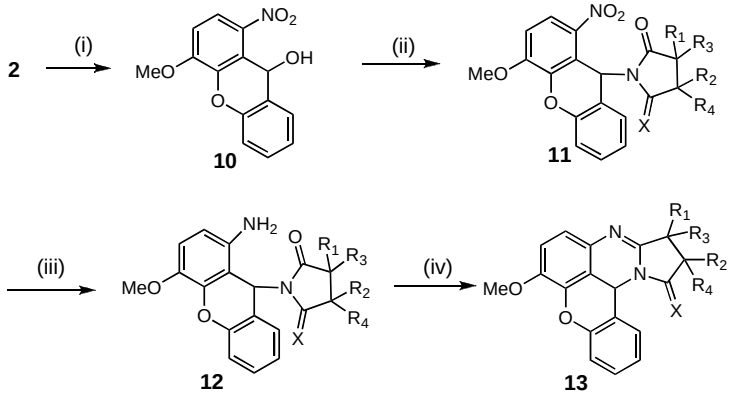


Table 2

Compounds prepared from xanthenol **10**.

Entry	X	R_1	R_2	R_3	R_4	Imide	Time (h)	Yield (%)	Yield (%)	Yield (%)
1	O	H	H	H	H	Succinimide	23	**11a** (88)	**12a** (61)	**13a** (47)
2	O	-C_4H_4-		-bond-		Phthalimide	7	**11b** (56)	**12b** (27)	**13b** (72)
3	H_2	H	H	H	H	Pyrrolidin-2-one	2	**11c** (57)	**12c** (74)	**13c** (-)

Scheme 2. Reagents and conditions: (i) $NaBH_4$, EtOH, reflux, 1 h, quant. (ii) Imide, AcOH, reflux (see Table 2 for conditions and yields). (iii) H_2, 10% Pd/C, MeOH, r.t., 5 h. (iv) $BF_3{\cdot}Et_2O$, THF, reflux, 3 h.

hydrogen and 10% Pd/C in THF, the reduced product **12b** spontaneously cyclized to the hexacyclic system in 28% and 21% yield respectively. However, unexpectedly these procedures failed to afford **13a** directly from **11a**.

In conclusion, we have synthesized a variety of new chromenoquinazolinones and quinazolines from easily prepared 4-methoxy-1-nitroxanthen-9-one by efficient assembly of the 1,3-diazine ring on the xanthene scaffold.

EXPERIMENTAL

Melting points were measured using a Büchi melting point apparatus and are uncorrected. IR spectra were recorded on a Bruker IFS-66v spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 500, a Varian Inova 400, a Varian Mercury 300 and a Bruker DPX 250. Mass spectra were recorded on a Hewlett-Packard 5988-A (Electron Impact, EI), a Finningan Trace-MS (Chemical Ionization, CI), a Hewlett-Packard 6890-N (GC-CI), a Micromass Autospec (high resolution EI and CI) and a Bruker Biotof II (ElectroSpray-Time of Flight, ESI-TOF). Elemental analysis were performed at the RIAIDT of the University of Santiago. Reactions were monitored by thin-layer chromatography (TLC) using Merck slides precoated with silica gel 60-F_{254}. Column chromatography was performed using Merck silica gel (60-120 mesh size).

4-Methoxy-1-nitro-9*H*-xanthen-9-one (2). A solution of 4-methoxy-9*H*-xanthen-9-one [9] (7.411 g, 32.79 mmol) in 60% HNO_3 (75 mL) was cooled to 0 °C for 20 min and then heated to 85 ºC. After 45 min at this temperature, ice/water was added (400 mL) and the mixture was stored in the refrigerator overnight. The resulting suspension was filtered and the collected solid was washed with ice/water until the washings were of pH 7, affording **2** (7.701g, 86%) as a yellow solid, MP: 235-240 ºC; IR (KBr): 1672, 1538 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.10 (s, 3 H, OCH_3), 7.19 (d, J = 8.6 Hz, 1 H, ArH), 7.41 (d, J = 8.6 Hz, 1 H, ArH), 7.42-7.47 (m, 1 H, ArH), 7.61 (d,

J = 8.6 Hz, 1 H, ArH), 7.75-7.81 (m, 1 H, ArH), 8.28 (dd, *J* = 7.8, 1.6 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 56.8 (OCH_3), 112.9 (CH), 114.8 (C), 118.0 (CH), 118.4 (CH), 121.8 (C), 125.1 (CH), 126.8 (CH), 135.5 (CH), 141.5 (C), 146.3 (C), 150.9 (C), 155.2 (C), 173.7 (CO); MS (CI): *m/z* (%) 272 (100) [M^+ + H]. MS (EI): *m/z* (%) 225 (41) [M^+ - NO_2], 271 (100) [M^+]; HRMS-EI: *m/z* calcd. for $C_{14}H_9NO_5$: 271.0481; found: 271.0480. *Anal.* Calcd. for $C_{14}H_9NO_5$: C, 62.00; H, 3.34; N, 5.16; found: C, 61.84; H, 3.33; N, 5.15.

1-Amino-4-methoxy-9*H*-xanthen-9-one (3). Ammonium formate (1.985 g, 30.4 mmol) and 10% Pd/C (0.25 g, 0.25 mmol) were added to a solution of nitroxanthenone **2** (1.327 g, 4.90 mmol) in EtOH (250 mL) and the mixture was refluxed under argon for 1 h, filtered through a celite pad and washed with EtOH (3 x 25 mL). The solvent was evaporated and the residue was partitioned between dichloromethane and water. The organic phase was washed with brine (3 x 10 mL), dried with Na_2SO_4 and filtered, and removal of the solvent under reduced pressure afforded **3** (1.122 g, 95%) as an orange solid, MP: 160-165 ºC; IR (KBr): 3465, 1647 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.92 (s, 3 H, OCH_3), 6.30 (br s, 2 H, NH_2), 6.38 (d, *J* = 8.8 Hz, 1 H, ArH), 7.13 (d, *J* = 8.8 Hz, 1 H, ArH), 7.28-7.34 (m, 1 H, ArH), 7.49 (d, *J* = 7.3 Hz, 1 H, ArH), 7.61-7.68 (m, 1 H, ArH), 8.23 (dd, *J* = 8.1, 1.5 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 58.2 (OCH_3), 107.6 (CH), 108.4 (C), 117.6 (CH), 121.5 (CH), 121.8 (C), 123.6 (CH), 126.1 (CH), 134.3 (CH), 137.8 (C), 144.9 (C), 147.3 (C), 155.2 (C), 179.8 (CO); MS (CI): *m/z* (%) 242 (100) [M^+ + H]. MS (EI): *m/z* (%) 226 (100) [M^+ – CH_3], 241 (39) [M^+]. HRMS-EI: *m/z* calcd.for $C_{14}H_{11}NO_3$: 241.0739; found: 241.0746. *Anal.* Calcd. for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81; found: C, 69.90; H, 4.58; N, 5.80.

1-(4-Methoxy-9-oxo-9*H*-xanthen-1-yl)urea (4). To a degassed solution of aminoxanthenone **3** (0.587 g, 2.44 mmol) in AcOH (130 mL), stirred at room temperature, KOCN (0.267 g, 3.17 mmol) was added portion wise for a period of 3 h. The solvent was evaporated and the residue was partitioned between dichloromethane and water. The organic phase was washed with brine (3 x 10 mL), dried with Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. Purification by flash chromatography on silica gel (97:3, CH_2Cl_2:MeOH) gave **4** (0.409 g, 63%) as an amorphous orange solid. IR (KBr): 3355, 2833, 1699, 1683 cm^{-1}; ^{1}H NMR ($(CD_3)_2SO$, 300 MHz): δ 3.91 (s, 3 H, OCH_3), 6.60 (br s, 2 H, NH_2), 7.43-7.51 (m, 2 H, ArH), 7.64 (d, *J* = 8.1 Hz, 1 H, ArH), 7.82-7.89 (m, 1 H, ArH), 8.15 (d, *J* = 8.1 Hz, 1 H, ArH), 8.28 (d, *J* = 9.5 Hz, 1 H, ArH), 11.07 (s, 1 H, NH). ^{13}C NMR ($(CD_3)_2SO$, 75 MHz): δ 56.6 (OCH_3), 109.3 (C), 111.7 (CH), 117.9 (CH), 118.9 (CH), 120.9 (C), 124.5 (CH), 125.7 (CH), 135.70 (CH), 135.73 (C), 141.0 (C), 145.7 (C), 154.6 (C), 155.9 (C), 179.5 (CO); MS (EI): *m/z* (%) 268 (7) [M^+ - NH_2], 284 (14) [M^+]. HRMS-EI: *m/z* calcd. for $C_{17}H_{18}N_2O_4$: 314.1267; found: 314.1270. *Anal.* Calcd. for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.77; N, 8.91; found: C, 64.89; H, 5.75; N, 8.89.

