Studies on Novel Synthetic Methodologies, Part XII: An Efficient One-Pot Access to 6,6a-Dihydroisoindolo[2,1-a]quinazoline-5,11-diones and 5-Phenylisoindolo[2,1-a]quinazolin-11(6aH)-ones

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Abstract: A simple and efficient procedure for the construction of 6,6a-dihydroisoindolo[2,1-a]quinazoline-5,11-dione and 5-phenyl-isoindolo[2,1-a]quinazolin-11(6aH)-one derivatives in acetic acid under catalyst-free conditions is described. Attractive features of this methodology are its versatility, ready availability of starting materials and the efficiency in creating a complex core in a single operation.

Key words: one-pot synthesis, catalyst-free, 6,6a-dihydroiso-indolo[2,1-a]quinazoline-5,11-dione, 5-phenylisoindolo[2,1-a]quin-azolin-11(6aH)-one, 2-formyl benzoic acid

Quinazolines, quinazolinones and isoindolinone, represent common structural units in many natural alkaloids including rutaecarpine (**1**). They also show a range of biological activities.[1] In addition many unnatural quinaz-olinones show significant biological activities acting as anticancer,[2] antibacterial,[3] anti-inflammatory,[4] antihypertensive,[5] antidiabetic,[6] anticonvulsant,[7] and antianxietic agents.[8] Figure 1 shows the chemical structures of some potent biologically important quinazolinone, isoindolin-1-one-based compounds and the general structure of our synthesized prototype. The kinesin spindle protein inhibitor **2**[9] displays antimitotic activity and is in phase II clinical trials, while methaqualone (**3**) is a clinically used sedative.[10] Furthermore, diproqualone **4** is used primarily for the treatment of inflammatory pain associated with osteoarthritis,[11] while compound **5** possesses potent nicotinic acid receptor agonist activity for the treatment of dyslipidemia.[12] The isoindolinone (phthalimidine) motif occurs as a core structure not only in several natural products such as lennoxamine (**6**)[13] but also in a number of pharmacologically relevant synthetic molecules, such as pagoclone (**7**).[14]

Hybrid molecules that combine two heterocyclic structural units of different nature generally lend themselves well to rational drug design and often possess improved biological activities.[15] A number of biologically potent hybrids have been described in the literature such as steroid antibiotics,[16] steroid nucleosides,[17] triterpenoid peptides,[18] and DNA-cleaving-agent amino acids.[19] Multicomponent reactions (MCRs), have proven to be one of the most powerful methods to access complex structures in a single synthetic operation from simple building blocks[20] and are very useful in the construction of diverse chemical libraries of 'drug-like' molecules.[21,22] Recently, Pal et al. synthesized 6,6a-dihydroisoindolo[2,1-a]quin-azoline-5,11-dione derivatives **8** by employing a three-component reaction of isatoic anhydride, an amine and 2-formylbenzoic acid, using montmorillonite K10 as the catalyst.[23a] Additionally, Bunce et al. reported the synthesis of substituted quinazolinones using a dissolving metal reduction–condensative cyclization strategy.[23b] However, such syntheses are still suboptimal because of use of catalysts, forcing reaction conditions and long reaction times.

