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Iodine-mediated electrophilic tandem cyclization of 2-alkynylbenzaldehydes with anthranilic acid leading to 1,2-dihydroisoquinoline-fused benzoxazinones☆

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ABSTRACT

An efficient iodine-mediated electrophilic tandem cyclization of substituted 2-alkynylbenzaldehydes with anthranilic acids under basic medium leading to iodo-1,2-dihydroisoquinoline-fused benzoxazinones is presented. Success of the protocol for the reaction of substituted 2-alkynylbenzaldehydes with 2-aminobenzamides to furnish isoquinoline-fused quinazolinones is also described.

1. Introduction

The fused 1,2-dihydroisoquinoline systems are of paramount importance as they are represented in several natural products and pharmaceutical agents.[1] A variety of bioactivities ascribed to these compounds include anticancer,[2] antitumor,[3] anti HIV,[4] PTP1B inhibitor.[5] Among several strategies to obtain fused-1,2-dihydroisoquinolines, the one originating from 2-(1-alkynyl)arenecarboxaldehyde has received considerable attention. The sequence of reaction involves initial activation of the formyl group of 2-(1-alkynyl)arenecarboxaldehyde by formation of an aldimine with an aryl amine, which then undergoes a cycloisomerization reaction with a pendent nucleophile in aryl amine in the presence of a metal catalyst that has the propensity to activate the alkyne unit for a nucleophilic attack. The usefulness of the methodology has been illustrated by several research groups by using differently substituted anilines carrying amino, amide, sulphonamide, methylamine, hydroxymethyl, di-*tert*-butyl malonate groups at *ortho*-position to the amino group and a variety of Lewis acid catalysts including AuCl,[6] $AgNO_3$,[7] AgOTf,[8] In(OTf)$_3$,[9] Yb(OTf),[10] CuI,[11] and Ph_3PAuMe/chiral Brønsted acids (Fig. 1).[12]

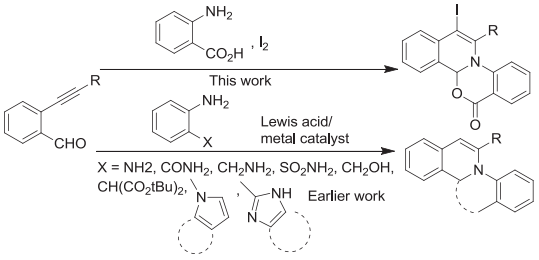

Fig. 1. Several substituted anilines employed for the synthesis of 1,2-dihydroisoquinoline-fused systems.

Despite formidable development, we noticed that the reaction of 2-alkynebenzaldehyde with anthranilic acid remains unreported. Since anthranilic acid is a viable precursor to 1,3-benzoxazinone system,[13] we envisaged that the reaction of 2-alkynylbenzaldehyde with anthranilic acid would result into a new 1,2-dihydroisoquinoline-fused 1,3-benzoxazinones. It is worth mentioning that compounds bearing 1,3-benzoxazinone

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core are also considered to be important as they are endowed with a variety of pharmacological properties.[14] Therefore we speculated that this novel skeleton containing both systems may generate significant interest in terms of biological activity as it has been noticed earlier with isoquinoline-fused benzimidazole, pyrimidine, imidazole and pyrazole systems.[3b,15] As a consequence, we initiated the study by exploring the reaction of 2-(phenylethynyl)benzaldehyde with anthranilic acid in the presence of silver salts including $AgNO_3$[7] and AgOTf,[8,16] but the reactions failed. An insight into the literature revealed that besides the metal-based Lewis acids, iodine had been also used as electrophile for inducing electrophilic cyclization for preparing isoquinoline derivatives.[17] Guided by these reports and in our interest to study the iodine-mediated electrophilic tandem cyclizations,[18] we considered investigating the reaction in the presence of iodine. In principle, an initial intermolecular imine formation between the formyl group of the 2-alkynylbenzaldehyde and the amino group of the anthranilic acid followed by the formation of iodonium cation would trigger an intramolecular nucleophilic attack of the carboxylate ion onto the imine moiety followed by endo-dig cyclization with the activated alkyne group (Fig. 2).[19] We were delighted to note that the reaction of 2-(phenylethynyl)benzaldehyde with anthranilic acid in the presence of iodine successfully afforded 1,2-dihydroisoquinoline-fused 1,3-benzoxazinone. We now wish to report for the first time an iodine-mediated protocol, which leads to an efficient synthesis of iodo-1,2-dihydroisoquinoline-fused benzoxazinones. In addition, we have found that the protocol works nicely for the efficient synthesis of iodoisoquinoline-fused quinazolinones via reaction of 2-alkynylbenzaldehydes with 2-aminobenzamides.