6-Methoxy-2,3-dihydrochromeno[4,3,2-*de*]quinazolin-2-one (5). KOH (0.117 g, 1.89 mmol) was added to a suspension of urea **4** (0.245 g, 0.86 mmol) in EtOH (150 mL) and the mixture was refluxed under argon for 30 min. Dichloromethane (20 mL) was added, the resulting suspension was filtered, and the collected solid was washed with water (3 x 10 mL), affording **5** (0.210 g, 92%) as an orange solid, MP: 290-295 ºC; IR (KBr): 3433, 1671, 1607 cm^{-1}; ^{1}H NMR ($(CD_3)_2SO$, 500 MHz): δ 3.91 (s, 3 H, OCH_3), 6.90 (d, *J* = 8.5 Hz, 1 H, ArH), 7.44-7.49 (m, 1 H, ArH), 7.58 (d, *J* = 8.1 Hz, 1 H, ArH), 7.62 (d, *J* = 8.5 Hz, 1 H, ArH), 7.77-7.83 (m, 1 H, ArH), 8.34 (d, *J* = 8.1 Hz, 1 H, ArH), 11.30 (br s, 1 H, NH); ^{13}C NMR ($(CD_3)_2SO$, 100 MHz): δ 56.8 (OCH_3), 105.0 (C), 106.2 (CH), 118.10 (CH), 118.13 (C), 121.3 (CH), 124.9 (CH), 125.0 (CH), 135.4 (CH), 135.6 (C), 140.0 (C), 140.1 (C), 154.6 (C), 155.9 (C), 159.9 (C); MS (CI): *m/z* (%) 267 (100) [M^+ + H]; MS (EI): *m/z* (%) 223 (93) [M^+ - HNCO], 251 (100) [M^+ - CH_3], 266 (M^+, 87); MS (ESI-TOF): *m/z* (%) 267 (62) [M^+ + H]; HRMS-ESI-TOF: *m/z* calcd. for $C_{15}H_{11}N_2O_3$: 267.0764; found: 267.0762. *Anal.* Calcd. for $C_{15}H_{10}N_2O_3$: C, 67.67; H, 3.79; N, 10.52; found: C, 67.70; H, 3.80; N, 10.54.

6-Methoxy-3-methyl-2,3-dihydrochromeno[4,3,2-*de*]-quinazolin-2-one (6). A solution of quinazolinone **5** (0.060 g, 0.22 mmol) in DMF (12 mL) was deoxygenated by passage of argon and added to a deoxygenated suspension of NaH (0.111 g, 2.42 mmol, washed with HPLC hexane) in DMF (3 mL). The mixture was stirred at room temperature under argon for 15 minutes, and was then cooled to 0 ºC for addition of MeI (0.750 mL, 1.25 mmol), after which stirring continued for 2 h. Aqueous NH_4Cl solution (30 mL) was added, the mixture was extracted with dichloromethane (3 x 10 mL), the organic layer was washed with brine (3 x 10 mL), dried with Na_2SO_4 and filtered, and removal of the solvent under reduced pressure afforded **6** (0.060 g, 95%) as an orange solid, MP: 230-233 ºC; IR (KBr): 3438, 1657, 1631, 1607, 1564 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.64 (s, 3 H, NCH_3), 4.01 (s, 3 H, OCH_3), 6.84 (d, *J* = 8.8 Hz, 1 H, ArH), 7.36-7.44 (m, 2 H, ArH), 7.51 (dd, *J* = 8.5, 0.9 Hz, 1 H, ArH), 7.67-7.75 (m, 1 H, ArH), 8.63 (dd, *J* = 8.6, 1.9 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 30.8 (NCH_3), 57.1 (OCH_3), 105.0 (CH), 106.3 (C), 117.8 (CH), 118.3 (C), 119.9 (CH), 124.8 (CH), 126.0 (CH), 134.9 (CH), 136.5 (C), 141.1 (C), 141.4 (C), 154.8 (C), 156.7 (C), 159.2 (C); MS (CI): *m/z* (%) 281 (100) [M^+ + H]; MS (EI): *m/z* (%) 265 (100) [M^+ - CH_3], 280 (61) [M^+]. HRMS-EI: *m/z* calcd. for $C_{16}H_{12}N_2O_3$: 280.0848; found: 280.0849. *Anal.* Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 9.99; found: C, 68.60; H, 4.34; N, 10.02.

2-Chloro-6-methoxychromeno[4,3,2-*de*]quinazoline (7). A suspension of quinazolinone **5** (0.155 g, 0.58 mmol) in $POCl_3$ (20 mL) was heated at 85 ºC under argon for 3.5 h. The solvent was evaporated, 1 *N* NaOH solution was added until the solution was pH 7 and this mixture was extracted with dichloromethane (3 x 20 mL), the organic layer was washed with brine (3 x 10 mL), dried with Na_2SO_4 and filtered, and removal of the solvent under reduced pressure, afforded **7** (0.163 g, 98%) as a yellow solid, MP: 250-260 ºC; IR (KBr): 1574 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 4.09 (s, 3 H, OCH_3), 7.32-7.40 (m, 1 H, ArH), 7.46 (dd, *J* = 8.5, 0.6 Hz, 1 H, ArH), 7.58 (d, *J* = 9.1 Hz, 1 H, ArH), 7.68-7.72 (m, 2 H, ArH), 8.49 (dd, *J* = 7.9, 1.6 Hz, 1 H, ArH). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 57.2 (OCH_3), 117.9 (CH), 118.4 (C), 118.5 (CH), 121.8 (CH), 124.8 (CH), 125.5 (CH), 135.0 (CH), 139.0 (C), 142.6 (C), 143.0 (C), 144.6 (C), 155.6 (C), 157.9 (C), 158.9 (C); MS (CI): *m/z* (%)249 (73) [M^+ – Cl], 285 (100) [M^+ + H], 287 (34) [M^+ + H + 2]; MS (EI): *m/z* (%) 269 (100) [M^+ - CH_3], 269 (35) [M^+ - CH_3 + 2], 271 (35) [M^+ - OCH_3 + 2], 284 (48) [M^+], 286 (17) [M^+ + 2]; HRMS-EI: *m/z* calcd.for $C_{15}H_9N_2O_2Cl$: 284.0353; found: 284.0356. *Anal.* Calcd. for $C_{15}H_9ClN_2O_2$: C, 63.28; H, 3.19; N, 9.84; found: C, 63.40; H, 3.20; N, 9.86.

6-Methoxychromeno[4,3,2-*de*]quinazolin-2-yl)hydrazine (8a). Hydrazine monohydrate (0.3 mL, 8.4 mmol) was added to

a suspension of chloroquinazoline **7** (0.069 g, 0.24 mmol) in EtOH (29 mL) and the mixture was refluxed under argon for 3 h. The solvent was evaporated, 1 *N* NaOH solution was added until the medium was basic, and this mixture was extracted with dichloromethane (3 x 20 mL). The organic phase was washed with brine (3 x 10 mL), dried with Na_2SO_4 and filtered, and the solvent was removed under reduced pressure, leaving **8a** (0.057 g, 85%) as an orange solid, MP: 225-235 ºC; ^{1}H NMR ($(CD_3)_2SO$, 300 MHz): δ 3.93 (s, 3 H, OCH_3), 4.30 (s, 2 H, NH_2), 7.14 (d, *J* = 9.0 Hz, 1 H, ArH), 7.35-7.40 (m, 1 H, ArH), 7.46 (d, *J* = 8.3 Hz, 1 H, ArH), 7.63-7.71 (m, 2 H, ArH), 8.17 (br s, 1 H, NH), 8.29 (d, *J* = 9.0 Hz, 1 H, ArH); ^{13}C NMR ($(CD_3)_2SO$, 75 MHz): δ 56.9 (OCH_3), 108.5 (C), 115.5 (CH), 117.4 (CH), 118.3 (C), 123.4 (CH), 123.9 (CH), 124.0 (CH), 133.8 (CH), 138.3 (C), 138.6 (C), 145.1 (C), 154.3 (C), 155.1 (C), 161.1 (C); MS (CI): *m/z* (%) 264 (18) [$M^+ - NH_2$], 265 (73) [$M^+ - CH_3$], 281 (100) [$M^+ + H$]; MS (ESI-TOF): *m/z* (%) 281 (100) [$M^+ + H$]; HRMS-ESI-TOF: *m/z* calcd. for $C_{15}H_{13}N_4O_2$: 281.1033; found: 281.1040. *Anal.* Calcd. for $C_{15}H_{12}N_4O_2$: C, 64.28; H, 4.32; N, 19.99; found: C, 64.40; H, 4.32; N, 19.97.

