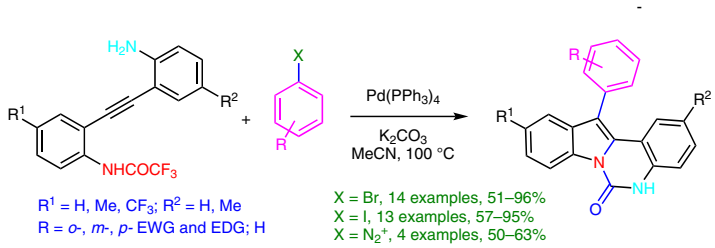
Synthesis A. Arcadi et al. Paper

Palladium-Catalyzed Cascade Approach to 12-(Aryl)indolo-[1,2-*c*]quinazolin-6(5*H*)-ones

Antonio Arcadi[a]
Sandro Cacchi[b]
Giancarlo Fabrizi[b]
Francesca Ghirga[c]
Antonella Goggiamani[b]
Antonia Iazzetti[*b]
Fabio Marinelli[*a]

[a] Dipartimento di Scienze Fisiche e Chimiche, Università di L'Aquila, Via Vetoio, 67010 Coppito (AQ), Italy
[b] Dipartimento di Chimica e Tecnologie del Farmaco, Sapienza, Università di Roma, P.le A. Moro 5, 00185, Rome, Italy
antonella.goggiamani@uniroma1.it
[c] Center for Life Nano Science@Sapienza, Istituto Italiano di Tecnologia, Viale Regina Elena 291, 00161 Rome, Italy



Received: 26.10.2017
Accepted after revision: 30.11.2017
Published online: 02.01.2018
DOI: 10.1055/s-0036-1589158; Art ID: ss-2017-t0692-op

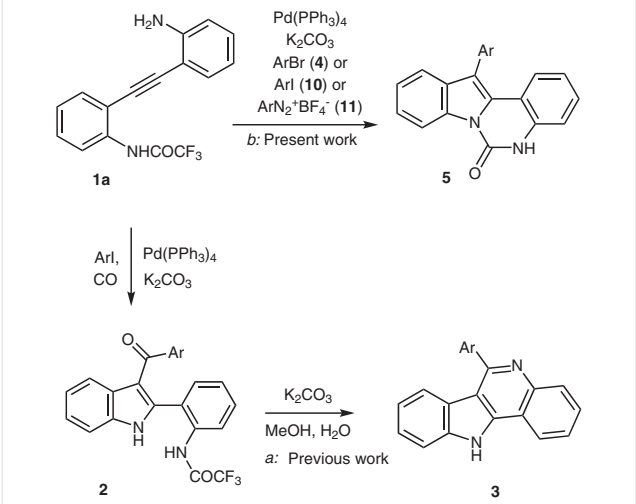
Abstract A straightforward one-pot approach to the synthesis of challenging 12-arylindolo[1,2-*c*]quinazolin-6(5*H*)-ones is described. Starting from readily available *o*-(*o*-aminophenylethynyl)trifluoroacetanilides, palladium-catalyzed aminoarylation of the triple bond with ArI, ArBr, and $ArN_2^+BF_4^-$ is followed by cyclization of the resulting *N*-trifluoroacetyl-2-(*o*-aminophenyl)-3-aryl indole. This sequential reaction provides the title compounds by means of a rare elimination of trifluoromethane.

Key words indoles, quinazolinones, palladium, trifluoromethane, elimination, polycycles

Indole derivatives are one of the most extensively studied class of heterocyclic compounds,[1] because the indole nucleus is a fundamental constituent of many natural and synthetic products with biological activity.[2] Moreover, fused indole derivatives display a number of interesting pharmacological properties. The tetracyclic alkaloid skeleton, consisting of a quinazolinone fused to an indole unit, is found in several natural products including tryptanthrin,[3a,b] and ophiuroidine,[3c] which exhibit antibiotic,[4] antiparasitic,[5] anticancer,[6] and antitubercular activities.[7] As such, the indoloquinazolinone system still motivates organic chemists to develop chemically and economically efficient and sustainable methodologies for their preparation.[8] Although a variety of synthetic methods have been developed for the preparation of natural indoloquinazolinones and their congeners,[3a,9] the synthesis of 12-(aryl)indolo[1,2-*c*]quinazolin-6(5*H*)-ones **5** is quite challenging.

Pd-catalyzed cyclization of *o*-alkynyltrifluoroacetanilides with organic electrophiles has been shown to represent a general methodology for the construction of functionalized indoles,[10] through an aminopalladation/reductive elimination sequence. We have also explored its application to the build-up of various fused indole scaffolds.[11]

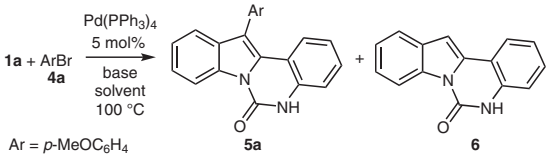
In particular, we previously reported that the readily available [*o*-(aminophenyl)ethynyl]trifluoroacetanilide (**1a**) led to 6-aryl-11*H*-indolo[3,2-*c*]quinolines **3** through a two-step procedure; namely, palladium-catalyzed carbonylative annulation with aryl iodides to give intermediate 3-acylindoles **2**, followed by hydrolysis of the trifluoroacetanilide group and cyclization (Scheme 1, a).[11a] Given the importance of the indoloquinazolinones, we were interested in extending our methodology to this class of compounds. Now, we wish to report that, under suitable reaction conditions, **1a** affords 12-arylindolo[1,2-*c*]quinazolin-6(5*H*)-ones **5** through a simple and efficient sequential process (Scheme 1, b).



Scheme 1 Present and previously reported reactions starting from **1a**

Initially, we examined the reaction of the alkynyltrifluoroacetanilide **1a** with an excess of 4-bromoanisole (**4a**) using 5 mol% $Pd(PPh_3)_4$ as catalyst and different base/solvent combinations at 100 °C.[12] The reaction proceeded to give 12-(4-methoxyphenyl)indolo[1,2-*c*]quinazolin-6(5*H*)-one (**5a**), together with variable amounts of 12-unsubstituted indoloquinazolinone **6**. To our knowledge, only compound **5b** (with Ph in place of *p*-$MeOC_6H_4$) has been previously prepared through a complex multistep reaction,[13] and other derivatives are unknown. Therefore, an efficient and simple strategy to build up indoloquinazolinones **5** is desirable, and we attempted the optimization of the reaction parameters to address the selective preparation of **5a** from **1a** (Table 1).

Table 1 Optimization of the Synthesis of **5a**[a]



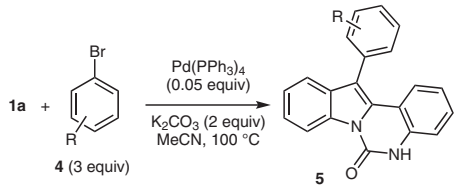
Entry	Base	Solvent	Time (h)	Yield (%)[b,c] of **5a** (**6**)
1	K_2CO_3	DMF	21	38 (35)
2	K_2CO_3	MeCN/DMF 1:1	20	78 (9)
3	K_2CO_3	MeCN	30	80 (11)
4	K_2CO_3	MeCN	24	68[d] (25)
5	Cs_2CO_3	MeCN	22	65 (30)
6	Na_2CO_3	MeCN	24	12 (59)
7	Li_2CO_3	MeCN	24	5[e] (10)

[a] Reaction conditions (0.35 mmol scale): ArBr (3 equiv), base (2 equiv), $Pd(PPh_3)_4$ (0.05 equiv), solvent (2 mL).
[b] Yield of isolated product.
[c] Figures in parentheses refer to the yield of **6**.
[d] Carried out with ArBr (2 equiv).
[e] **1a** was recovered in 51% yield.