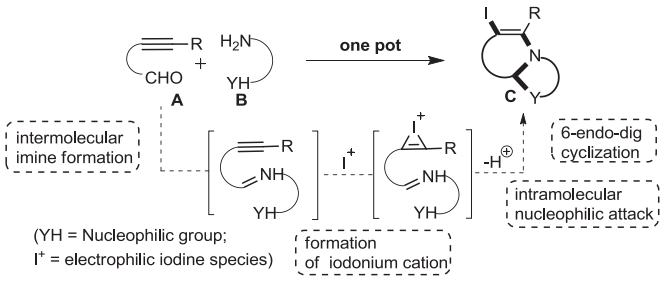


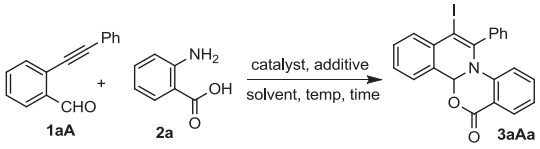
Fig. 2. Iodocyclization route to the formation of 1,2-dihydroisoquinolines-fused systems from 2-alkynylbenzaldehyde.

2. Results and discussion

In order to find out the feasibility of our approach in the initial exploring experiments, we investigated different reaction conditions using 2-(phenylethynyl)benzaldehyde **1aA** and anthranilic acid **2a** as the starting substrates (Table 1). As indicated in the preceding text, initially the reaction was attempted with $AgNO_3$ and AgOTf according to the reported procedures[7,8] but no product was detected (entries 1–4). Subsequently the same reaction was repeated in the presence of molecular iodine using MeCN as the medium. It was pleasing to note that after 24 h the reaction was complete and afforded a product (72%), which upon spectroscopic characterization was established to be the desired iodo-1,2-dihydroisoquinoline-fused benzoxazinone derivative **3aAa** (entry 5). Next, the same reaction was performed in the presence of CuI and I_2 in DMSO at 120 °C on one hand and in the presence of I_2 and K_2CO_3 in MeCN at room temperature on the other (entries 6, 7). Both reactions were completed in 12 h to afford the product **3aAa** in 64 and 68% yields, respectively. In the light of these results it became apparent that the reaction can be realized even in the absence of a metal catalyst and the presence of a base increases the rate immensely. Subsequent optimization with respect to the amount of iodine and the base used for the reaction indicated that the use of 1.5 equiv of I_2 and 1.5 equiv of $NaHCO_3$ in MeCN as medium and anhydrous Na_2SO_4 (1.0 equiv) as additive (for removing the water liberated during the aldimine formation) furnished the best yield of **3aAa** within 5 h (entries 8, 9). Replacing the iodine source to NIS or use of $CHCl_3$ in place of MeCN resulted in **3aAa** in inferior yields and took longer reaction time (entries 10, 11). During the optimization, fate of the reaction under the influence of other Lewis acids including $In(OTf)_3$ and $Yb(OTf)_3$ was also investigated but we did not observe the formation of **3aAa** with either of them (entries 12, 13). It may be noted that reaction failed in the absence of any catalyst/additive (entry 14).