6-Methoxy-*N*-propyl-chromeno[4,3,2-*de*]quinazolin-2-amine (8b). Propylamine (4.0 mL, 47.6 mmol) was added to a suspension of 2-chloroquinazoline **7** (0.058 g, 0.20 mmol) in 2-propanol (25 mL) and the mixture was refluxed under argon for 14 h. The solvent was evaporated and the residue was partitioned between dichloromethane and water. The organic layer was washed with brine (3 x 10 mL), dried with Na_2SO_4 and filtered, and the solvent was removed under reduced pressure, leaving **8b** (0.061 g, 100%) as an orange solid, MP: 143-145 ºC; IR (KBr): 3366, 1571 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.04 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.67-1.74 (m, 2 H, CH_2), 3.49-3.56 (m, 2 H, CH_2), 4.00 (s, 3 H, OCH_3), 5.18 (br s, 1 H, NH), 7.17 (d, *J* = 9.0 Hz, 1 H, ArH), 7.24-7.29 (m, 1 H, ArH), 7.35 (d, *J* = 8.3 Hz, 1 H, ArH), 7.43 (d, *J* = 9.3 Hz, 1 H, ArH), 7.49-7.54 (m, 1 H, ArH), 8.32 (d, *J* = 7.8 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.7 (CH_3), 23.1 (CH_2), 43.4 (CH_2), 57.8 (OCH_3), 109.4 (C), 115.9 (CH), 117.7 (CH), 119.2 (C), 122.2 (CH), 123.9 (CH), 124.6 (CH), 133.4 (CH), 138.7 (C), 139.8 (C), 146.3 (C), 155.2 (C), 156.4 (C), 159.8 (C); MS (CI): *m/z* (%) 308 (100) [$M^+ + H$]; MS (EI): *m/z* (%) 249 (13) [$M^+ - NHPr$], 264 (18) [$M^+ - CH_2CH_2CH_3$], 278 (38) [$M^+ - CH_2CH_3$], 292 (53) [$M^+ - CH_3$], 307 (59) [$M]^+$; EI-HRMS: *m/z* calcd. for $C_{18}H_{17}N_3O_2$: 307.1321; found: 307.1310. *Anal.* Calcd. for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67; found: C, 70.50; H, 5.60; N, 13.65.

***N*-Butyl-6-methoxychromeno[4,3,2-*de*]quinazolin-2-amine (8c).** Butylamine (2.0 mL, 19.8 mmol) was added to a suspension of 2-chloroquinazoline **7** (0.045 g, 0.16 mmol) in 2-propanol (25 mL) and the mixture was refluxed under argon for 16 h. Work-up as for **8b** afforded **8c** (0.051 g, 100%) as an orange solid, MP: 130-135 ºC; IR (KBr): 3365, 1567 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.98 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.41-1.53 (m, 2 H, CH_2), 1.71-1.61 (m, 2 H, CH_2), 3.51-3.58 (m, 2 H, CH_2), 3.98 (s, 3 H, OCH_3), 5.17 (t, *J* = 5.4 Hz, 1 H, NH), 7.15 (d, *J* = 9.0 Hz, 1 H, ArH), 7.21-7.27 (m, 1 H, ArH), 7.37 (dd, *J* = 8.2, 0.7 Hz, 1 H, ArH), 7.44 (d, *J* = 9.0 Hz, 1 H, ArH), 7.50-7.56 (m, 1 H, ArH), 8.34 (dd, *J* = 7.9, 1.6 Hz, 1 H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.0 (CH_3), 20.3 (CH_2), 32.1 (CH_2), 41.3 (CH_2), 57.7 (OCH_3), 109.3 (C), 115.9 (CH), 117.6 (CH), 119.2 (C), 122.1 (CH), 123.8 (CH), 124.5 (CH), 133.4 (CH), 138.6 (C), 139.7 (C), 146.3 (C), 155.1 (C), 156.3 (C), 159.7 (C);MS (CI): *m/z* (%) 322 (100) [$M^+ + H$]; MS (EI): *m/z* (%) 264 (55) [$M^+ - CH_2CH_2CH_2CH_3$], 278 (57) [$M^+ - CH_2CH_2CH_3$], 309 (35) [$M^+ - CH_2CH_3$], 306 (32) [$M^+ - CH_3$], 321 (74) [M^+]; HRMS-EI: *m/z* calcd. for $C_{19}H_{19}N_3O_2$: 321.1511; found: 321.1470. *Anal.* Calcd. for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.08; found: C, 71.10; H, 5.95; N, 13.10.

***N*-Benzyl-6-methoxychromeno[4,3,2-*de*]quinazolin-2-amine (8d).** Benzylamine (0.5 mL, 4.54 mmol) was added to a suspension of 2-chloroquinazoline **7** (0.030 g, 0.11 mmol) in 2-propanol (4 mL) and the mixture was refluxed under argon for 27 h. Work-up as for **8b** led to a crude product that was purified by flash chromatography on silica gel (3:1, hexanes:EtOAc), providing **8d** (0.032 g, 82%) as an orange solid, MP: 175-180 ºC; IR (KBr): 3427, 1602 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.97 (s, 3 H, OCH_3), 4.74 (d, *J* = 5.8 Hz, 2 H, CH_2), 5.50 (br s, 1 H, NH), 7.14-7.30 (m, 5 H, ArH), 7.34-7.39 (m, 3 H, ArH), 7.44 (d, *J* = 9.0 Hz, 1 H, ArH), 7.48-7.54 (m, 1 H, ArH), 8.31 (d, *J* = 7.8 Hz, 1 H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 45.7 (CH_2), 57.7 (OCH_3), 109.5 (C), 116.0 (CH), 117.6 (CH), 119.1 (C), 122.1 (CH), 123.9 (CH), 124.6 (CH), 127.0 (CH), 127.6 (2 x CH), 128.4 (2 x CH), 133.4 (CH), 138.8 (C), 139.3 (C), 139.7 (C), 146.0 (C), 155.1 (C), 156.5 (C), 159.4 (C); MS (EI): *m/z* (%) = 340 (41) [$M^+ - CH_3$], 355 (81) [M^+]; EI-HRMS: *m/z* calcd. for $C_{22}H_{17}N_3O_2$: 355.1321; found: 355.1305. *Anal.* Calcd. for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82; found: C, 74.40; H, 4.80; N, 11.80.

6-Methoxychromeno[4,3,2-*de*]quinazolin-2-amine (8e). A suspension of 2-benzylaminoquinazoline **8d** (0.060 g, 0.17 mmol), ammonium formate (0.202 g, 3.01mmol) and 10% Pd/C (0.068 g, 0.07 mmol) in EtOH (30 mL) was refluxed under argon for 1 day. The mixture was filtered through a celite pad and washed with EtOH (3 x 15 mL), and the solvent was evaporated. The residue was partitioned between dichloromethane and water, and the organic layer was washed with water (3 x 10 mL), dried with Na_2SO_4, filtered and concentrated. Purification by flash chromatography on silica gel (95:5, CH_2Cl_2:MeOH) gave **8e** (0.023 g, 51%) as an orange solid, MP: 230-235 ºC; IR (KBr): 3484, 1567 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.98 (s, 3 H, OCH_3), 5.05 (br s, 2 H, NH_2), 7.13 (d, *J* = 9.0 Hz, 1 H, ArH), 7.20-7.27 (m, 1 H, ArH), 7.37 (d, *J* = 8.3 Hz, 1 H, ArH), 7.47 (d, *J* = 9.0 Hz, 1 H, ArH), 7.51-7.57 (m, 1 H, ArH), 8.35 (dd, *J* = 7.8, 1.4 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 57.7 (OCH_3), 109.7 (C), 115.9 (CH), 117.8 (CH), 119.1 (C), 122.4 (CH), 124.1 (CH), 124.8 (CH), 133.8 (CH), 139.3 (C), 139.7 (C), 145.9 (C), 155.2 (C), 157.3 (C), 160.2 (C); MS (CI): *m/z* (%)266 (100) [$M^+ + H$]; MS (EI): *m/z* (%) = 250 (100) [$M^+ - CH_3$], 265 (35) [M^+]; EI-HRMS: *m/z* calcd. for $C_{15}H_{11}N_3O_2$: 265.0851; found: 265.0858. *Anal.* Calcd. for $C_{15}H_{11}N_3O_2$: C, 67.92; H, 4.18; N, 15.84; found: C, 67.85; H, 4.20; N, 15.82.