As a part of our ongoing studies devoted towards the development of a practical synthesis of biologically interesting heterocyclic molecules,[24] we have explored the possibility of an operatively simple, catalyst-free synthesis of 6,6a-dihydroisoindolo[2,1-a]quinazoline-5,11-dione derivatives. In the initial phase of this study we investigated the cyclization reaction of 2-formylbenzoic acid (**3**) with isatoic anhydride (**1**) and p-toluidine (**2i**) in the absence of catalyst in ethanol under heating (Scheme 1) for two hours which yielded the required compound **4i** in 45% yield (Table 1, entry 1). Further optimization re-
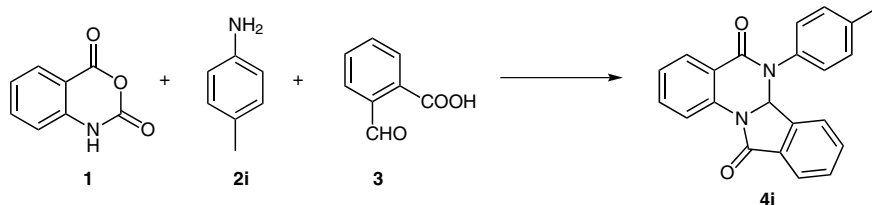
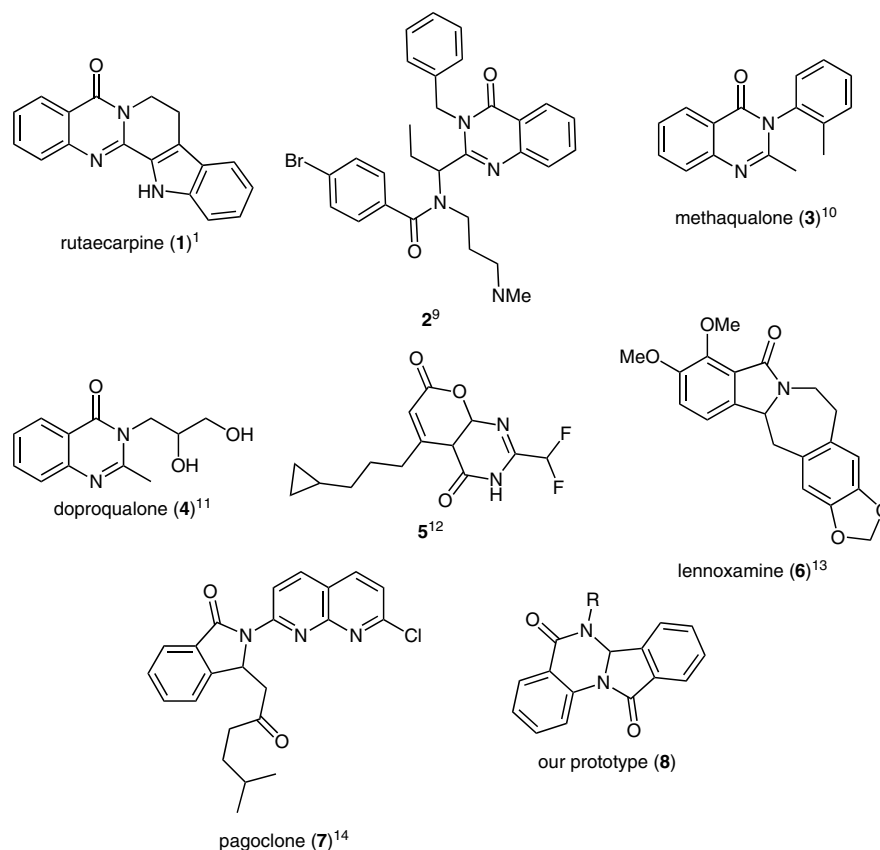**Scheme 1** Reaction of isatoic anhydride (**1**), p-toluidine (**2i**) and 2-formylbenzoic acid (**3**)

Figure 1 Biologically active quinazolinone, isoindolinone-based compounds **1–7** and our prototype **8**

sults are presented in Table 1. Replacement of ethanol with acetic acid caused a sharp increase in the yield of this reaction (85%; Table 1, entry 6). The solvent was found to have a dramatic impact on the efficiency of the reaction (Table 1, entries 9–13). On the other hand, the use of CF$_3$COOH completely closed down the reaction (Table 1, entry 8). The cyclization ability of various binary solvent systems such as ethanol–acetic acid (Table 1, entry 9), acetonitrile–acetic acid (Table 1, entry 10) and DMF–acetic acid (Table 1, entry 11) was also tried without success.

We also carried out the reaction in the absence of acetic acid to confirm the cyclization ability of acetic acid. Thus, among the solvents screened, only the acetic acid promoted effective cyclization in high yield and short reaction time (Table 1, entry 13). Further increases in the reaction time did not increase the yield of the reaction (Table 1, entries 6 and 12).