The solvent was found to play a key role in controlling the product selectivity, as were the excess of aryl bromide and the nature of the base. The use of a mixture of DMF/MeCN or MeCN instead of DMF improved both yields and selectivity of the process (Table 1, entries 2 and 3). Decreasing the excess of **4a** to 2 equiv (entry 4) led to a lower yield. Among the bases tested, a moderate yield of **5a** was obtained with Cs_2CO_3 (entry 5), whereas using Na_2CO_3 afforded **5a** in low yield, with the main product being **6** (entry 6). Disappointing results were observed with Li_2CO_3 (entry 7).

The conditions described in Table 1, entry 3 were then selected to explore the scope and limitations of the methodology. The reaction of **1a** with different aryl bromides under palladium catalysis proceeded smoothly to give the target indoloquinazolinones **5a**–**k** in moderate to high yield (Table 2). Several substituents, including methyl, methoxy, fluoro, chloro, cyano, and nitro groups, were tolerated on the aromatic ring of **4**. Good results were also achieved in the presence of substituents at the *ortho*-position of ArBr (entries 4 and 8), whereas the outcome of the palladium-catalyzed reaction of **1a** with 1-bromo-3-(trifluoromethyl)benzene **4k** was less favorable (entry 11). In this case, increasing the temperature to 120 °C led to a better result (entry 12).

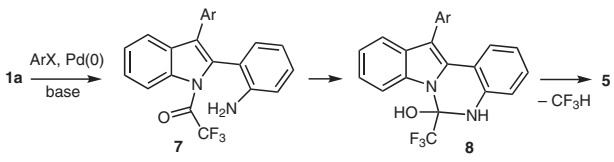
Table 2 Scope of the Reaction of **1a** with Aryl Bromides **4**[a]



Entry	**4**/**5**	R	Time (h)	Yield (%)[b] of **5**
1	**a**	4-OMe	30	80
2	**b**	H	16	86
3	**c**	3-OMe	26	83
4	**d**	2-Me	25	61
5	**e**	4-F	23	66
6	**f**	4-Cl	24	62
7	**g**	3-CN	40	64
8	**h**	2-CN	18	67
9	**i**	3-Ac	42	73
10	**j**	4-NO_2	25	96
11	**k**	3-CF_3	15	51[c]
12	**k**	3-CF_3	15	63[d]

[a] Reaction conditions: **1a** (0.35 mmol), **4** (1.05 mmol), K_2CO_3 (0.7 mmol), $Pd(PPh_3)_4$ (0.0175 mmol), MeCN (2 mL), 100 °C under argon atmosphere.
[b] Isolated yield.
[c] **6** was isolated in 20% yield.
[d] Carried out at 120 °C.

A plausible reaction path that accounts for the formation of products **5** is shown in Scheme 2.

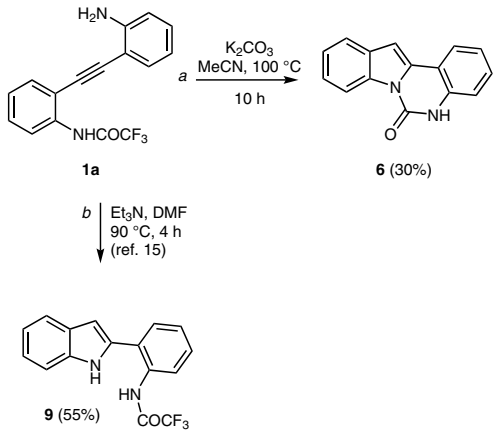


Scheme 2 Plausible reaction path for the formation of **5**

After the Pd-catalyzed cyclization of **1a**, the resulting *N*-trifluoroacetylindole **7** affords intermediate **8**. Finally, elimination of trifluoromethane (or trifluoromethyl anion) from **8** generates quinazolinones **5**. This elimination is quite rare, and there are only some precedents in the literature.[14]

We also attempted to shed light on the formation of by-product **6**. We have previously reported that **1a** undergo a base-promoted cyclization/transamidation when treated with Et_3N in DMF at 90 °C, affording *N*-(2-(1*H*-indol-2-yl)phenyl)-2,2,2-trifluoroacetamide **9** (Scheme 3, b).[15]

Therefore, base-promoted cyclization of **1a** could also be involved in the formation of **6**. To confirm this hypothesis, **1a** was reacted with K_2CO_3 in CH_3CN at 100 °C (omitting ArBr and Pd catalyst); quinazolinone **6** was isolated in 30% yield, and **1a** was recovered in 63% yield (Scheme 3, a). Therefore, the formation of **6** is due, at least in part, to the presence of the base.[16]



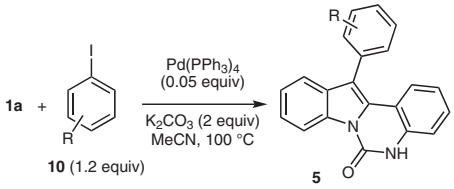
Scheme 3 Base-promoted reactions of **1a**

It is worth nothing that the different outcomes between the present reaction and the Pd-catalyzed carbonylative cyclization of **1a** (Scheme 1), as well as the differences in the base-promoted cyclizations reported in Scheme 3, demonstrates that the tendency of intermediates of type **8** to undergo elimination of trifluoromethane (affording quinazolinones) or transamidation is strongly dependent on the base/solvent/temperature combination, as well as on the particular structure of the initially formed indole ring. Further work is needed to clarify this intriguing aspect.

We then tested the formation of 12-arylindolo[1,2-*c*]quinazolin-6(5*H*)-ones **5** from aryl iodides **10**.[17] According to the higher reactivity of these electrophiles in the oxidative addition step, palladium-catalyzed reaction of **1** with a near stoichiometric amount of **10** (1.2 equiv) resulted in an efficient reaction (Table 3).