***N*,*N*-Dimethyl-6-methoxychromeno[4,3,2-*de*]quinazolin-2-amine (8f).** A suspension of 2-chloroquinazoline **7** (0.015 g, 0.05 mmol) in DMF (4 mL) was treated with an ethanolic solution of ammonia (1.0 mL, 7.76 mmol) and refluxed under argon for 6 h. The ethanol was removed under vacuum, the mixture was brought to pH 5 with 10% HCl solution and then extracted with dichloromethane (3 x 20 mL). The organic phase was washed with brine (3 x 10 mL), dried with Na_2SO_4 and filtered, and the solvent was removed under reduced pressure, leaving **8f** (0.013 g, 90%) as an orange solid, MP: 150-153 ºC; IR (KBr): 1600, 1565; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.32 (s, 6 H, $N(CH_3)_2$), 3.99 (s, 3 H, OCH_3), 7.15 (d, *J* = 9.0 Hz, 1 H, ArH), 7.22-7.28 (m, 1 H, ArH), 7.37 (dd, *J* = 8.3, 0.9 Hz, 1 H, ArH), 7.43 (d, *J* = 9.0 Hz, 1 H, ArH), 7.49-7.56 (m, 1 H, ArH),

8.40 (dd, *J* = 7.9, 1.7 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 37.2 ($N(CH_3)_2$), 57.9 (OCH_3), 108.3 (C), 115.9 (CH), 117.6 (CH), 119.7 (C), 122.4 (CH), 123.7(CH), 124.6 (CH), 133.2 (CH), 138.2 (C), 139.7 (C), 146.8 (C), 155.2 (C), 155.6 (C), 159.9 (C); MS (CI): *m/z* (%)294 (100) [M^+ + H]; MS (EI): *m/z* (%) = 249 (9) [M^+ - $N(CH_3)_2$], 278 (100) [M^+ - CH_3], 293 (56) [M^+]; EI-HRMS: *m/z* calcd. for $C_{17}H_{15}N_3O_2$: 293.1164; found: 293.1162. *Anal.* Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33; found: C, 69.82; H, 5.17; N, 14.33.

***N,N*-Diethyl-6-methoxychromeno[4,3,2-*de*]quinazolin-2-amine (8g).** Diethylamine (1.0 mL, 9.53 mmol) was added to a suspension of 2-chloroquinazoline **7** (0.024 g, 0.12 mmol) in 2-propanol (3.0 mL) and the mixture was refluxed under argon for 23 h. The solvent was evaporated and the residue was dissolved in dichloromethane (50 mL) and was washed with a saturated solution of $NaHCO_3$ (3 x 10 mL), dried with Na_2SO_4 and filtered, and the solvent was removed under reduced pressure, leaving **8g** (0.026 g, 90%) as an amorphous orange solid. IR (KBr): 2932, 1560 cm^{-1}; ^{1}H-RMN ($CDCl_3$, 300 MHz): δ 1.27 (t, *J* = 7.0 Hz, 6 H, CH_3), 3.79 (q, *J* = 7.0 Hz, 4 H, CH_2), 5.58 (s, 3 H, OCH_3), 7.15 (d, *J* = 9.0 Hz, 1 H, ArH), 7.24-7.30 (m, 1 H, ArH), 7.39 (dd, *J* = 8.4, 0.8 Hz, 1 H, ArH), 7.45 (d, *J* = 9.1 Hz, 1 H, ArH), 7.51-7.59 (m, 1 H, ArH), 8.42 (dd, *J* = 7.8, 1.5 Hz, 1 H, ArH); ^{13}C-RMN ($CDCl_3$, 75 MHz): δ = 13.4 (2 x CH_3), 41.8 (2 x CH_2), 57.9 (OCH_3), 108.5 (C), 116.1 (CH), 117.7 (CH), 120.0 (C), 122.5 (CH), 123.8 (CH), 124.7 (CH), 133.1 (CH), 138.0 (C), 139.9 (C), 147.4 (C), 155.3 (C), 155.7 (C), 158.9 (C); MS (CI): *m/z* (%) 321 (59) [M^+], 322 (100) [M^+ + H]; MS (EI): *m/z* (%) 249 (21) [M^+ – $N(CH_2CH_3)_2$], 306 (38) [M^+- CH_3], 321 (49) [M^+]; EI-HRMS: *m/z* calcd. for $C_{19}H_{19}N_3O_2$: 321.1477; found: 321.1476. *Anal.* Calcd. for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.08; found: C, 71.10; H, 5.94; N, 13.10.

6-Methoxy-2-(pyrrolidin-1-yl)chromeno[4,3,2-*de*]quinazoline (8h). Pyrrolidine (1.6 mL, 19.0 mmol) was added to a suspension of 2-chloroquinazoline **7** (0.052 g, 0.18 mmol) in 2-propanol (3.4 mL) and the mixture was refluxed under argon for 22 h. Work-up as for **8g** led to a crude product that was purified by flash chromatography on silica gel (6:4, hexanes:EtOAc) giving **8h** (0.046 g, 81%) as an orange solid, MP: 155-157 ºC; IR (KBr): 2930, 1559 cm^{-1}; ^{1}H-RMN ($CDCl_3$, 250 MHz): δ 1.96-2.06 (m, 4 H, CH_2), 3.69-3.74 (m, 4 H, CH_2), 3.98 (s, 3 H, OCH_3), 7.16 (d, *J* = 9.1 Hz, 1 H, ArH), 7.20-7.27 (m, 1 H, ArH), 7.35 (dd, *J* = 8.4, 0.8 Hz, 1 H, ArH), 7.42 (d, *J* = 9.1 Hz, 1 H, ArH), 7.48-7.55 (m, 1 H, ArH), 8.39 (dd, *J* = 7.9, 1.6 Hz, 1 H, ArH); ^{13}C-RMN ($CDCl_3$, 62.5 MHz): δ = 25.5 (2 x CH_2), 46.7 (2 x CH_2), 57.7 (OCH_3), 108.5 (C), 115.8 (CH), 117.5 (C), 119.7 (CH), 122.2 (CH), 123.7 (CH), 124.6 (CH), 133.1 (CH), 138.0 (C), 139.7 (C), 147.0 (C), 155.2 (C), 155.6 (C), 158.1 (C); MS (EI): *m/z* (%) 249 (31) [M^+ – $N(CH_2)_4$], 304 (95) [M^+- CH_3], 319 (100) [M^+]; EI-HRMS: *m/z* calcd. for $C_{19}H_{17}N_3O_2$: 319.1321; found: 319.1308. *Anal.* Calcd. for $C_{19}H_{17}N_3O_2$: C, 71.46; H, 5.37; N, 10.02; found: C, 71.50; H, 5.40; N, 10.01.