With the optimized conditions in hand, we tested the scope of both substituted 2-ethynylbenzaldehydes **1** and anthranilic acids **2** partners for the iodine-mediated electrophilic tandem cyclization. As shown in Table 2, it was observed that except for the anthranilic

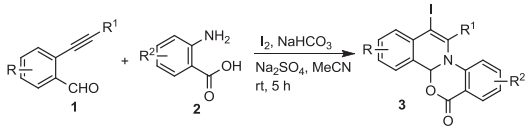
Table 1
Results of the screening of conditions[a] for reaction between 2-(phenylethynyl)benzaldehyde and anthranilic acid

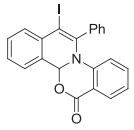
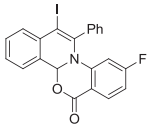
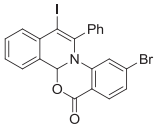
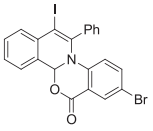
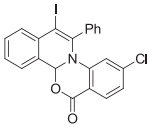
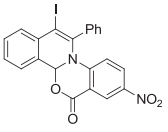
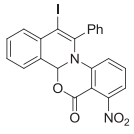
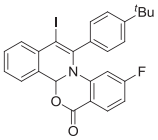


Entry	Catalyst (equiv)	Additive/base (equiv)	Solvent	Temp (°C)	Time (h)	Yield[d] (%) of **3aAa**
1[b]	$AgNO_3$ (0.05)	—	PhMe	80	3	—
2[b]	$AgNO_3$ (0.1)	—	H_2O	rt	12	—
3[b]	AgOTf (0.1)	—	DCE	rt	12	—
4[b]	AgOTf (0.1)	L-Proline (0.1)	EtOH	60	12	—
5	I_2 (3.0)	—	MeCN	rt	24	72
6	CuI/I_2 (0.1/1.0)	—	DMSO	120	12	64
7	I_2 (3.0)	K_2CO_3 (3.0)	MeCN	rt	12	68
8[c]	I_2 (3.0)	$NaHCO_3$ (3.0)	MeCN	rt	5	94
9[c]	I_2 (1.5)	$NaHCO_3$ (1.5)	MeCN	rt	5	94
10	NIS (3.0)	$NaHCO_3$ (3.0)	MeCN	rt	12	18
11	I_2 (1.5)	$NaHCO_3$ (1.5)	$CHCl_3$	rt	8	75
12[b]	$Yb(OTf)_3$ (0.1)	—	DCE	rt	12	—
13[b]	$In(OTf)_3$ (0.1)	—	DCE	70	12	—
14	No cat./additive	—	DMF	120	2	—

[a] Reaction conditions: **1aA** (100 mg, 0.48 mmol), **2a** (66 mg, 0.48 mmol), solvent (7 mL).
[b] Reactions were performed under inert atmosphere.
[c] Anhydrous Na_2SO_4 (69 mg, 0.48 mmol) was added.
[d] Isolated yields.

Table 2
Scope of iodine-mediated reaction[a] for the synthesis of fused iodo-1,2-dihydroisoquinoline-fused benoxazinones[b]



Entry	**1** (R)	**1** (R^1)	**2** (R^2)	3	Yield (%)
1	**a** (H)	**A** (Ph)	**a** (H)	 **3aAa**	94
2	**a** (H)	**A** (Ph)	**b** (4-F)	 **3aAb**	84
3	**a** (H)	**A** (Ph)	**c** (4-Br)	 **3aAc**	92
4	**a** (H)	**A** (Ph)	**d** (5-Br)	 **3aAd**	86
5	**a** (H)	**A** (Ph)	**e** (4-Cl)	 **3aAe**	90
6	**a** (H)	**A** (Ph)	**f** (5-NO_2)	 **3aAf**	0
7	**a** (H)	**A** (Ph)	**g** (6-NO_2)	 **3aAg**	0
8	**a** (H)	**B** (4-^{t}Bu-C_6H_4)	**b** (4-F)	 **3aBb**	88

(*continued on next page*)

Table 2 (*continued*)