Furthermore, attempts to set up the use of arene diazonium salts **11** as a useful alternative to the aryl halides showed the feasibility of the reaction.[18] However, the reaction of **1a** with 2 equiv of **11a** under the usual reaction conditions (2 equiv K_2CO_3 and 5% $Pd(PPh_3)_4$ in MeCN at 100 °C for 10 h) afforded **5a** in unsatisfactory yield (41%), together with **9** (20%), **6** (16%) and other unidentified byproducts. A preliminary optimization of the reaction parameters was

Table 3 Scope of the Reaction of **1a** with Aryl Iodides **10**[a]

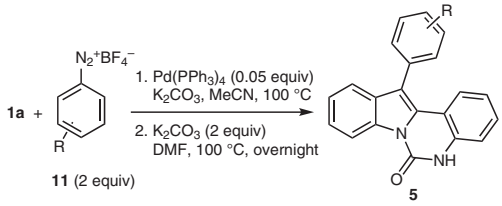


Entry	**10**/**5**	R	Time (h)	Yield (%)[b] of **5**
1	**a**	4-OMe	26	78
2	**b**	H	16	86
3	**c**	3-OMe	17	80
4	**e**	4-F	48	88
5	**f**	4-Cl	24	90
6	**k**	3-CF_3	24	90
7	**l**	4-CN	22	94
8	**m**	4-COOEt	24	95
9	**n**	2-OMe	18	80
10	**o**	2-Ac	24	57

[a] Reaction conditions: **1a** (0.35 mmol), **10** (0.42 mmol), K_2CO_3 (0.7 mmol), $Pd(PPh_3)_4$ (0.0175 mmol), MeCN (2 mL), 100 °C under argon atmosphere.
[b] Isolated yield.

then performed. The best results were obtained by treating the crude reaction mixture, after the Pd-catalyzed cyclization, with two additional equivalents of K_2CO_3 in DMF (Table 4).

Table 4 Scope of the Reaction of **1a** with Arenediazonium Tetrafluoroborates **11**[a]



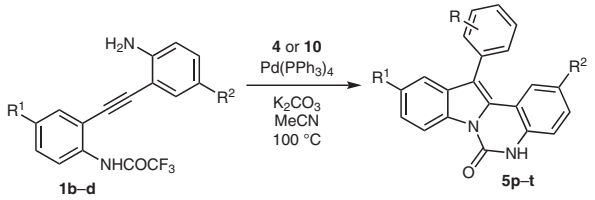
Entry	**11**/**5**	R	Time (h)	Yield (%)[b] of **5**
1	**a**	4-OMe	8	58
2	**b**	H	9	50
3	**f**	4-Cl	7	63
4	**m**	4-COOEt	5	61

[a] Reaction conditions: **1a** (0.35 mmol), **11** (0.7 mmol), K_2CO_3 (0.7 mmol), $Pd(PPh_3)_4$ (0.0175 mmol), MeCN (2 mL), 80 °C under argon atmosphere (step 1); then K_2CO_3 (0.7 mmol) (step 2) in DMF (2 mL) at 100 °C.
[b] Isolated yield.

Finally, we tested an extension of the methodology to the synthesis of disubstituted indoloquinazolinones **5p–t**. Starting compounds **1b–d** were easily obtained from Sonogashira coupling of substituted 2-iodotrifluoroacetanilides with ethynylaniline derivatives.

Target disubstituted products were obtained in satisfactory yields, using either aryl bromides or iodides as source Ar group (Table 5).

Table 5 Synthesis of Disubstituted Indoloquinazolinones **5p–t**[a]



Entry	1	R^1, R^2	4 or 10	R	Time (h)	Yield (%)[b] of 5
1	**1b**	CF_3, H	**4a**	4-OMe	24	**5p** (52)
2	**1b**	CF_3, H	**4b**	H	20	**5q** (69)
3	**1c**	H, Me	**10m**	4-COOEt	48	**5r** (66)
4	**1d**	Me, H	**10a**	4-OMe	51	**5s** (78)
5	**1d**	Me, H	**10m**	4-COOEt	24	**5t** (83)

[a] Reaction conditions: **1** (0.35 mmol), **4** (1.05 mmol) or **10** (0.42 mmol), K_2CO_3 (0.70 mmol), $Pd(PPh_3)_4$ (0.017 mmol), CH_3CN (2 mL), 100 °C under argon atmosphere.
[b] Isolated yield.

In conclusion, we have reported here an efficient protocol for the synthesis of challenging 12-arylindolo[1,2-*c*]quinazolin-6(5*H*)-ones **5** through a straightforward sequential reaction that involves an unusual elimination of trifluoromethane. Aryl iodides, aryl bromides, and arenediazonium salts can be used as σ-donors. The methodology is quite versatile and tolerates a variety of useful functional groups; substituents can also be introduced in the benzenic ring of both indole and quinazolinone moieties. Further work is in progress to extend the methodology to other σ-donors.

All of the reagents, catalysts, and solvents are commercially available and were used as purchased, without further purification. 2-(2-Aminophenyl)trifluoroacetanilides **1** were prepared through Sonogashira cross-coupling of 2-iodotrifluoroacetanilides with 2-ethynylanilines according to previous reports.[19] Starting materials were purified on axially compressed columns, packed with SiO_2 25–40 μm, connected to a preparative pump for solvent delivery and to a refractive index detector, and eluting with *n*-hexane/EtOAc mixtures. Reaction products were purified by flash chromatography using SiO_2 as stationary phase, eluting with *n*-hexane/EtOAc or hexane/EtOAc/MeOH or $CHCl_3/CH_2Cl_2$ mixtures, depending on the solubility. Melting points are uncorrected. ^{1}H NMR (400.13 MHz), ^{13}CNMR (100.6 MHz), and ^{19}F NMR (376.5 MHz) spectra were recorded with a Bruker Avance 400 spectrometer. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br s (broad singlet). Compounds **5d**, **5h**, **5p** were derivatized as *N*-methyl derivatives to obtain suitable NMR data. IR spectra were recorded with a Jasco FT/IR-430 spectrophotometer. ESI accurate mass measurements were recorded with a Finnigan TSQ Quantum Ultra Mass spectrometer with accurate mass options instrument (**5a–p**) and with an Orbitrap Exactive Mass spectrometer with ESI source (**1b**, **6**). The following compounds were identified by comparison of their physical and spectral data with those given in the cited references: **1a**[11a] and **6a**.[14a] Compounds **1b–d** were prepared by Sonogashira coupling of 2-ethynylaniline or 2-ethynyl-4-methylaniline with the appropriate 2-iodotrifluoroacetanilide derivative using the same general procedure previously described for **1a**.[11a]

N-{2-[(2-Aminophenyl)ethynyl]-4-(trifluoromethyl)phenyl}-2,2,2-trifluoroacetamide (1b)

Yield: 0.669 g (65%); beige powder; mp 140–142 °C.

IR (KBr): 3354, 2197, 1712, 1596 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 11.47 (br s, 1 H), 8.23 (d, J = 1.6 Hz, 1 H), 7.79 (dd, J_1 = 8.4, J_2 = 1.6 Hz, 1 H), 7.72 (d, J = 8.4 Hz, 1 H), 7.16 (dd, J_1 = 7.6; J_2 = 1.2 Hz, 1 H), 7.12–7.06 (m, 1 H), 6.71 (d, J = 8.0 Hz, 1 H), 6.53 (t, J = 7.6 Hz, 1 H), 5.74 (br s, 2 H).

^{13}C NMR (DMSO-d_6): δ = 155.6 (q, J_{C-F} = 36.8 Hz), 150.6, 138.9, 132.5, 131.1, 129.9, 128.4 (q, J_{C-F} = 32.3 Hz), 127.6, 125.8, 124.1 (q, J_{C-F} = 270.8 Hz), 121.5, 116.4 (q, J_{C-F} = 286.8 Hz), 116.1, 114.5, 104.7, 94.9, 89.0.

^{19}F NMR (DMSO-d_6): δ = –61.1, –73.9.