6-Methoxy-2-(piperidin1-yl)chromeno[4,3,2-*de*]quinazoline (8i). Piperidine (1.2 mL, 12.0 mmol) was added to a suspension of 2-chloroquinazoline **7** (0.033 g, 0.12 mmol) in 2-propanol (3.8 mL) and the mixture was refluxed under argon for 22 h. Work-up as for **8g** led to a crude product that was purified by flash chromatography on silica gel (6:4, hexanes:EtOAc) giving **8i** (0.026 g, 65%) as an orange solid, MP: 147-149 ºC; IR (KBr): 2920, 1563 cm^{-1}; ^{1}H-RMN ($CDCl_3$, 250 MHz): δ 1.62-1.74 (m, 6 H, CH_2), 3.96-3.99 (m, 4 H, CH_2), 4.00 (s, 3 H, OCH_3), 7.15 (d, *J* = 9.0 Hz, 1 H, ArH), 7.24-7.30 (m, 1 H, ArH), 7.39 (dd, *J* = 8.4, 0.8 Hz, 1 H, ArH), 7.45 (d, *J* = 9.1 Hz, 1 H, ArH), 7.50-7.60 (m, 1 H, ArH), 8.42 (dd, *J* = 7.9, 1.7 Hz, 1 H, ArH); ^{13}C-RMN ($CDCl_3$, 62.5 MHz): δ 25.0 (CH_2), 26.0 (2 x CH_2), 45.0 (2 x CH_2), 57.7 (OCH_3), 108.5 (C), 116.0 (CH), 117.7 (CH), 119.8 (C), 122.3 (CH), 123.8 (CH), 124.8 (CH), 133.3 (CH), 138.4 (C), 139.8 (C), 146.9 (C), 155.3 (C), 155.9 (C), 159.4 (C); MS (EI): *m/z* (%) 249 (20) [M^+ – $N(CH_2)_5$], 318 (83) [M^+- CH_3], 333 (100) [M^+]; MS (CI): *m/z* (%) = 333 (57) [M^+], 334 (100) [M^+ + H]; EI-HRMS: *m/z* calcd. for $C_{20}H_{19}N_3O_2$: 333.1477; found: 333.1483; CI-HRMS: *m/z* calcd. for $C_{20}H_{19}N_3O_2$: 333.1477; found: 333.1484. *Anal.* Calcd. for $C_{20}H_{19}N_3O_2$: C, 72.05; H, 5.74; N, 12.60; found: C, 72.10; H, 5.70; N, 12.57.

6-Methoxy-2-morpholinochromeno[4,3,2-*de*]quinazoline (8j). Morpholine (1.0 mL, 11.4 mmol) was added to a suspension of 2-chloroquinazoline **7** (0.034 g, 0.12 mmol) in 2-propanol (4.0 mL) and the mixture was refluxed under argon for 22 h. Work-up as for **8g** gave **8j** (0.036 g, 95%) as an orange solid, MP: 200-204 ºC; IR (KBr): 2949, 1564 cm^{-1}; ^{1}H-RMN ($CDCl_3$, 250 MHz): δ 3.82-3.85 (m, 4 H, CH_2), 3.97-4.01 (m, 7 H, OCH_3 + CH_2), 7.18 (d, *J* = 9.0 Hz, 1 H, ArH), 7.24-7.30 (m, 1 H, ArH), 7.40 (dd, *J* = 8.4, 0.8 Hz, 1 H, ArH), 7.48 (d, *J* = 9.1 Hz, 1 H, ArH), 7.53-7.60 (m, 1 H, ArH), 8.39 (dd, *J* = 7.9, 1.6 Hz, 1 H, ArH); ^{13}C-RMN ($CDCl_3$, 62.5 MHz): δ 44.6 (2 x CH_2), 57.6 (OCH_3), 67.0 (2 x CH_2), 109.0 (C), 116.2 (CH), 117.7 (CH), 119.5 (C), 122.3 (CH), 123.9 (CH), 124.7 (CH), 133.5 (CH), 138.9 (C), 139.7 (C), 146.4 (C), 155.3 (C), 156.2 (C), 159.3 (C); MS (CI): *m/z* (%) 335 (39) [M]$^+$, 336 (100) [M^+ + H]; MS (EI): *m/z* (%) 249 (22) [M^+ - $N(CH_2)_4O$], 304 (74) [M^+ - OCH_3], 320 (41) [M^+- CH_3], 335 (100) [M^+]; EI-HRMS: *m/z* calcd. for $C_{19}H_{17}N_3O_3$: 335.1270; found: 335.1262. *Anal.* Calcd. for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53; found: C, 68.15; H, 5.14; N, 12.50.

6-Methoxy-2-(4-methylpiperazin-1-yl)chromeno[4,3,2-*de*]-quinazoline (8k). *N*-Methylpiperazine (1.0 mL, 8.9 mmol) was added to a suspension of 2-chloroquinazoline **7** (0.055 g, 0.19 mmol) in 2-propanol (15 mL) and the mixture was refluxed under argon for 4 h. Work-up as for **8b** led to a crude product that was purified by flash chromatography on silica gel (94:6, CH_2Cl_2:MeOH), providing **8k** (0.042 g, 63%) as an orange solid, MP: 160-164 ºC; IR (KBr): 1596, 1564 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.36 (s, 3 H, CH_3), 2.53 (t, *J* = 5.0 Hz, 4 H, CH_2), 3.99-4.04 (m, 7 H, OCH_3 + CH_2), 7.17 (d, *J* = 9.0 Hz, 1 H, ArH), 7.24-7.30 (m, 1 H, ArH), 7.39 (d, *J* = 8.4 Hz, 1 H, ArH), 7.47 (d, *J* = 9.0 Hz, 1 H, ArH), 7.52-7.59 (m, 1 H, ArH), 8.41 (d, *J* = 7.9 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 44.0 (2 x CH_2), 46.3 (CH_3), 55.1 (2 x CH_2), 57.7 (OCH_3), 108.9 (C), 116.2 (CH), 117.7 (CH), 119.6 (C), 122.3 (CH), 123.9 (CH), 124.8 (CH), 133.5 (CH), 138.7 (C), 139.7 (C), 146.6 (C), 155.3 (C), 156.1 (C), 159.3 (C); MS (EI): *m/z* (%) = 249 (33) [M^+ – $N(CH_2)_4NCH_3$], 333 (9) [M^+ - CH_3], 348 (66) [M^+]; EI-HRMS: *m/z* calcd. for $C_{20}H_{20}N_4O_2$: 348.1586; found: 348.1575. *Anal.* Calcd. for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08; found: C, 68.85; H, 5.74; N, 16.10.

6-Methoxychromeno[4,3,2-*de*]quinazoline (9a). A suspension of aminoxanthenone **3** (0.070 g, 0.29 mmol) in a mixture of formamide (14 mL) and water (0.2 mL) was heated at 175 ºC under argon for 4 h, brought to pH 2 with aqueous 10% HCl solution and extracted with dichloromethane (3 x 20 mL). The organic layer was washed with brine (3 x 10 mL), dried with Na_2SO_4 and filtered and the solvent was removed under reduced pressure, leaving **9a** (0.075 g, 95%) as a yellow solid, MP: 160-164 ºC; IR (KBr): 1613, 1578, 1552 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400

MHz): δ 4.09 (s, 3 H, OCH_3) 7.32-7.36 (m, 1 H, ArH,), 7.42 (dd, *J* = 8.2, 0.8 Hz, 1 H, ArH), 7.61-7.63 (m, 1 H, ArH), 7.64 (d, *J* = 9.0 Hz, 1 H, ArH), 7.70 (d, *J* = 9.0 Hz, 1 H, ArH), 8.47 (dd, *J* = 7.8, 1.6 Hz, 1 H, ArH), 9.00 (s, 1 H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 57.2 (OCH_3), 114.3 (C), 117.9 (CH), 118.0 (C), 119.3 (CH), 119.4 (C), 121.3 (CH), 124.6 (CH), 124.9 (CH), 134.1 (CH), 142.2 (C), 143.5 (C), 144.6 (C), 155.4 (CH), 155.8 (C); MS (CI): *m/z* (%) 251 (100) [M^+ + H]; MS (EI): *m/z* (%) 234 (100) [M^+ – CH_3], 250 (37) [M^+]; EI-HRMS: *m/z* calcd. for $C_{15}H_{10}N_2O_2$: 250.0742; found: 250.0735. *Anal.* Calcd. for $C_{15}H_{10}N_2O_2$: C, 71.99; H, 4.03; N, 11.19; found: C, 71.89; H, 4.08; N, 11.15.