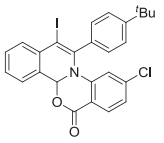
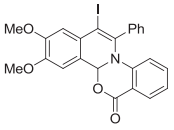
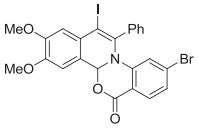
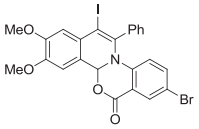
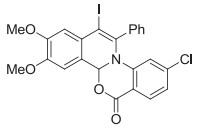
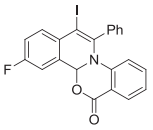
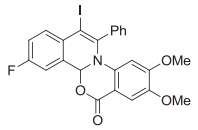
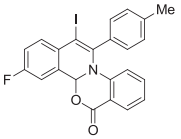
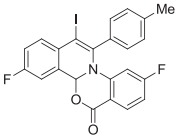
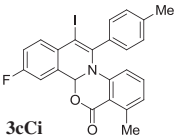
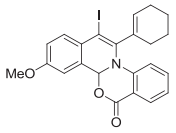
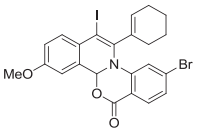
Entry	**1** (R)	**1** (R^1)	**2** (R^2)	3	Yield (%)
9	**a** (H)	**B** (4-^{t}Bu-C_6H_4)	**e** (4-Cl)	 **3aBe**	78
10	**b** (4,5-$(OMe)_2$)	**A** (Ph)	**a** (H)	 **3bAa**	92
11	**b** (4,5-$(OMe)_2$)	**A** (Ph)	**c** (4-Br)	 **3bAc**	86
12	**b** (4,5-$(OMe)_2$)	**A** (Ph)	**d** (5-Br)	 **3bAd**	89
13	**b** (4,5-$(OMe)_2$)	**A** (Ph)	**e** (4-Cl)	 **3bAe**	91
14	**c** (5-F)	**A** (Ph)	**a** (H)	 **3cAa**	93
15	**c** (5-F)	**A** (Ph)	**h** (4,5-$(OMe)_2$)	 **3cAh**	80
16	**c** (5-F)	**C** (4-Me−C_6H_4)	**a** (H)	 **3cCa**	91
17	**c** (5-F)	**C** (4-Me−C_6H_4)	**b** (4-F)	 **3cCb**	84
18	**c** (5-F)	**C** (4-Me−C_6H_4)	**i** (6-Me)	 **3cCi**	79

Table 2 (*continued*)

Entry	**1** (R)	**1** (R^1)	**2** (R^2)	3	Yield (%)
19	**d** (5-OMe)	**D** (Cyclohex-1-eneyl)	**a** (H)	 **3dDa**	83
20	**d** (5-OMe)	**D** (Cyclohex-1-eneyl)	**c** (4-Br)	 **3dDc**	84

[a] Reaction conditions: **1** (2 mmol), **2** (2 mmol), $NaHCO_3$ (3 mmol, 0.25 g), I_2 (3 mmol, 0.76 g), Na_2SO_4 (2 mmol, 0.28 g), MeCN (15 mL).
[b] Isolated yields.

acids **2f** and **2g** carrying a strong electron withdrawing substituent, such as nitro group (entries 6, 7), all other acids underwent the required reaction to afford the respective products **3** in excellent yields. In contrast, the changes in the alkyne part did not influence the formation of product and in all cases high yields of iodo-1,2-dihydroisoquinoline-fused benzoxazinones **3** were obtained. The structure of the products was unambiguously secured from the X-ray diffraction analysis of a single crystal of **3aAe** obtained from a mixture of MeOH/CH_2Cl_2 (9:1, v/v) (Fig. 3, see SD for details).

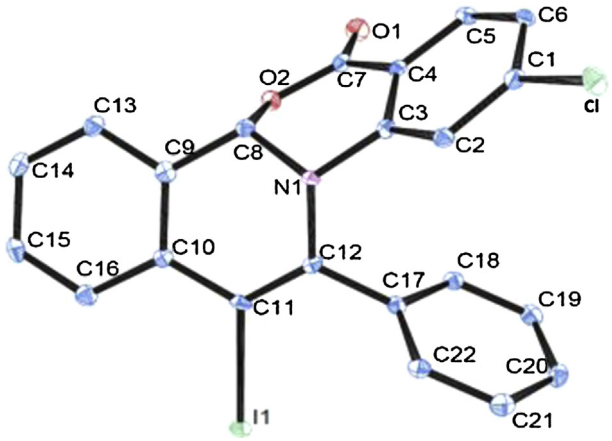


Fig. 3. The ORTEP diagram for **3aAe** at 35% probability level.