HRMS: m/z [M–H]$^-$ calcd for $C_{17}H_9F_6N_2O$: 371.0625; found: 371.0618.

N-{2-[(2-Amino-5-methylphenyl)ethynyl]phenyl}-2,2,2-trifluoroacetamide (1c)

Yield: 0.648 g (68%); white powder; mp 141–143 °C.

IR (KBr): 3445, 2194, 1728, 1586, 1545 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.88 (br s, 1 H), 8.39 (d, J = 8.4 Hz, 1 H), 7.57 (dd, J_1 = 7.6 Hz, J_2= 1.2 Hz, 1 H), 7.46–7.40 (m, 1 H), 7.24 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1 H), 7.18 (s, 1 H), 7.05 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1 H), 6.70 (d, J = 8.4 Hz), 4.15 (br s, 2 H), 2.28 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 154.5 (q, J_{C-F} = 37.2 Hz), 145.7, 135.8, 132.2, 131.8, 131.7, 129.7, 127.6, 125.6, 119.8, 115.7 (q, J_{C-F} = 289.0 Hz), 115.0, 113.9, 106.3, 95.0, 87.8, 20.3.

^{19}F NMR ($CDCl_3$): δ = –75.6.

HRMS: m/z [M + H]$^+$ calcd for $C_{17}H_{14}F_3N_2O$: 319.1053; found: 319.1046.

N-{2-[(2-Aminophenyl)ethynyl]-4-methylphenyl}-2,2,2-trifluoroacetamide (1d)

Yield: 0.715 g (75%); white powder; mp 137–139 °C.

IR (KBr): 3338, 2200, 1710, 1545 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 11.16 (br s, 1 H), 7.57 (s, 1 H), 7.35 (d, J = 8.4 Hz, 1 H), 7.27 (d, J = 8.0 Hz, 1 H), 7.18 (d, J = 7.2 Hz, 1 H), 7.10 (t, J = 8.0 Hz, 1 H), 6.73 (d, J = 8.4 Hz, 1 H), 6.55 (t, J = 7.2 Hz, 1 H), 5.57 (br s, 2 H), 2.35 (s, 3 H).

^{13}C NMR (DMSO-d_6): δ = 155.70 (q, J_{C-F} = 36.5 Hz), 150.2, 137.6, 133.1, 132.9, 132.2, 130.6, 130.0, 126.9, 120.5, 116.6 (q, J_{C-F} = 284.2 Hz), 116.2, 114.4, 105.5, 92.3, 90.5, 20.8.

^{19}F NMR ($CDCl_3$): δ = –75.6.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{14}F_3N_2O$: 319.1053; found: 319.1045.

Synthesis of 12-(Aryl)indolo[1,2-*c*]quinazolin-6(5*H*)-ones 5 from ArBr; Typical Procedure

Preparation of 12-(4-Methoxyphenyl)indolo[1,2-*c*]quinazolin-6(5*H*)-one (5a) from 1a and 1-Bromo-4-methoxybenzene (4a)

In a 50 mL Carousel Tube Reactor (Radely Discovery Technology) containing a magnetic stirring bar 2-(2-aminophenyl)ethynyl trifluoroacetanilide (**1a**; 106.5 mg, 0.350 mmol) was dissolved at r.t. with anhydrous MeCN (1.0 mL). Then, $Pd(PPh_3)_4$ (20.2 mg, 0.018 mmol), 1-bromo-4-methoxybenzene (**4a**; 196.0 mg, 1.050 mmol), K_2CO_3 (96.7 mg, 0.7 mmol), and MeCN (1.0 mL) were added. The mixture was stirred for 30 h at 100 °C under argon. After this time, the reaction mixture was cooled to r.t., diluted with EtOAc, and washed with water. The organic extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel; *n*-hexane/EtOAc 80:20 v/v; $CHCl_3/CH_2Cl_2$ 75:25 v/v as eluent) to afford 12-(4-methoxyphenyl)indolo[1,2-*c*]quinazolin-6(5*H*)-one **5a**.

Yield: 95 mg (80%); pale-yellow powder; mp 290–292 °C.

IR (KBr): 3375, 3204, 3147, 2990, 1702, 1605, 1516 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 11.42 (br s, 1 H), 8.65 (d, *J* = 8.1 Hz, 1 H), 7.52–7.31 (m, 7 H), 7.27 (d, *J* = 7.5 Hz, 1 H), 7.17 (d, *J* = 8.6 Hz, 2 H), 7.01–6.95 (m, 1 H), 3.88 (s, 3 H).

^{13}C NMR (DMSO-d_6): δ = 159.4, 147.6, 135.2, 132.8, 131.9, 131.2, 129.6, 128.9, 125.8, 124.14, 124.09, 123.7, 122.9, 119.0, 116.1, 116.0, 115.2, 115.0, 114.5, 55.6.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{17}N_2O_2$: 341.1286; found: 341.1285.

Synthesis of 12-(Aryl)indolo[1,2-*c*]quinazolin-6(5*H*)-ones 5 from ArI: Typical Procedure

Preparation 5a from 1a and 1-Iodo-4-methoxybenzene (10a)

This procedure was similar to that of the reaction of **1a** with 1-bromo-4-methoxybenzene (**4a**), the only differences being the amount of **10a** (98 mg, 0.420 mmol) and reaction time (26 h).

Yield: 93.0 mg (78%).

12-Phenylindolo[1,2-*c*]quinazolin-6(5*H*)-one (5b)

Purified with *n*-hexane/EtOAc (85:15) as eluent.

Yield: 93.4 mg from ArBr (86%); 93.2 mg from ArI (86%); white powder; mp 274–276 °C (Lit.[13] 277–279 °C).

IR (KBr): 3447, 1693, 1482, 1451, 1410 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 11.40 (br s, 1 H), 8.62 (d, *J* = 8.2 Hz, 1 H), 7.63–7.46 (m, 5 H), 7.43–7.21 (m, 6 H), 6.94–6.87 (m, 1 H).

^{13}C NMR (DMSO-d_6): δ = 147.6, 135.2, 134.0, 132.9, 130.9, 130.7, 129.74, 129.69, 128.9, 128.5, 124.20, 124.16, 123.7, 122.8, 118.9, 116.13, 116.09, 115.2, 114.3.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{15}N_2O$: 311.1180; found: 311.1179.

12-(3-Methoxyphenyl)indolo[1,2-*c*]quinazolin-6(5*H*)-one 5c

Purified with *n*-hexane/EtOAc (85:15 v/v), $CHCl_3/CH_2Cl_2$ (75:25 v/v) as eluent.

Yield: 98.9 mg from ArBr (83%); 95.3 from ArI (80%); pale-yellow powder; mp 215–217 °C.

IR (KBr): 3376, 2999, 2930, 1702 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 11. 41 (br s, 1 H), 8.65 (d, *J* = 8.4 Hz, 1 H), 7.56–7.46 (m, 2 H), 7.44–7.31 (m, 4 H), 7.28 (d, *J* = 8.0 Hz, 1 H), 7.13–7.06 (m, 3 H), 6.97 (t, *J* = 7.9 Hz, 1 H), 3.77 (3 H).