The scope of this one-pot three-component synthesis of 6,6a-dihydroisoindolo[2,1-a]quinazoline-5,11-dione derivatives was next investigated. To explore the applicability of our reaction, we employed a variety of substituted aliphatic and aromatic amine derivatives in the reaction. Though the reaction worked well in all cases, the yields were better for the more nucleophilic aliphatic amines than aromatic amines (Table 2).

Table 1 Effect of Reaction Conditions on the Cyclization of Isatoic Anhydride (**1**), *p*-Toluidine (**2i**) and 2-Formylbenzoic Acid (**3**)

Entry	Solvent	Temp (°C)	Time (h)	Yield (%)[a]
1	EtOH	90	2.0	45
2	*i*-PrOH	90	2.0	35
3	DMF	110	2.0	30
4	DMSO	110	2.0	30
5	MeCN	90	2.0	40
6	AcOH	110	2.0	85
7	1,4-dioxane	110	2.0	40
8	CF$_3$COOH	110	2.0	–
9	AcOH–EtOH (7:3)	100	2.0	70
10	AcOH–MeCN (7:3)	100	2.0	73
11	AcOH–DMF (7:3)	110	2.0	70
12	AcOH	110	1.0	85
13	AcOH	110	0.75	85
14	AcONa	90	2.0	10

[a] Yields after recrystallization from chloroform–hexane (2:8).

All the synthesized[25] compounds were confirmed by ^{1}H NMR, ^{13}C NMR, IR spectroscopy and mass spectrometry and their comparison with published data in the case of known compounds (**4a–e**,**h**,**m**,**n**).[23]

A plausible mechanism for the formation of 6,6a-di-hydroisoindolo[2,1-*a*]quinazoline-5,11-diones is depicted in Scheme 2.[23a] In order to elucidate the possible role of acetic acid the reaction was performed at two different pK_a values. The reaction with sodium acetate (a weak base) in ethanol (Table 1, entry 14) resulted in low yield of the product. The best results were obtained in acetic acid (pK_a 4.76; Table 1, entries 6, 12 and 13), while the reaction when performed in trifluoroacetic acid (pK_a 0.23; Table 1, entry 8) did not give any products, possibly because trifluoroacetic acid used in large excess as solvent, is too strong an acid. These initial results indicate the important role of acetic acid as a solvent with optimum pKa and, in some way, as an activator of the cyclization process.
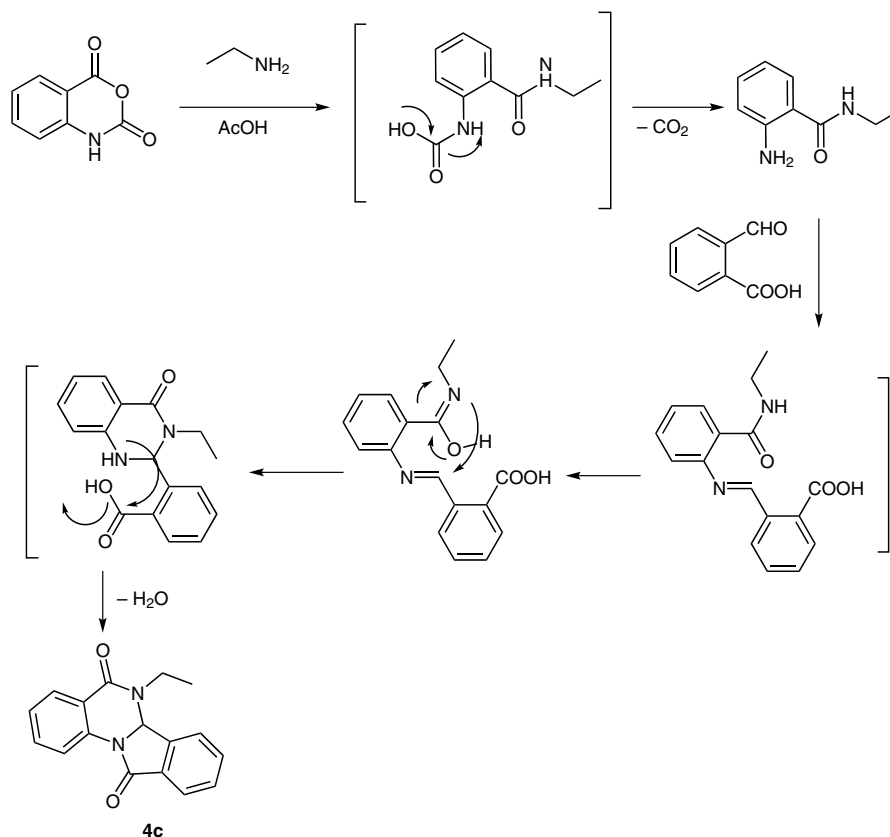
Scheme 2 Plausible mechanism for the formation of 6,6a-dihydroisoindolo[2,1-*a*]quinazoline-5,11-diones derivatives