A plausible mechanism for the formation of iodo-1,2-dihydroisoquinoline-fused benzoxazinones is presented in Fig. 4. It is likely that initial aldimine (**I**) formation is followed by the generation of an iodonium cation (**II**), which undergoes an endo-dig cyclization via an intramolecular attack of imine. The base in the reaction abstracts the proton from the acid in **III** to generate an anion, which initiates an intramolecular nucleophilic attack followed by elimination of HI. The failure of this protocol with anthranilic acids bearing a strong electron withdrawing group, such as nitro, may be attributed to difficulty in the aldimine formation with such substrates.

Mechanistic considerations generated interest for investigating the fate of reaction of 2-ethynylbenzaldehydes with 2-aminobenzamides under identical conditions. It is worth mentioning that though this reaction was reported to afford 1,2-

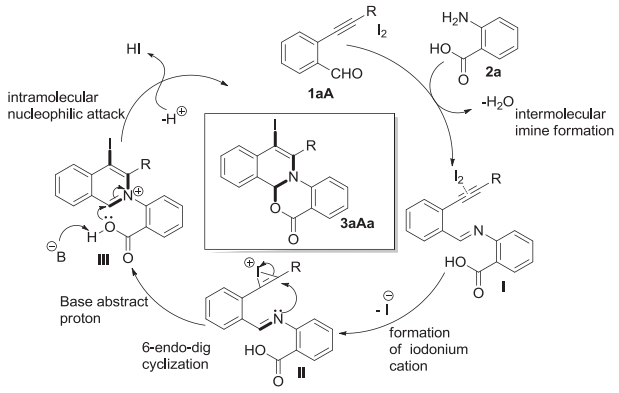
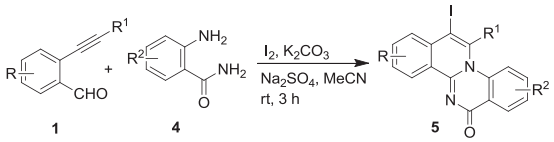


Fig. 4. Plausible mechanism for the formation of iodo-1,2-dihydroisoquinoline-fused benzoxazinones.

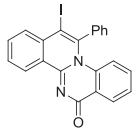
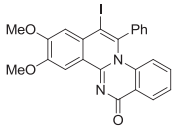
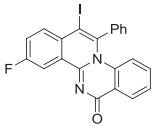
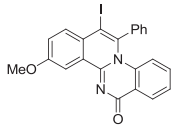
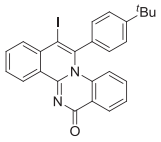
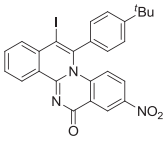
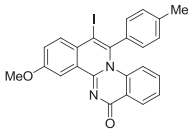
dihydroisoquinoline-fused quinazolines under the influence of a variety of metal catalysts,[6,7,11] iodine had not been used to realize this reaction. Accordingly, the 2-(phenylethynyl)benzaldehyde **1aA** was treated with 2-aminobenzamide ***4l*** in the presence of iodine under the optimized conditions. This reaction however afforded the product, which was identified as iodoisoquinoline-fused quinazolinone ***5aA1*** in 48% yields only. But during screening we found that use of K_2CO_3 in place of $NaHCO_3$ as the base in the reaction not only reduced the reaction time to 3 h but enhanced the yield of ***5aA1*** to 92% without the need of column chromatography for purification (Table 3). Notably, isoquinoline-fused quinazolinone were described to display antiinflammatory activity.[20]