^{13}C NMR (DMSO-d_6): δ = 159.8, 147.1, 134.9, 134.7, 132.3, 130.4 (overlapping), 129.2, 128.4, 123.7, 123.4, 122.4, 118.5, 115.6, 115.5, 114.6, 113.8, 113.7, 55.2.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{17}N_2O_2$: 341.1286; found: 341.1287.

12-(*o*-Tolyl)indolo[1,2-*c*]quinazolin-6(5*H*)-one (5d)

Purified with *n*-hexane/EtOAc (85:15 v/v) as eluent.

Yield: 69.3 mg from ArBr (61%); white powder; mp 330–332 °C.

IR (KBr): 3364, 3058, 3000, 1700, 1593, 1513, 1488, 1460 cm^{-1}.

^{1}H NMR (DMSO-d_6; as *N*-methyl derivative): δ = 8.69 (d, *J* = 8.2 Hz, 1 H), 7.55–7.38 (m, 6 H), 7.38–7.32 (m, 2 H), 7.24–7.15 (m, 2 H), 7.08–7.01 (m, 1 H), 3.71 (s, 3 H), 2.03 (s, 3 H).

^{13}C NMR (DMSO-d_6; as *N*-methyl derivative): δ = 147.8, 137.7, 136.2, 133.4, 133.2, 131.11, 131.09, 129.9, 129.0, 127.9, 127.2, 124.29, 124.28, 123.5, 123.3, 119.0, 116.3, 115.7, 115.6, 113.9, 30.8, 19.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{19}N_2O$: 339.1493; found: 339.1492.

12-(4-Fluorophenyl)indolo[1,2-*c*]quinazolin-6(5*H*)-one (5e)

Purified with *n*-hexane/EtOAc (85:15 v/v) as eluent.

Yield: 75.8 mg from ArBr (66%); 101.1 mg from ArI (88%); pale-yellow powder; mp 290–292 °C.

IR (KBr): 3382, 1703, 1592, 1510, 1486 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 11.43 (br s, 1 H), 8.62 (d, *J* = 8.2 Hz, 1 H), 7.62–7.56 (m, 2 H), 7.49–7.30 (m, 7 H), 7.24 (d, *J* = 7.6 Hz, 1 H), 7.02–6.96 (m, 1 H).

^{13}C NMR (DMSO-d_6): δ = 162.4 (d, J_{C-F} = 244.8 Hz), 147.5, 135.3, 132.9 (d, J_{C-F} = 8.6 Hz), 132.8, 130.9, 130.31, 130.28, 129.8, 129.2, 124.25, 124.22, 123.7, 122.9, 118.8, 116.7 (d, J_{C-F} = 21.4 Hz), 116.1, 114.2, 114.1.

^{19}F NMR (DMSO-d_6): δ = –113.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{14}FN_2O$: 329.1083; found: 329.1085.

12-(4-Chlorophenyl)indolo[1,2-*c*]quinazolin-6(5*H*)-one (5f)

Purified with *n*-hexane/EtOAc (85:15 v/v) as eluent.

Yield: 74.8 mg (62%) from ArBr; 108.7 mg from ArI (90%); white powder; mp 287–289 °C.

IR (KBr): 3440, 1714, 1483, 1450 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 11.50 (br s, 1 H), 8.66 (d, *J* = 8.2 Hz, 1 H), 7.68 (dt, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 2 H), 7.69–7.56 (m, 2 H), 7.46–7.33 (m, 5 H), 7.28 (d, *J* = 7.4 Hz, 1 H), 7.04–7.00 (m, 1 H).

^{13}C NMR (DMSO-d_6): δ = 147.5, 135.3, 133.2, 133.0, 132.9, 132.7, 130.7, 129.9 (overlapping), 129.2, 124.32, 124.28, 123.7, 123.0, 118.7, 116.2 (overlapping), 114.1, 113.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{14}ClN_2O$: 345.0788; found: 345.0789.

3-(6-Oxo-5,6-dihydroindolo[1,2-*c*]quinazolin-12-yl)benzonitrile (5g)

Purified with *n*-hexane/EtOAc (75:25), *n*-hexane/EtOAc/MeOH (70:20:10) as eluent.

Yield: 75.1 mg (64%) from ArBr; pale-yellow powder; mp 278–280 °C.

IR (KBr): 3376, 2229, 1701, 1606, 1482, 1452 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 11.53 (br s, 1 H), 8.66 (d, *J* = 8.1 Hz, 1 H), 8.08–8.00 (m, 2 H), 7.92 (d, *J* = 7.8 Hz, 1 H), 7.83 (t, *J* = 7.7 Hz, 1 H), 7.48–7.34 (m, 5 H), 7.30 (t, *J* = 8.1 Hz, 1 H), 7.01 (t, *J* = 7.6 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 147.5, 136.0, 135.6, 135.4, 134.3, 132.9, 132.4, 131.1, 130.5, 130.0, 129.6, 124.3, 124.39, 123.7, 123.1, 119.1, 118.6, 116.3, 116.2, 113.9, 112.98, 112.96.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{14}N_3O$: 336.1131; found: 336.1131.

2-(6-Oxo-5,6-dihydroindolo[1,2-*c*]quinazolin-12-yl)benzonitrile (5h)

Purified with *n*-hexane/EtOAc (75:25), *n*-hexane/EtOAc/MeOH (70:20:10) as eluent.

Yield: 78.6 mg (67%) from ArBr; pale-yellow powder; mp 305–307 °C.

IR (KBr): 3364, 2221, 1694, 1479, 1450 cm^{-1}.

^1H NMR ($CDCl_3$; as *N*-methyl derivative): δ = 8.80 (d, *J* = 8.4 Hz, 1 H), 7.91 (d, *J* = 7.6 Hz, 1 H), 7.80 (t, *J* = 7.6 Hz, 1 H), 7.63 (m, 2 H), 7.48–7.34 (m, 3 H), 7.32–7.23 (m, 3 H), 6.99–6.96 (m, 1 H), 3.77 (s, 3 H).

^{13}C NMR ($CDCl_3$; as *N*-methyl derivative): δ = 147.9, 138.6, 136.2, 133.9, 133.5, 133.4, 132.2, 130.3, 129.5, 129.0, 128.6, 124.5, 124.2, 124.0, 123.0, 118.2, 117.7, 116.6, 115.3, 114.7, 114.6, 111.0, 30.5.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{14}N_3O$: 336.1131; found: 336.1131.

12-(3-Acetylphenyl)indolo[1,2-*c*]quinazolin-6(5*H*)-one (5i)

Purified with *n*-hexane/EtOAc (75:30), *n*-hexane/EtOAc/MeOH (70:20:10) as eluent.

Yield: 90.0 mg (73%) from ArBr; white powder; mp 262–264 °C.

IR (KBr): 3371, 3208, 3149, 1699, 1604, 1560 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 11.49 (br s, 1 H), 8.66 (d, *J* = 8.2 Hz, 1 H), 8.13–8.10 (m, 2 H), 7.82 (dt, J_1 = 7.6 Hz, J_2 = 1.4 Hz, 1 H), 7.75 (t, *J* = 8.2 Hz, 1 H), 7.44–7.31 (m, 5 H), 7.27 (d, *J* = 7.8 Hz, 1 H), 6.97–6.93 (m, 1 H), 2.62 (s, 3 H).