Table 2 General Synthesis of 6,6a-Dihydroisoindolo[2,1-*a*]quinazoline-5,11-diones Derivatives from Suitable Precursors
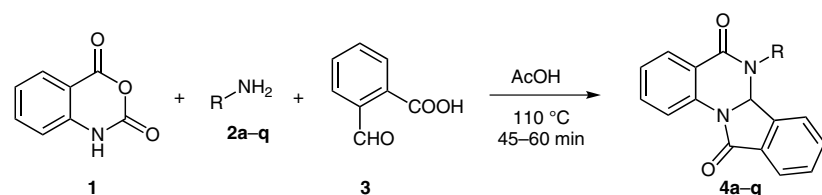
Entry	Amine **2**	Product **4**	Time (min)	Yield (%)[a]
1	NH$_4$OAc **2a**	**4a**	45	92

Table 2 General Synthesis of 6,6a-Dihydroisoindolo[2,1-*a*]quinazoline-5,11-diones Derivatives from Suitable Precursors (continued)
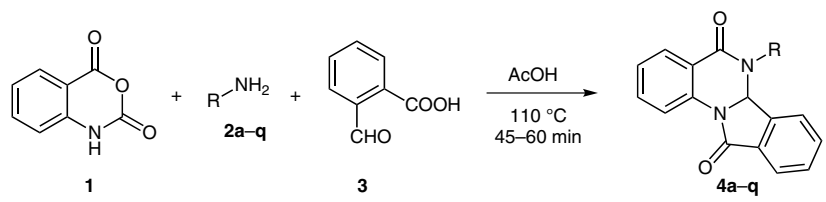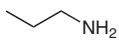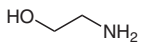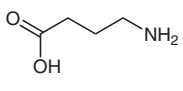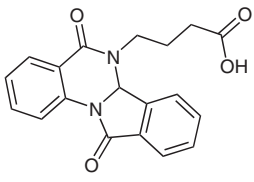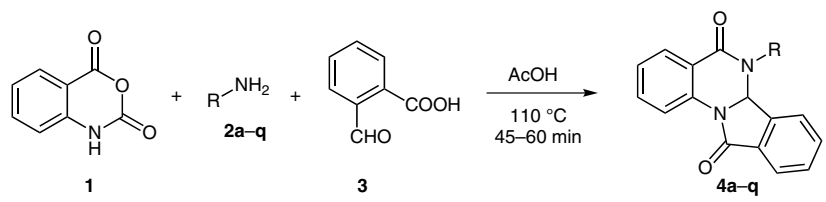

Entry	Amine **2**	Product **4**	Time (min)	Yield (%)[a]
2	MeNH$_2$ **2b**	**4b**	50	92
3	**2c**	**4c**	45	91
4	**2d**	**4d**	48	90
5	**2e**	**4e**	50	92
6	**2f**	**4f**	50	90
7	**2g**	**4g**	55	89