The scope of the strategy was investigated further by including more 2-ethynylbenzaldehydes **1** and substituted 2-aminobenzamides **4**. Gratifyingly, all substrates afforded the respective products **5** in excellent yields without the need of purification (Table 3). The formation isoquinoline-fused benzquinazolinone was confirmed by performing single crystal X-ray diffraction analysis of ***5aB2*** (Fig. 5, see SD for details). Mechanism wise, we speculate that initially, like the mechanism delineated in Fig. 4, 1,2-dihydroisoquinoline-fused quinazolinone must have been formed, which underwent oxidization in the presence of molecular iodine to afford the observed product. Nevertheless, to ascertain it chemically, in a representative experiment, **1aA** was reacted with ***4l*** in the presence of AgOTf (0.1 equiv) to obtain **6** in 64% yields (Scheme 1).[6] Treating compound **6** with iodine (2.0 equiv) in MeCN, however resulted in ***5aA1*** in 96% yields. The formation of ***5aA1*** could be readily explained via initial

Table 3
Scope of iodine-mediated reaction[a] for the synthesis of fused iodoisoquinoline-fused benzquinazolinone[b]



1 4 5

Entry	**1** (R)	**1** (R^1)	**4** (R^2)	5	Yield (%)
1	**a** (H)	**A** (Ph)	***1*** (H)	 **5aA*1***	92
2	**b** (4,5-$(OMe)_2$)	Ph	***1*** (H)	 **5bA*1***	86
3	**c** (5-F)	Ph	***1*** (H)	 **5cA*1***	85
4	**d** (5-OMe)	Ph	***1*** (H)	 **5dA*1***	88
5	**a** (H)	4-^{t}Bu–C_6H_4	***1*** (H)	 **5aB*1***	88
6	**a** (H)	4-^{t}Bu–C_6H_4	***2*** (5-NO_2)	 **5aB*2***	90
7	**d** (5-OMe)	4-Me–C_6H_4	***1*** (H)	 **5dC*1***	92

[a] **1** (2 mmol), **4** (2 mmol), K_2CO_3 (3 mmol, 0.41 g), I_2 (3 mmol, 0.76 g), Na_2SO_4 (2 mmol, 0.28 g), MeCN (15 mL).
[b] Isolated yields.

iodonium cation formation at the double bond of **6** followed by oxidation.

Finally, in order to demonstrate the suitability of these substrates for transition-metal catalyzed-coupling reactions, compounds **3aAa** and **5aA*1*** were subjected to Sonogashira and Suzuki coupling reactions.[21,22] Treating **3aAa** with phenylacetylene and phenylboronic acid under the influence of Pd-catalyst resulted in the formation of products **7** and **8**, respectively (Scheme 2). Likewise, treating **5aA*1*** with same reagents under identical conditions afforded the products **9** and **10**, respectively, in excellent yields.

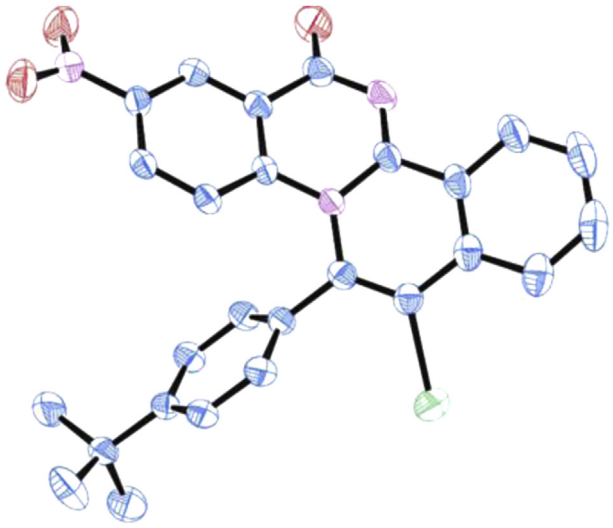
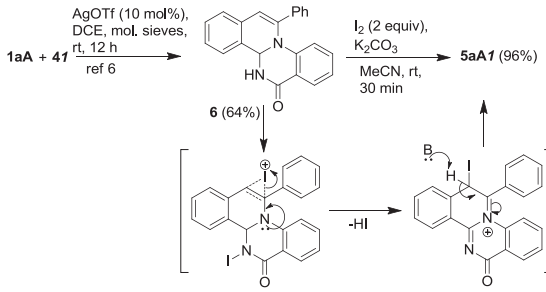
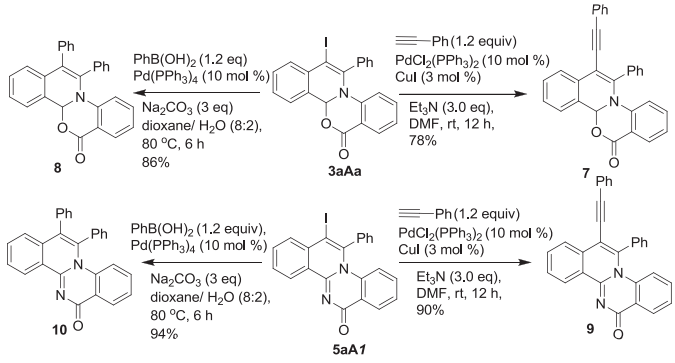