^{13}C NMR (DMSO-d_6): δ = 198.3, 147.6, 138.2, 135.5, 135.3, 134.6, 132.9, 130.7, 130.4, 130.3, 129.9, 129.3, 128.4, 124.4, 124.3, 123.6, 123.0, 118.7, 116.2, 114.2, 114.1 (overlapping), 27.4.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{17}N_2O_2$: 353.1286; found: 353.1285.

12-(4-Nitrophenyl)indolo[1,2-*c*]quinazolin-6(5*H*)-one (5j)

Purified with *n*-hexane/EtOAc (75:25), *n*-hexane/EtOAc/MeOH (60:30:10) as eluent.

Yield: 119.4 mg (96%) from ArBr; yellow powder; mp 330–332 °C.

IR (KBr): 3455, 1702, 1515, 1482, 1452 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 11.60 (br s, 1 H), 8.68 (d, *J* = 8.2 Hz, 1 H), 8.46 (d, *J* = 8.6 Hz, 2 H), 7.89 (d, *J* = 8.6 Hz, 2 H), 7.40–7.34 (m, 5 H), 7.30 (d, *J* = 8.0 Hz, 1 H), 7.00 (t, *J* = 7.7 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 147.5, 147.1, 141.6, 135.5, 133.0, 132.3, 130.2, 130.1, 129.8, 124.9, 124.51, 124.50, 123.9, 123.1, 118.5, 116.3 (overlapping), 113.7, 113.0.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{14}N_3O_3$: 356.1026; found: 356.1030.

12-(3-(Trifluoromethyl)phenyl)indolo[1,2-*c*]quinazolin-6(5*H*)-one (5k)

Purified with *n*-hexane/EtOAc (80:20) as eluent.

Yield: 67.5 mg (51%) from ArBr; 119.2 mg (90%) from ArI; white powder; mp 254–256 °C.

IR (KBr): 3419, 1697, 1481, 1452 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 11.47 (br s, 1 H), 8.64 (d, *J* = 8.2 Hz, 1 H), 7.92–7.78 (m, 4 H), 7.44–7.23 (m, 6 H), 6.94 (t, *J* =7.3 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 147.5, 135.5, 135.4, 135.1, 132.9, 131.0, 130.520 (q, J_{C-F} = 31.4 Hz), 130.519, 130.0, 129.6, 127.3 (q, J_{C-F} = 3.4 Hz), 125.3 (q, J_{C-F} = 3.1 Hz), 124.6 (q, J_{C-F} = 272.7 Hz), 124.4 (overlapping), 123.5, 122.9, 118.5, 116.3, 116.2, 114.0, 113.4.

^{19}F NMR (DMSO-d_6): δ = –61.0.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{14}F_3N_2O$: 379.1048; found: 379.1053.

4-(6-Oxo-5,6-dihydroindolo[1,2-*c*]quinazolin-12-yl)benzonitrile (5l)

Purified with *n*-hexane/EtOAc (75:25), *n*-hexane/EtOAc/MeOH (70:20:10) as eluent.

Yield: 110.4 mg (94%) from ArI; yellow powder; mp 262–264 °C.

IR (KBr): 3378, 2228, 1702, 1603, 1485, 1451 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 11.56 (br s, 1 H), 8.67 (d, *J* = 8.4 Hz, 1 H), 8.09 (d, *J* = 8.4 Hz, 2 H), 7.80 (d, *J* = 8.0 Hz, 2 H), 7.46–7.37 (m, 5 H), 7.30 (d, *J* = 8.4 Hz, 1 H), 7.04–7.00 (m, 1 H).

^{13}C NMR (DMSO-d_6): δ = 147.4, 139.5, 135.4, 133.6, 132.96, 131.94, 130.2, 130.1, 129.5, 124.42, 124.39, 123.8, 123.1, 119.3, 118.5, 116.2 (overlapping), 113.8, 113.4, 111.2.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{14}N_3O$: 336.1131; found: 336.1131.

Ethyl 4-(6-Oxo-5,6-dihydroindolo[1,2-*c*]quinazolin-12-yl)benzoate (5m)

Purified with *n*-hexane/EtOAc (70:30), $CHCl_3/CH_2Cl_2$ (75:25) as eluent.

Yield: 127.1 mg (95%) from ArI; white powder; mp 292–294 °C.

IR (KBr): 3374, 3080, 2997, 2930, 1704, 1565, 1511 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 11.48 (br s, 1 H), 8.64 (d, *J* = 8.3 Hz, 1 H), 8.15 (d, *J* = 8.1 Hz, 2 H), 7.69 (d, *J* = 8.1 Hz, 2 H), 7.43–7.31 (m, 5 H), 7.26 (d, *J* = 8 Hz, 1 H), 6.95 (t, *J* = 7.9 Hz, 1 H), 4.36 (q, *J* = 7.2 Hz, 2 H), 1.35 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (DMSO-d_6): δ = 166.0, 147.5, 139.3, 135.3, 132.9, 131.2, 130.5, 130.4, 129.9, 129.8, 129.3, 125.0, 124.4, 124.3, 123.0, 118.7, 116.20, 116.23, 114.02, 113.95, 61.3, 14.7.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{19}N_2O_3$: 383.1391; found: 383.1390.

12-(2-Methoxyphenyl)indolo[1,2-*c*]quinazolin-6(5*H*)-one (5n)

Purified with *n*-hexane/EtOAc 80:20, $CHCl_3/CH_2Cl_2$ 75:25 as eluent.

Yield: 93.7 mg (80%) from ArI; white powder; mp 215–217 °C.

IR (KBr): 3418, 2927, 1706, 1485, 1450 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 11.43 (br s, 1 H), 8.65 (d, *J* = 8.2 Hz, 1 H), 7.58–7.52 (m, 1 H), 7.43–7.224 (m, 8 H), 7.17 (dt, J_1 = 7.6 Hz, J_2 = 0.7 Hz, 1 H), 6.99–6.93 (m, 1 H), 3.64 (s, 3 H).

^{13}C NMR (DMSO-d_6): δ = 157.9, 147.6, 135.6, 132.8, 131.0, 130.4, 129.6, 129.4, 123.97, 123.96, 123.87, 122.9, 122.2, 121.5, 119.2, 116.0, 115.8, 114.7, 112.4, 111.3, 55.8.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{17}N_2O_2$: 341.1286; found: 341.1285.

12-(2-Acetylphenyl)indolo[1,2-]quinazolin-6(*5H*)-one (5o)

Purified with *n*-hexane/EtOAc/MeOH (65:25:10), as eluent.

Yield: 98.6 mg (57%) from ArI; pale-yellow powder; mp 275–277 °C.

IR (KBr): 3212, 3155, 2926, 1691, 1610, 1592, 1494, 1477 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 11.49 (br s, 1 H), 8.65 (d, *J* = 8.0 Hz, 1 H), 7.95 (dd, J_1 = 7.6 Hz, J_2= 1.1 Hz, 1 H), 7.78–7.66 (m, 2 H), 7.52 (dd, J_1 = 7.6 Hz, J_2 = 1.0 Hz, 1 H), 7.44–7.32 (m, 4 H), 7.16 (d, *J* = 7.8 Hz, 1 H), 7.12 (d, *J* = 7.8 Hz, 1 H), 6.97–6.91 (m, 1 H), 2.10 (s, 3 H).