Table 2   General Synthesis of 6,6a-Dihydroisoindolo[2,1-*a*]quinazoline-5,11-diones Derivatives from Suitable Precursors (continued)
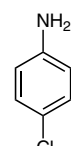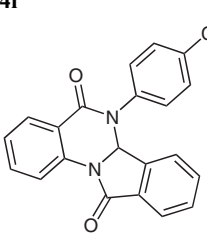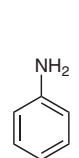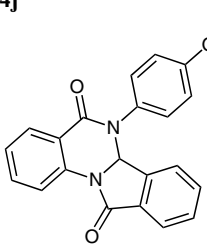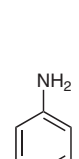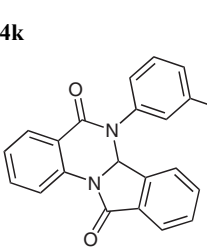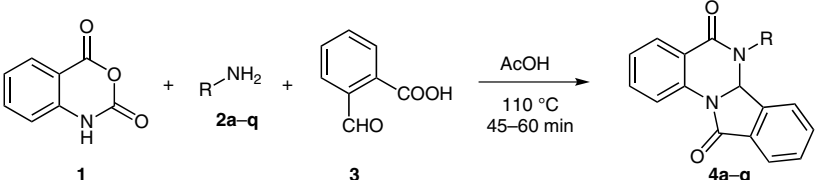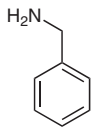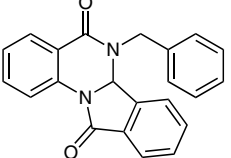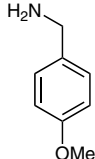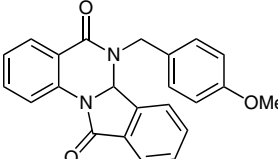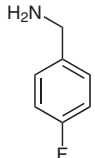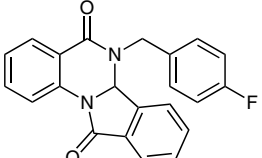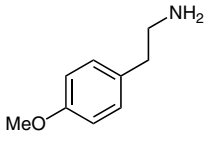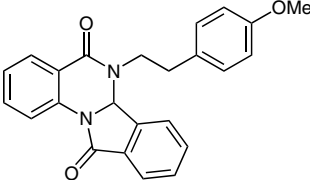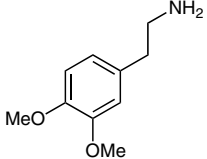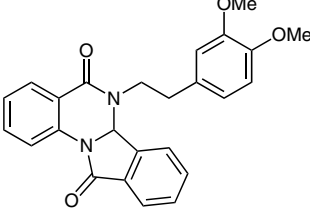
Entry	Amine **2**	Product **4**	Time (min)	Yield (%)[a]
8	**2h**	**4h**	48	80
9	**2i**	**4i**	45	85
10	**2j**	**4j**	50	80
11	**2k**	**4k**	60	80
12	**2l**	**4l**	60	82

Table 2   General Synthesis of 6,6a-Dihydroisoindolo[2,1-*a*]quinazoline-5,11-diones Derivatives from Suitable Precursors (continued)
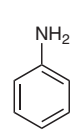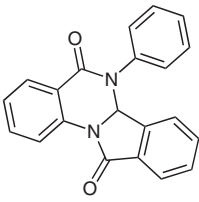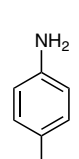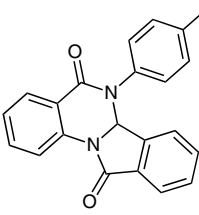

Entry	Amine **2**	Product **4**	Time (min)	Yield (%)[a]
13	**2m**	**4m**	50	85
14	**2n**	**4n**	55	85
15	**2o**	**4o**	60	83
16	**2p**	**4p**	60	85
17	**2q**	**4q**	60	82

[a] Yields after recrystallization from chloroform–hexane (2:9).