6-Methoxy-2-methylchromeno[4,3,2-*de*]quinazoline (9b). A solution of aminoxanthenone **3** (0.101 g, 0.42 mmol) and acetamide (0.234 g, 3.91 mmol) in acetonitrile (19 mL) was treated with phosphorus oxychloride (0.6 mL, 6.3 mmol) and the mixture refluxed under argon for 3 h, brought to basic pH with aqueous 1 *M* NaOH solution, and the mixture was extracted with ethyl acetate (3 x 20 mL). The organic phase was washed with brine (3 x 10 mL), dried with Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. Purification by flash chromatography on silica gel (96:4, CH_2Cl_2:MeOH) gave **9b** (0.052 g, 47%) as a yellow solid, MP: 178-180 ºC; IR (KBr): 1576 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.80 (s, 3 H, CH_3), 4.07 (s, 3 H, OCH_3), 7.28-7.35 (m, 1 H, ArH), 7.42 (d, *J* = 8.3 Hz, 1 H, ArH), 7.52-7.69 (m, 3 H, ArH), 8.50 (dd, *J* = 7.9, 1.6 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 26.5 (CH_3), 57.0 (OCH_3), 111.8 (C), 117.6 (CH), 118.2 (CH), 119.2 (C), 120.9 (CH), 124.1 (CH), 124.7 (CH), 133.7 (CH), 138.5 (C), 141.3 (C), 143.8 (C), 155.2 (C), 155.4 (C), 164.2 (C);MS (CI): *m/z* (%) 265 (100) [M^+ + H]; MS (EI): *m/z* (%) 249 (100) [M^+ - CH_3], 264 (47) [M^+]; EI-HRMS: *m/z* calcd. for $C_{16}H_{12}N_2O_2$: 264.0899; found: 264.0899. *Anal.* Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60; found: C, 72.50; H, 4.54; N, 10.55.

2-Ethyl-6-methoxychromeno[4,3,2-*de*]quinazoline (9c). A solution of 2-chloroquinazoline **7** (0.050 g, 0.18 mmol) and $Fe(acac)_3$ (0.048 g, 0.14 mmol) in THF (16 mL) was treated with a 1M THF solution of EtMgBr (1.1 mL, 1.08 mmol), stirred under argon for 1 h, and diluted with ether (40 mL) before the reaction was quenched with brine (10 mL). The organic phase was washed with brine (3 x 10 mL), dried with Na_2SO_4 and filtered and the solvent was removed under reduced pressure. Purification by flash chromatography on silica gel (60:40, hexanes:EtOAc) gave **9c** (0.020 g, 41%) as a yellow solid, MP: 135-139 ºC; IR (KBr): 1578, 1559 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.47 (t, *J* = 7.6 Hz, 3 H, CH_3), 3.04 (q, *J* = 7.6 Hz, 2 H, CH_2), 4.06 (s, 3 H, OCH_3), 7.27-7.33 (m, 1 H, ArH), 7.40 (d, *J* = 8.3 Hz, 1 H, ArH), 7.52-7.65 (m, 3 H, ArH), 8.51 (d, *J* = 7.8 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 12.9 (CH_3), 33.3 (CH_2), 57.2 (OCH_3), 112.3 (C), 117.7 (CH), 118.6 (CH), 119.6 (C), 121.1 (CH), 124.3 (CH), 124.9 (CH), 133.8 (CH), 138.8 (C), 141.5 (C), 144.1 (C), 155.4 (C), 155.7 (C), 168.6 (C); MS (CI): *m/z* (%) 279 (100) [M^+ + H]; MS (EI): *m/z* (%) 263 (100) [M^+ – CH_3], 277 (45) [M^+ – H], 278 (88) [M]$^+$; EI-HRMS: *m/z* calcd. for $C_{17}H_{14}N_2O_2$: 278.1055; found: 278.1054. *Anal.* Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07; found: C, 73.50; H, 5.10; N, 10.10.

6-Methoxy-2-phenylchromeno[4,3,2-*de*]quinazoline (9d). A solution of 2-chloroquinazoline **7** (0.030 g, 0.11 mmol) and $Fe(acac)_3$ (0.013 g, 0.04 mmol) in THF (16 mL) was treated with a 3 *M* Et_2O solution of PhMgBr (0.22 mL, 0.66 mmol) and stirred under argon for 10 min. Work-up as for **9c** and purification by flash chromatography on silica gel (80:20, hexanes:EtOAc) gave **9d** (0.020 g, 57%) as a yellow solid, MP: 223-226 ºC; IR (KBr): 1569, 1550 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.08 (s, 3 H, OCH_3), 7.30-7.36 (m, 1 H, ArH), 7.42 (d, *J* = 8.1 Hz, 1 H, ArH), 7.46-7.55 (m, 3 H, ArH), 7.55-7.62 (m, 1 H, ArH), 7.64-7.68 (m, 2 H, ArH), 8.60-8.68 (m, 3 H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 57.3 (OCH_3), 112.7 (C), 117.8 (CH), 119.5 (CH), 119.8 (C), 121.3 (CH), 124.3 (CH), 125.0 (CH), 128.1 (2 x CH), 128.2 (2 x CH), 130.2 (CH), 133.8 (CH), 138.3 (C), 138.8 (C), 141.8 (C), 144.4 (C), 155.3 (C), 155.6 (C), 160.6 (C); MS (EI): 311 (100) [M^+ - CH_3], 326 (51) [M^+]; MS (CI): *m/z* (%)327 (100) [M^+ + H]; ESI-TOF-HRMS: *m/z* calcd. for $C_{21}H_{15}N_2O_2$. 327.113. Found: 327.113. *Anal.* Calcd. for $C_{21}H_{14}N_2O_2$: C, 77.29; H, 4.32; N, 8.58; found: C, 77.40; H, 4.30; N, 8.55.

4-Methoxy-1-nitro-9*H*-xanthen-9-ol (10). $NaBH_4$ (0.072 g, 1.82 mmol) was added to a suspension of nitroxanthenone **2** (0.290 g, 1.07 mmol) in EtOH (20 mL) and the mixture was refluxed under argon for 1 h. The solvent was evaporated, the residue was dissolved in dichloromethane (50 mL), and this solution was washed with brine (3 x 10 mL), dried with Na_2SO_4 and filtered. The solvent was removed under reduced pressure, leaving **10** (0.292 g, 100%) as a brown solid, MP: 170-175 ºC; IR (KBr): 3508, 1530 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.77 (s, 1 H, OH), 4.04 (s, 3 H, OCH_3), 6.38 (s, 1 H, H-9), 6.99 (d, *J* = 9.2 Hz, 1 H , ArH), 7.19-7.25 (m, 1 H, ArH), 7.28 (dd, *J* = 8.2, 0.8 Hz, 1 H, ArH), 7.36-7.42 (m, 1 H, ArH), 7.57 (dd, *J* = 7.7, 1.5 Hz, 1 H, ArH), 7.97 (d, *J* = 9.1 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 56.7 (OCH_3), 60.4 (CH-9), 109.5 (CH), 116.7 (CH), 119.5 (C), 120.3 (C), 121.7 (CH), 123.4 (C), 124.4 (CH), 130.0 (CH), 130.3 (CH), 141.0 (C), 150.2 (C), 153.3 (C); MS (CI): *m/z* (%) 256 (100) [M^+ – OH], 274 (5) [M^+ + H]; MS (EI): *m/z* (%) 210 (96) [M^+ - NO_2 – OH], 225 (90) [M^+ - OH - OMe], 227 (27) [M^+ - NO_2], 255 (100) [M^+ - H_2O], 256 (77) [M^+ - OH], 273 (33) [M^+]; CI-HRMS: *m/z* calcd. for $C_{14}H_{10}NO_4$: 256.0698; found: 256.0606. *Anal.* Calcd. for $C_{14}H_{11}NO_5$: C, 61.54; H, 4.06; N, 4.06.; found: C, 61.82; H, 4.08; N, 4.10.