^{13}C NMR (DMSO-d_6): δ = 201.5, 147.6, 141.1, 135.3, 132.8, 132.7, 132.6, 132.2, 131.0, 129.7, 129.6, 129.3, 129.2, 124.3, 124.2, 123.7, 123.0, 118.7, 116.12, 116.08, 114.2, 113.9, 29.6.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{17}N_2O_2$: 353.1287; found: 353.1285.

12-(4-Methoxyphenyl)-10-(trifluoromethyl)indolo[1,2-*c*]quinazolin-6(5*H*)-one (5p)

Purified with *n*-hexane/EtOAc (75:30), CH_2Cl_2/$CHCl_3$ (75:25) as eluent.

Yield: 70.3 mg (52%) from ArBr; pale-brown powder; mp 272–274 °C.

IR (KBr): 3080, 2929, 1704, 1596, 1492 cm^{-1}.

^1H NMR (DMSO-d_6; as *N*-methyl derivative): δ = 8.83 (d, *J* = 8.7 Hz, 1 H), 7.71 (dd, J_1 = 8.8 Hz, J_1 = 1.3 Hz, 1 H),7.59 (d, *J* = 7.8 Hz, 1 H), 7.54 (s, 1 H), 7.52–7.42 (m, 4 H), 7.18 (d, *J* = 8.7 Hz, 2 H), 7.11–7.06 (m, 1 H), 3.87 (s, 3 H), 3.68 (s, 3 H).

^{13}C NMR (DMSO-d_6; as *N*-methyl derivative): δ = 159.7, 147.6, 136.4, 134.7, 131.9, 131.0, 130.5, 130.0, 125.2 (q, J_{C-F} = 272.8 Hz), 124.82, 124.83 (q, J_{C-F} = 31.4 Hz), 124.2, 123.3, 120.5 (q, J_{C-F} = 3.3 Hz), 117.2, 116.0, 115.5, 115.1, 114.7, 55.7, 31.0.

^{19}F NMR (DMSO-d_6; as *N*-methyl derivative): δ = –59.3.

HRMS: *m*/*z* [M + H]$^+$ as *N*-methyl derivative calcd for $C_{24}H_{18}F_3N_2O_2$: 423.1312; found: 423.1315.

12-Phenyl-10-(trifluoromethyl)indolo[1,2-*c*]quinazolin-6(5*H*)-one (5q)

Purified with *n*-hexane/EtOAc (75:30) as eluent.

Yield: 87.4 mg (69%) from ArBr; pale-yellow powder; mp 330–332 °C.

IR (KBr): 3678, 1712, 1618, 1440, 1408 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 11.67 (br s, 1 H), 8.81 (d, *J* = 8.6 Hz, 1 H), 7.73 (dd, J_1 = 8.8 Hz, J_1 = 1.4 Hz, 1 H), 7.68–7.54 (m, 7 H), 7.46–7.37 (m, 2 H), 7.29 (d, *J* = 7.6 Hz, 1 H), 7.02–6.96 (m, 1 H).

^{13}C NMR (DMSO-d_6): δ = 147.3, 135.4, 134.9 (overlapping), 134.4, 133.1, 131.1, 130.7, 130.6, 130.4, 130.0, 125.2 (q, J_{C-F} = 272.1 Hz), 124.9 (q, J_{C-F} = 31.5 Hz), 124.0, 123.1, 120.3 (q, J_{C-F} = 4.2 Hz), 117.0, 116.3, 115.7 (q, J_{C-F} = 4.2 Hz), 115.0, 113.9.

^{19}F NMR (DMSO-d_6): δ = –59.5.

HRMS: *m*/*z* [M–H]$^-$ calcd for $C_{22}H_{12}F_3N_2O$: 377.0903; found: 377.0907.

Ethyl 4-(2-Methyl-6-oxo-5,6-dihydroindolo[1,2-c]quinazolin-12-yl)benzoate (5r)

Purified with *n*-hexane/EtOAc (75:25), *n*-hexane/EtOAc/MeOH (70:20:10) as eluent.

Yield: 91.6 mg (66%) from ArI; white powder; mp 276–278 °C.

IR (KBr): 3854, 2924, 1700, 1606, 1513, 1497, 1455 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 11.43 (br s, 1 H), 8.66 (d, *J* = 8.1 Hz, 1 H), 8.18 (d, *J* = 8.1 Hz, 2 H), 7.72 (d, *J* = 8.1 Hz, 2 H), 7.45–7.31 (m, 3 H), 7.24 (s, 1 H), 7.23–7.16 (m, 3 H), 4.39 (q, *J* = 7.1 Hz, 2 H), 2.06 (s, 3 H), 1.38 (t, *J* = 8.1 Hz, 3 H).

^{13}C NMR (DMSO-d_6): δ = 166.0, 147.5, 139.3, 133.2, 133.0, 131.8, 131.3 (overlapping), 130.9, 130.39, 130.37, 129.8, 129.3, 124.3, 123.8, 118.7, 116.2, 116.1, 113.9, 113.8, 61.4, 21.1, 14.7.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{21}N_2O_3$: 397.1549; found: 397.1547.

12-(4-Methoxyphenyl)-10-methylindolo[1,2-*c*]quinazolin-6(5*H*)-one (5s)

Purified with *n*-hexane/EtOAc (75:25), CH_2Cl_2/$CHCl_3$ (75:25) as eluent.

Yield: 96.7 mg (78%) from ArI; white powder; mp 330–332 °C.

IR (KBr): 3364, 3058, 3000, 1700, 1593, 1513, 1488, 1460 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 11.39 (br s, 1 H), 8.50 (d, *J* = 8.4 Hz, 1 H), 7.49–7.42 (m, 3 H), 7.36–7.32 (m, 1 H), 7.27–7.20 (m, 2 H), 7.17 (d, *J* = 8.7 Hz, 2 H), 7.12 (s, 1 H), 7.00–6.93 (m, 1 H), 3.88 (s, 3 H), 2.40 (s, 3 H).

^{13}C NMR (DMSO-d_6): δ = 159.4, 147.6, 135.2, 133.2, 131.9, 131.5, 131.1, 129.4, 128.9, 125.9, 125.6, 123.6, 122.8, 118.6, 116.0, 115.8, 115.2, 114.7, 114.5, 55.6, 21.6.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{19}N_2O_2$: 355.1438; found: 355.1441.

Ethyl 4-(10-Methyl-6-oxo-5,6-dihydroindolo[1,2-c]quinazolin-12-yl)benzoate (5t)

Purified with *n*-hexane/EtOAc (70:30), *n*-hexane/EtOAc/MeOH (70:20:10) as eluent.

Yield: 111.1 mg (83%) from ArI; pale-yellow powder; mp 307–309 °C.