Fig. 5. The ORTEP diagram for **5aB*2*** at 35% probability level.



Scheme 1. Reaction of 1,2-dihydroisoquinoline-fused quinazolinone with iodine.



Scheme 2. Transition-metal catalyzed-coupling reactions of **3aAa** and **5aA*1***.

3. Conclusion

In summary, we have demonstrated a metal-free iodine-mediated electrophilic tandem cyclization in reaction between substituted 2-alkynylbenzaldehydes and anthranilic acids leading to the synthesis of iodo-1,2-dihydroisoquinoline-fused benzoxazinones in excellent yields. The methodology accommodates a broad range of substrates, which are either readily available or can be easily prepared. In addition, the protocol works efficiently for the reaction between 2-alkynylbenzaldehydes and 2-aminobenzamides to afford iodoisoquinoline-fused quinazolinones. The presence of the iodo group confers an advantage for further derivatization via robust cross coupling reactions, which has been exemplified via Sonogashira and Suzuki cross-couplings.

4. Experimental

4.1. General

Melting points are uncorrected and were determined in capillary tubes on a Precision melting point apparatus containing silicon oil. IR spectra were recorded using a Perkin Elmer's RX I FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded either on Bruker Avance DRX-300 or Bruker 400 MHz spectrometers, using TMS as an internal standard. The ESMS were recorded on Thermo Finnigan LCQ Advantage, Ion Trap Mass spectrometer. The HRMS spectra were recorded as EI-HRMS on Agilent 6520 Q-TOF, LC-MS/MS mass spectrometer.

4.2. General procedure for the iodine-mediated reaction of 2-alkynylbenzaldehydes *1* and anthranilic acid *2* as exemplified by the preparation of 3aAa

To a stirred mixture of **1aA** (0.42 g, 2.0 mmol) and **2a** (0.279 g, 2.0 mmol) in MeCN (15 mL) were added $NaHCO_3$ (0.252 g, 3.0 mmol), I_2 (0.762 g, 3.0 mmol) and anhydrous Na_2SO_4 (0.289 g, 2.0 mmol) at room temperature. The reaction was allowed to proceed at room temperature until complete consumption of starting material as monitored by TLC (ca. 5 h). After the reaction was complete, the mixture was washed with saturated $Na_2S_2O_3$ solution, extracted with EtOAc (2×25 mL), dried over anhydrous Na_2SO_4, and evaporated in vacuum on a rotary evaporator to afford a residue. This residue was purified by column chromatography on silica gel using hexanes–EtOAc (70:30, v/v) as the eluent to furnish 0.85 g (94%) of **3aAa** as a white solid.