The structural diversity of this reaction was further increased by using 2-aminobenzophenone (**5b**) instead of isatoic anhydride under similar reaction conditions, leading to the formation of new 5-phenylisoindolo[2,1-*a*]quinazolin-11(6a*H*)-one derivatives (Table 3, compounds **6a–e**).

According to Table 3, in all the cases the reactions were accomplished in relatively short reaction time and the products were obtained in good to excellent yields (more than 70%). To determine the scope of this protocol, various aliphatic and aromatic amine derivatives were employed. However the reaction worked well with 2-amino-
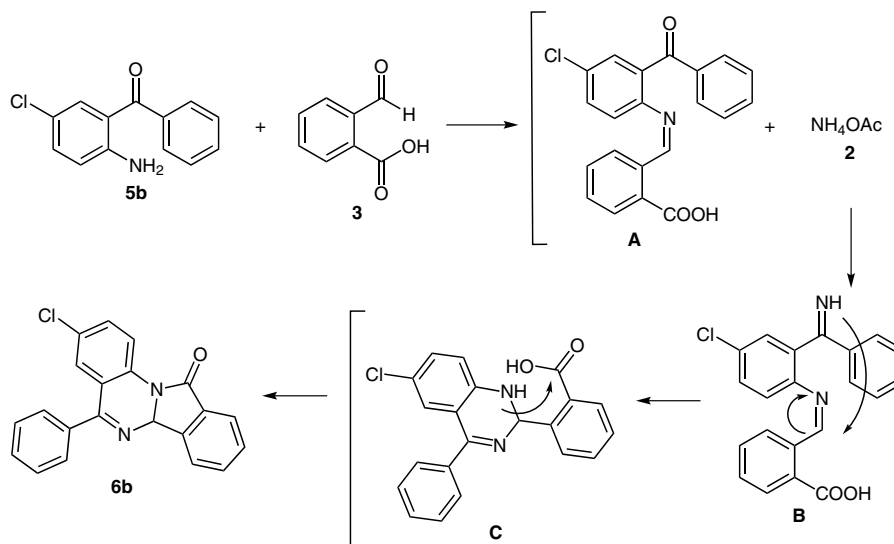
Scheme 3 Plausible mechanism for the formation of **6b**

benzophenone derivatives only. All compounds were characterized through ^{1}H NMR, ^{13}C NMR, HRMS and IR spectroscopic studies[26] (please refer to the Supporting Information).

The proposed mechanism for the formation of the 5-phenylisoindolo[2,1-*a*]quinazolin-11(6a*H*)-ones is shown in Scheme 3.[23a,27,28] The reaction is expected to proceed via aldimine benzophenone intermediate **A** generated in situ from the reaction of **5b** with 2-formylbenzoic acid in acetic acid. The reaction of intermediate **A** with ammonium acetate results in the second intermediate imine **B** which subsequently participates in an intramolecular cyclization (**C**) followed by nucleophilic attack of the ring nitrogen on the carbonyl of the carboxylic acid leading to the formation of **6b**.

In summary, we have developed an alternative, catalyst-free synthesis of 6,6a-dihydroisoindolo[2,1-*a*]quinazoline-5,11-diones and 5-phenylisoindolo[2,1-*a*]quinazolin-11(6a*H*)-ones with excellent yields and short reaction times. Attractive features of this methodology are its versatility, the readily available starting materials needed, and the efficiency in creating a complex core in a single operation.