IR (KBr): 3378, 2228, 1702, 1603, 1485, 1451 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 11.44 (br s, 1 H), 8.48 (d, *J* = 8.4 Hz, 1 H), 8.14 (d, *J* = 8.1 Hz, 2 H), 7.66 (d, *J* = 8.1 Hz, 2 H), 7.37–7.30 (m, 2 H), 7.26–7.17 (m, 2 H), 7.11 (s, 1 H), 6.93 (t, *J* = 7.6 Hz, 1 H), 4.35 (q, *J* = 7.1, 2 H), 2.35 (s, 3 H), 1.34 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (DMSO-d_6): δ = 166.0, 147.4, 139.4, 135.3, 133.5, 131.25, 131.23, 130.6, 130.5, 129.83, 129.78, 129.3, 125.8, 123.7, 122.9, 118.3, 116.2, 115.9, 114.0, 113.8, 61.3, 21.6, 14.7.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{21}N_2O_3$: 397.1551; found: 397.1547.

Acknowledgment

We gratefully acknowledge the University of l'Aquila and the Sapienza, University of Rome, for financial support.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1589158.

References

(1) (a) Chelucci, G. *Coor. Chem. Rev.* **2017**, *331*, 37. (b) Platon, M.; Amardeil, R.; Djakovitchb, L.; Hierso, J.-C. *Chem. Soc. Rev.* **2012**, *41*, 3929. (c) Shiri, M. *Chem. Rev.* **2012**, *112*, 3508. (d) Vincente, R. *Org. Biomol. Chem.* **2011**, *9*, 6469. (e) Taber, D. F.; Tirunahari,

P. K. *Tetrahedron* **2011**, *67*, 7195. (f) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2011**, *111*, PR 215. (g) Barluenga, J.; Rodríguez, F.; Fañañas, F. T. *Chem. Asian J.* **2009**, *4*, 1036. (h) Kruger, K.; Tillack, A.; Beller, M. *Adv. Synth. Catal.* **2008**, *350*, 2153. (i) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (j) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (k) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (l) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (m) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045.

(2) (a) Zhang, M.-Z.; Chen, Q.; Yang, G.-F. *Eur. J. Med. Chem.* **2015**, *89*, 421. (b) Zi, W.; Zuo, Z.; Ma, D. *Acc. Chem. Res.* **2015**, *48*, 702. (c) Lancianesi, S.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2014**, *114*, 7108. (d) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489.

(3) (a) Tucker, A. M.; Grundt, P. *ARKIVOC* **2012**, *(i)*, 546; and references cited therein. (b) Jao, C.-W.; Lin, W.-C.; Wu, Y.-T.; Wu, P.-L. *J. Nat. Prod.* **2008**, *71*, 1275. (c) Utkina, N. K.; Denisenko, V. A. *Tetrahedron Lett.* **2007**, *48*, 4445. (d) Bergman, J.; Egestad, B.; Lindström, J.-O. *Tetrahedron Lett.* **1977**, 2625.

(4) Honda, G.; Tabata, M.; Tsuda, M. *Planta Med.* **1979**, *37*, 172.

(5) Krivogorsky, B.; Nelson, A. C.; Douglas, K. A.; Grundt, P. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1032.

(6) Sharma, V. M.; Prasanna, P.; Seshu, K. V. A.; Renuka, B.; Rao, C. V. L.; Kumar, G. S.; Narasimhulu, C. P.; Babu, P. A.; Puranik, R. C.; Subramanyam, D.; Venkateswarlu, A.; Rajagopal, S.; Kumar, K. B. S.; Rao, C. S.; Mamidi, D. S.; Deevi, N. V. S. R.; Ajaykumar, R.; Rajagopalan, R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2303.

(7) Hwang, J.-M.; Oh, T.; Kaneko, T.; Upton, A. M.; Franzblau, S. G.; Ma, Z.; Cho, S.-N.; Kim, P. *J. Nat. Prod.* **2013**, *76*, 354.

(8) Tsukano, C.; Okuno, M.; Nishiguchi, H.; Takemoto, Y. *Adv. Synth. Catal.* **2014**, *356*, 1533.

(9) (a) Vaidya, S. D.; Argade, N. P. *Org. Lett.* **2013**, *15*, 4006. (b) Wang, C.; Zhang, L.; Ren, A.; Lu, P.; Wang, Y. *Org. Lett.* **2013**, *15*, 2982. (c) Nelson, A. C.; Kalinowski, E. S.; Jacobson, T. L.; Grundt, P. *Tetrahedron Lett.* **2013**, *54*, 6804. (d) Xia, Z.; Wang, K.; Zheng, J.; Ma, Z.; Jiang, Z.; Wang, X.; Lv, X. *Org. Biomol. Chem.* **2012**, *10*, 1602. (e) Mason, J. J.; Janosik, T.; Bergman, J. *Synthesis* **2009**, 3642. (f) Lee, E. S.; Park, J.-G.; Jahng, Y. *Tetrahedron Lett.* **2003**, *44*, 1883. (g) Staskun, B.; Wolfe, J. F. *S. Afr. J. Chem.* **1992**, *45*, 5. (h) Bergman, J.; Tilstam, U.; Tçrnroos, K.-W. *J. Chem. Soc., Perkin Trans. 1* **1987**, 519.

(10) (a) Cacchi, S.; Marinelli, F. *In, Organopalladium Chemistry for Organic Synthesis*; Neghishi, E., Ed.; John Wiley & Sons: New York, **2002**, 2227. (b) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Eur. J. Org. Chem.* **2002**, 2671. (c) Arcadi, A.; Chiarini, M.; Marinelli, F.; Picchini, S. *Synthesis* **2011**, 4084; and references therein.

(11) (a) Cacchi, S.; Fabrizi, G.; Pace, P.; Marinelli, F. *Synlett* **1999**, 620. (b) Battistuzzi, G.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Parisi, L. M. *Org. Lett.* **2002**, *4*, 1355. (c) Arcadi, A.; Cacchi, S.; Cassetta, A.; Fabrizi, G.; Parisi, L. M. *Synlett* **2001**, 1605.

(12) (a) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Synthesis* **2004**, 1889. (b) Cacchi, S.; Fabrizi, G.; Lamba, D.; Marinelli, F.; Parisi, L. M. *Synthesis* **2003**, 728.

(13) Molina, P.; Alajarin, M.; Vidal, A. *Tetrahedron* **1990**, *46*, 1063.

(14) (a) Ponpandian, T.; Muthusubramanian, S. *Tetrahedron Lett.* **2012**, *53*, 4248. (b) Gerfaud, T.; Wei, H.-L.; Zhu, J. *Org. Lett.* **2011**, *13*, 6175. (c) Olivella, S.; Solé, A.; Jiménez, Ó.; Bosch, M. P.; Guerrero, A. *J. Am. Chem. Soc.* **2005**, *127*, 2620. (d) Cordaro, J. G.; Bergman, R. G. *J. Am. Chem. Soc.* **2004**, *126*, 16912.

(15) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Parisi, L. M. *Heterocycles* **2004**, *64*, 475.

(16) Formation of **6** also through a concomitant Pd-catalyzed route cannot be ruled out, see: Abbiati, G.; Arcadi, A.; Beccalli, E.; Bianchi, G.; Marinelli, F.; Rossi, E. *Tetrahedron* **2006**, *62*, 3033.

(17) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1992**, *33*, 3915.

(18) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Perboni, A.; Sferrazza, A.; Stabile, P. *Org. Lett.* **2010**, *12*, 3279.

(19) Cacchi, S.; Fabrizi, G.; Pace, P. *J. Org. Chem.* **1998**, *63*, 1001.