1-(4-Methoxy-1-nitro-9*H*-xanthen-9-yl)pyrrolidine-2,5-dione (11a). A solution of nitroxanthenol **10** (0.175 g, 0.64 mmol) and succinimide (0.505 g, 4.99 mmol) in AcOH (20 mL) was refluxed under argon for 23 h. The solvent was evaporated and 1 *M* NaOH solution was added until the resulting mixture was basic, and this mixture was then extracted with dichloromethane (3 x 20 mL), The organic layer was washed with brine (3 x 10 mL), dried with Na_2SO_4 and filtered, and the solvent was removed under reduced pressure, leaving **11a** (0.200 g, 88%) as a brown solid, MP: 218-224 ºC; IR (KBr): 1709, 1576 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.57 (s, 4 H, CH_2), 4.04 (s, 3 H, OCH_3), 6.97 (d, *J* = 9.1 Hz, 1 H, ArH), 7.08-7.13 (m, 1 H, ArH), 7.24-7.27 (m, 2 H, ArH), 7.30-7.36 (m, 1 H, ArH), 7.45 (dd, *J* = 7.8, 1.5 Hz, 1 H, ArH), 7.91 (d, *J* = 9.1 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.0 (2 x CH_2), 43.4 (CH-9), 56.6 (OCH_3), 109.9 (CH), 113.1 (C), 116.6 (CH), 118.0 (C), 121.1 (CH), 124.5 (CH), 128.7 (CH), 129.9 (CH), 139.9 (C), 144.2 (C), 150.5 (C), 152.3 (C), 175.5 (2 x CO); MS (CI): *m/z* (%) 256 (100) [M^+ – $N(CO)_2(CH_2)_2$]; CI-HRMS: *m/z* calcd. for $C_{14}H_{10}NO_4$: 256.0610; found: 256.0609. *Anal.* Calcd. for $C_{18}H_{14}N_2O_6$: C, 61.02; H, 3.98; N, 7.91; found: C, 61.00; H, 3.94; N, 7.88.

2-(4-Methoxy-1-nitro-9*H*-xanthen-9-yl)isoindoline-1,3-dione (11b). A suspension of nitroxanthenol **10** (0.786 g, 2.88 mmol) and phthalimide (0.850 g, 5.76 mmol) in AcOH (10 mL) was heated at 130 ºC for 7 h in a sealed vessel. The mixture was made basic with aqueous 1M NaOH solution, and was then

extracted with dichloromethane (3 x 20 mL). The organic layer was washed with brine (3 x 10 mL), dried with Na_2SO_4 and filtered, and the solvent was removed under reduced pressure, leaving a residue that was triturated with ether/hexane and collected by filtration affording **11b** (0.648 g, 56%) as a brown solid, MP: 236-246 ºC; IR (KBr): 1717, 1578, 1517 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 4.08 (s, 3 H, OCH_3), 5.31 (s, 1 H, H-9), 7.02 (d, *J* = 9.4 Hz, 1 H, ArH), 7.11-7.13 (m, 1 H, ArH), 7.34 (dd, *J* = 6.0, 1.6 Hz, 1 H, ArH), 7.49-7.54 (m, 2 H, ArH), 7.62-7.69 (m, 2 H, H_{NPht}), 7.70-7.77 (m, 2 H, H_{NPht}), 7.97 (d, *J* = 9.1 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 42.5 (CH-9), 56.5 (OCH_3), 109.8 (CH), 113.7 (C), 116.7 (CH), 118.5 (C), 121.4 (CH), 123.3 (2 x CH_{NPht}), 124.5 (CH), 128.9 (CH), 129.9 (CH), 131.4 (2 x C), 134.0 (2 x CH_{NPht}), 139.9 (C), 144.1 (C), 150.5 (C), 152.5 (C), 167.0 (2 x CO); MS (EI): *m/z* (%) 210 (53) [M^+ - NO_2 - NPht], 255 (100) [M^+ - NPht – H], 256 (54) [M^+ – NPht], 356 (27) [M^+ - NO_2]; MS (CI): *m/z* (%)256 (100) [M^+ – NPht]; CI-HRMS: *m/z* calcd. for $C_{14}H_{10}NO_4$: 256.0610; found: 256.0605. *Anal.* Calcd. for $C_{22}H_{14}N_2O_6$: C, 65.67; H, 3.51; N, 6.96; found: C, 65.70; H, 3.56; N, 6.94.

1-(4-Methoxy-1-nitro-9*H*-xanthen-9-yl)pyrrolidin-2-one (11c). A suspension of nitroxanthenol **10** (0.031 g, 0.11 mmol) and 2-pyrrolidinone (0.100 mL, 1.32 mmol) in AcOH (3 mL) was heated at 115 ºC for 2 h in a sealed vessel. Work-up as for **11a** and purification by flash chromatography on silica gel (97:3, CH_2Cl_2: MeOH) gave **11c** (0.021 g, 57%) as a brown solid,MP: 184-186 ºC; IR (KBr): 1685, 1521 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.73-1.85 (m, 2 H, CH_2), 2.20-2.47 (m, 2 H, CH_2), 2.71-2.91 (m, 2 H, CH_2), 4.05 (s, 3 H, OCH_3), 6.99 (d, *J* = 9.0 Hz, 1 H, ArH), 7.13-7.40 (m, 4 H, ArH), 7.60 (d, *J* = 7.6 Hz, 1 H, ArH), 7.80 (d, *J* = 9.0 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 17.7 (CH_2), 30.7 (CH_2), 42.8 (CH_2), 43.7 (CH-9), 56.5 (OCH_3), 109.6 (CH), 109.7 (CH), 114.5 (CH), 116.2 (C), 119.2 (CH), 120.7 (C), 124.9 (CH), 129.6 (CH), 141.4 (C), 142.9 (C), 150.5 (C), 151.9 (C), 174.0 (CO); MS (CI): *m/z* (%) 256 (100) [M^+ – $N(CO)(CH_2)_3$], 340 (35) [M^+]; CI-HRMS: *m/z* calcd. for $C_{18}H_{16}N_2O_5$: 340.1059; found: 340.1052. *Anal.* Calcd. for $C_{18}H_{16}N_2O_5$: C, 63.52; H, 4.74; N, 8.23; found: C, 63.40; H, 4.76; N, 8.30.

General procedure for the preparation of amines 12. To a solution of nitro compound **11** (1.0 eq) in MeOH (40 mL/mmol) was added 10% Pd/C (0.1 eq). The suspension was degassed under reduced pressure and then stirred under hydrogen for 5 h. The resulting suspension was degassed with argon, filtered through a celite pad and washed with MeOH (3 x 10 mL), and the solvent was evaporated. The residue was partitioned between dichloromethane and water, and the organic layer was washed with brine (3 x 10 mL), dried with Na_2SO_4 and filtered, after which the solvent was removed under reduced pressure.

1-(1-Amino-4-methoxy-9*H*-xanthen-9-yl)pyrrolidine-2,5-dione (12a). The crude obtained from **11a** (0.090 g, 0.25 mmol) was purified by flash chromatography on silica gel (95:5, CH_2Cl_2:MeOH), giving **12a** (0.050 g, 61%) as an amorphous orange solid. IR (KBr): 3444, 1701 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 2.58 (br s, 4 H, CH_2), 3.68 (s, 2 H, NH_2), 3.88 (s, 3 H, OCH_3), 6.30 (d, *J* = 8.6 Hz, 1 H, ArH), 6.61 (s, 1 H, CH-9), 6.79 (d, *J* = 8.6 Hz, 1 H, ArH), 7.01-7.07 (m, 1 H, ArH), 7.17 (d, *J* = 7.3 Hz, 1 H, ArH), 7.25-7.34 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 27.8 (2 x CH_2), 43.1 (CH-9), 67.2 (OCH_3), 104.0 (C), 107.9 (CH), 114.3 (CH), 116.7 (CH), 117.0 (C), 123.1(CH), 128.1 (CH), 129.7 (CH), 138.4 (C), 140.1 (C), 143.8 (C), 152.4 (C), 176.4 (2 x CO); MS (EI): *m/z* (%) 210 (100) [M^+ – $N(CO)_2(CH_2)_2$ - NH_2], 226 (25) [M^+ – $N(CO)_2(CH_2)_2$], 324 (20) [M]$^+$; EI-HRMS: *m/z* calcd. for $C_{18}H_{16}N_2O_4$: 324.1110; found: 324.1108. *Anal.* Calcd. for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64; found: C, 66.80; H, 4.90; N, 8.70.