Acknowledgment

Table 3 Three-Component Synthesis of 5-Phenylisoindolo[2,1-*a*]quinazolin-11(6a*H*)-one Derivatives **6a–e** in One Pot
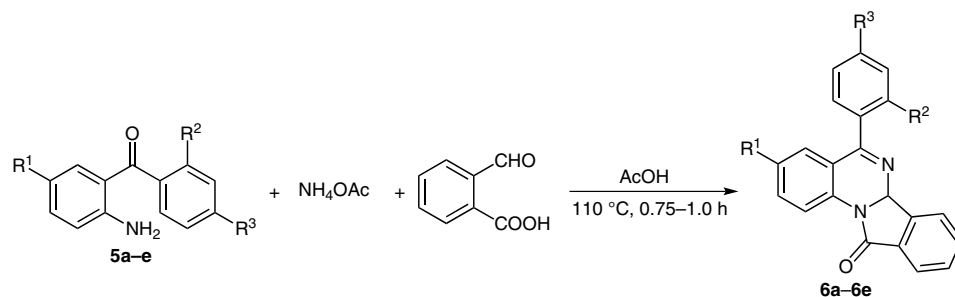
Entry	R^1	R^2	R^3	Time (min)	Product (yield, %)^a
1	H	H	H	60	**6a** (75)
2	Cl	H	H	45	**6b** (80)
3	Cl	F	H	60	**6c** (75)
4	Cl	F	F	60	**6d** (80)
5	H	H	Br	60	**6e** (70)

^{a} Yields are of the isolated product after purification by column chromatography.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(25) **Representative Procedure for the Synthesis of 6-Ethyl-6,6a-dihydroisoindolo[2,1-*a*]quinazoline-5,11-dione**: Isatoic anhydride (1.0 mmol) was added to a 50-mL round-bottom flask containing AcOH (10 mL). Ethylamine (1.1 mmol) and 2-formylbenzoic acid (1.0 mmol) were added and the reaction mixture was heated for 45 min at 110 °C (initially effervescence was observed due to the generation of CO_2 gas). After completion of the reaction (TLC), the

reaction mixture was cooled to r.t. and poured into cold H_2O to precipitate the crude product which was filtered off. The crude product was recrystallized from $CHCl_3$–hexane (2:8) to give the pure product **4c** as a white solid; yield: 91%; mp 156–158 ºC. IR (KBr): 3016, 2854, 1718, 1655, 1487, 1064 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.09–8.16 (m, 2 H), 8.05 (d, J = 6.9 Hz, 1 H), 7.60–7.80 (m, 4 H), 7.31–7.35 (m, 1 H), 6.25 (s, 1 H), 3.98–4.10 (m, 1 H), 3.69–3.81 (m, 1 H), 1.23 (t, J = 7.0 Hz, 3 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 164.8, 163.5, 138.1, 136.6, 133.3, 132.8, 132.7, 130.5, 128.9, 125.1, 125.1, 125.0, 120.5, 120.1, 70.2, 37.7, 13.3. ESI–MS: m/z = 279 [M + H]$^+$.

(26) **General Procedure for the Preparation of 3-Chloro-5-phenylisoindolo[2,1-*a*]quinazolin-11(6a*H*)-one (6b)**: 2-Amino-5-chlorobenzophenone (1.0 mmol) was added to a 50-mL round-bottom flask containing AcOH (10 mL). Ammonium acetate (excess) and 2-formylbenzoic acid (1.0 mmol) were then added and the reaction mixture was heated for 45 min at 110 °C. After completion of the reaction (TLC), the reaction mixture was cooled to r.t. and poured into cold H_2O to precipitate the crude product which was filtered off. The crude product was purified by column chromatography (CH_2Cl_2–hexane, 5:5). The product **6b** was obtained as a pale green solid; yield: 80%; mp 216–218 ºC. IR (KBr): 2922, 1646, 1218 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.07 (d, J = 7.4 Hz, 1 H), 7.80 (d, J = 7.3 Hz, 1 H), 7.69–7.73 (m, 1 H), 7.60–7.65 (m, 1 H), 7.48 (d, J = 8.4 Hz, 1 H), 7.25–7.30 (m, 6 H), 7.05 (d, J = 2.2 Hz, 1 H), 6.27 (s, 1 H). ^{13}C NMR (50 MHz, CDCl$_3$): δ = 166.5, 149.3, 141.7, 138.7, 134.5, 133.3, 133.2, 132.4, 130.4, 129.1, 129.1, 128.5, 128.1, 127.7, 127.4, 123.6, 122.4, 55.7. HRMS (ESI): m/z [M + H] calcd for $C_{21}H_{13}N_2ClO$: 345.0795; found: 345.0785.

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