2-(1-Amino-4-methoxy-9*H*-xanthen-9-yl)isoindoline-1,3-dione (12b). Obtained from **11b** (0.307 g, 0.76 mmol), was purified by flash chromatography on silica gel (50:50, hexanes:EtOAc), giving **12b** (0.076 g, 27%) as an amorphous orange solid. IR (KBr): 3365, 1708 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.73 (s, 2 H, NH_2), 3.90 (s, 3 H, OCH_3), 6.30 (d, *J* = 8.7 Hz, 1 H, ArH), 6.55 (s, 1 H, H-9), 6.80 (d, *J* = 8.3 Hz, 1 H, ArH), 7.00-7.05 (m, 1 H, ArH), 7.26 (d, *J* = 7.6 Hz, 1 H, ArH), 7.29-7.32 (m, 2 H, ArH), 7.60-7.65 (m, 2 H, H_{NPht}), 7.68-7.75 (m, 2 H, H_{NPht}); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 42.4 (CH-9), 57.3 (OCH_3), 104.7 (C), 108.1 (CH), 114.4 (CH), 116.8 (CH), 117.6 (C), 123.2 (CH), 123.4 (2 x CH_{NPht}), 128.5 (CH), 129.7 (CH), 131.5 (2 x C), 134.0 (2 x CH_{NPht}), 138.5 (C), 140.1 (C), 143.7 (C), 152.3 (C), 167.4 (2 x CO); MS (EI): *m/z* (%) = 210 (100) [M^+ - NPht – NH_2], 225 (61) [M^+ - NPht – H], 226 (23) [M^+ – NPht], 372 (15) [M^+]. *Anal.* Calcd. for $C_{22}H_{16}N_2O_4$: C, 70.96; H, 4.33; N, 7.52; found: C, 71.00; H, 4.40; N, 7.50.

1-(1-Amino-4-methoxy-9*H*-xanthen-9-yl)pyrrolidin-2-one (12c). Obtained from **11c** (0.174 g, 0.51 mmol), gave **12c** (0.117 g, 74%) as an orange foam. ^1H NMR ($CDCl_3$, 250 MHz): δ 1.73-1.95 (m, 2H, CH_2), 2.39-2.52 (m, 2 H, CH_2), 2.71-3.00 (m, 2 H, CH_2), 3.87 (s, 3 H, OCH_3), 4.18 (br s, 2 H, NH_2), 6.36 (d, *J* = 8.6 Hz, 1 H, ArH), 6.48 (s, 1 H, H-9), 6.79 (d, *J* = 8.6 Hz, 1 H, ArH), 7.08-7.17 (m, 1 H, ArH), 7.22-7.37 (m, 3 H, ArH); ^{13}C NMR ($CbDCl_3$, 62.5 MHz): δ 17.1 (CH_2), 30.8 (CH_2), 42.2 (CH_2), 43.6 (CH-9), 57.0 (OCH_3), 105.0 (C), 107.8 (CH), 113.6 (CH), 116.5 (CH), 118.2 (C), 123.6 (CH), 129.1 (CH), 129.2 (CH), 139.4 (2 x C), 143.0 (C), 152.0 (C), 174.6 (CO). MS (CI): *m/z* (%) 310 (35) [M^+]; CI-HRMS: *m/z* calcd. for $C_{18}H_{18}N_2O_3$: 310.1317; found: 310.1320. *Anal.* Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03; found: C, 69.50; H, 5.80; N, 9.00.

7-Methoxy-1,2,3,12b-tetrahydrochromeno[4,3,2,*de*]pyrrolo-[2,1-*b*]quinazolin-1-one (13a). $BF_3{\cdot}Et_2O$ (0.030 mL, 0.24 mmol) was added to a solution of amine **12a** (0.046 g, 0.14 mmol) in THF (5 mL) and the mixture was refluxed under argon for 2 h. The white solid recovered by filtration was washed with Et_2O (3 x 10 mL) and dissolved in dichloromethane (50 mL), and this solution was washed with aqueous $NaHCO_3$ (3 x 10 mL), dried with Na_2SO_4 and filtered, after which the solvent was removed under reduced pressure, leaving **13a** (0.020 g, 47%) as an amorphous white solid. IR (KB): 1652, 1500 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.71-3.27 (m, 4 H, CH_2), 3.93 (s, 3 H, OCH_3), 5.91 (s, 1 H, H-9), 6.81 (d, *J* = 8.6 Hz, 1 H, ArH),), 6.95 (d, *J* = 8.5 Hz, 1 H, ArH), 7.13-7.16 (m, 2 H, ArH), 7.25-7.34 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.7 (CH_2), 27.9 (CH_2), 47.4 (CH-9), 56.4 (OCH_3), 110.2 (C), 111.3 (CH), 117.5 (CH), 120.0 (CH), 123.8 (CH), 124.6 (CH), 125.1 (C), 128.0 (CH), 131.0 (C), 142.5 (C), 147.0 (C), 153.4 (C), 154.6 (C), 176.3 (CO); MS (CI): *m/z* (%)307 (100) [M^+ + H]; MS (EI): *m/z* (%)305 (100) [M^+ – H], 306 (91) [M^+]. EI-HRMS: *m/z* calcd. for $C_{18}H_{14}N_2O_3$: 306.1004; found: 306.1011. *Anal.* Calcd. for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15; found: C, 70.40; H, 4.60; N, 9.20.

6-Methoxy-14,15a-dihydrochromeno[4,3,2-*de*]isoindolo-[1,2-*b*]-quinazolin-14-one (13b).

Procedure A. $BF_3{\cdot}Et_2O$ (0.2 mL, 0.09 mmol) was added to a solution of amine **12b** (0.019 g, 0.05 mmol) in THF (9 mL) and the mixture was refluxed under argon for 3 h. Ether was added

(40 mL), the organic phase was washed with 1 *M* NaOH solution (3 x 10 mL), dried with Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. Purification by flash chromatography on silica gel (50:50, hexanes:EtOAc) gave **13b** (0.013 g, 72%) as a yellow solid.

Procedure B. 10% Pd/C (0.019 g, 0.01 mmol) was added to a solution of nitro compound **11b** (0.056 g, 0.14 mmol) in THF (5 mL). The resulting suspension was degassed under reduced pressure and then stirred under hydrogen for 4 days. The mixture was degassed with argon, filtered through a celite pad and washed with dichloromethane (3 x 10 mL), and the solvent was evaporated under reduced pressure. Purification by flash chromatography on silica gel (70:30, hexanes:EtOAc) gave **13b** (0.011 g, 28%) as a yellow solid.

Procedure C. $SnCl_2$ (0.408 g, 2.1 mmol) was added in three portions to a solution of nitro compound **11b** (0.058 g, 0.14 mmol) in DMF (3 mL) and the mixture was stirred at room temperature for 3 h. The suspension was filtered, and the solid collected washed with water (3 x 10 mL), taken-up with dichloromethane (40 mL) and preabsorbed on silica gel. Purification by flash chromatography on silica gel (70:30, hexanes:EtOAc) gave **13b** (0.011 g, 21%) as a yellow solid, MP: 218-220 ºC; IR (KBr): 1723, 1648, 1498 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.99 (s, 3 H, OCH_3), 6.07 (s, 1 H, H-9), 6.91 (d, *J* = 8.6 Hz, 1 H, ArH), 7.18 (td, *J* = 8.0, 1.7 Hz, 1 H, ArH), 7.26 (d, *J* = 8.6 Hz, 1 H, ArH), 7.28-7.33 (m, 1 H, ArH), 7.37 (dd, *J* = 8.2, 1.2 Hz, 1 H, ArH), 7.42 (dt, *J* = 7.8, 2.3 Hz, 1 H, ArH), 7.72 (td, *J* = 8.0, 1.7 Hz, 1 H, ArH), 7.77 (td, *J* = 8.0, 1.7 Hz, 1 H, ArH), 8.01 (d, *J* = 7.1 Hz, 1 H, ArH), 8.09 (d, *J* = 7.4 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 47.0 (CH-9), 56.4 (OCH_3), 111.2 (CH), 111.8 (C), 117.4 (CH), 122.3 (CH), 122.5 (CH), 123.5 (CH), 124.1 (CH), 125.2 (C), 125.5 (CH), 128.1 (CH), 130.3 (C), 131.5 (C), 132.0 (CH), 133.4 (CH), 135.2 (C), 142.8 (C), 147.5 (C), 148.3 (C), 153.5 (C), 168.1 (CO); MS (EI): *m/z* (%) 323 (7) [M^+ - OCH_3], 338 (30) [M^+ - CH_3 - H], 339 (16) [M^+ - CH_3], 353 (100) [M^+ - H], 354 (76) [M^+]; EI-HRMS: *m/z* calcd. for $C_{22}H_{14}N_2O_3$: 354.1004; found: 354.1005. *Anal.* Calcd. for $C_{22}H_{14}N_2O_3$: C, 74.57; H, 3.98; N, 7.91; found: C, 74.40; H, 3.90; N, 7.90.

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