*4.2.1. Iodo-18-phenyl-9-oxa-1-azatetracyclo[8.8.0.0^{2,7}.0^{11,16}]octadeca-2,4,6,11(16),12,14,17-eptaen-8-one (**3aAa**).* Mp: 142–143 °C; R_f=0.65 (CH_2Cl_2–MeOH, 9.5:0.5, v/v); IR (KBr) ν: 1722, 1592, 1464, 1280, 758 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=6.44 (d, 1H, J=7.8 Hz, ArH), 6.89 (s, 1H, CH), 7.08–7.19 (m, 4H, ArH), 7.26–7.29 (m, 3H, ArH), 7.38–7.46 (m, 2H, ArH), 7.57 (t, 1H, J=6.6 Hz, ArH), 7.74 (d, 1H, J=8.1 Hz, ArH), 8.07 (dd, 1H, J_1=1.4 Hz, J_2=7.5 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=89.5, 122.7, 123.5, 124.7, 126.2, 127.9, 128.2, 128.5, 128.9, 129.1, 130.1, 123.6, 131.1, 131.4, 132.9, 133.3, 138.7, 142.3, 144.2, 163.5. MS (ESI+): m/z=452.0. ESI-HRMS calculated for $C_{22}H_{14}INO_2$ $[MH]^+$: 452.0147, found: 452.0143.

*4.2.2. 4-Fluoro-17-iodo-18-phenyl-9-oxa-1-azatetracyclo[8.8.0.0^{2,7}.0^{11,16}]octadeca-2,4,6,11,13,15,17-heptaen-8-one (**3aAb**).* Yield: 84% (0.78 g from 0.42 g) as a gray solid, mp: 156–158 °C; R_f=0.68 (CH_2Cl_2–MeOH, 9.5:0.5, v/v); IR (KBr) ν: 1726, 1292, 788 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=6.15 (d, 1H, J=8.7 Hz, ArH), 6.87 (d, 1H, J=8.1 Hz, ArH), 7.11 (s, 2H, CH), 7.26–7.61 (m, 7H, ArH), 7.76 (d, 1H, J=7.2 Hz, ArH), 8.06 (s, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=90.6, 100.8, 103.9, 112.4 (d, J=25.5 Hz), 114.5 (d, J=22.5 Hz), 123.3, 125.6(2C), 128.7, 129.2, 130.2, 131.6, 132.8, 134.5, 134.9, 142.9, 145.6, 151.7, 153.2, 153.5158.5, 162.9. MS (ESI+): m/z=470.0. ESI-HRMS calculated for $C_{22}H_{13}FINO_2$ $[MH]^+$: 470.0053, found: 470.0034.

*4.2.3. 4-Bromo-17-iodo-18-phenyl-9-oxa-1-azatetracyclo[8.8.0.0^{2,7}.0^{11,16}]octadeca-2,4,6,11,13,15,17-heptaen-8-one (**3aAc**).* Yield: 92% (0.97 g from 0.42 g) as a white solid, mp: 163–165 °C; R_f=0.68 (CH_2Cl_2–MeOH, 9.5:0.5, v/v); IR (KBr) ν: 1721, 1593, 1385, 1075, 765 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 6.65 (s, 1H, ArH), 6.99 (s, 1H, CH), 7.15 (s, 2H, ArH), 7.32–7.51 (m, 6H,

ArH), 7.64 (d, 1H, J=6.5 Hz, ArH), 7.82 (d, 1H, J=7.9 Hz, ArH), 7.96 (d, 1H, J=8.3 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=89.4, 120.6, 127.5, 128.1, 128.3, 128.5, 128.7, 129.6(4C), 130.5(3C), 131.2(2C), 131.3, 131.6, 133.2, 138.2, 144.7, 162.8. MS (ESI+): m/z=530.2. ESI-HRMS calculated for $C_{22}H_{13}BrINO_2$ $[MH]^+$: 529.9253, found: 529.9233.

*4.2.4. 5-Bromo-17-iodo-18-phenyl-9-oxa-1-azatetracyclo [8.8.0.0^{2,7}.0^{11,16}]octadeca-2,4,6,11,13,15,17-heptaen-8-one (**3aAd**).* Yield: 86% (0.91 g from 0.42 g) as a white solid, mp: 176–178 °C; R_f=0.67 (CH_2Cl_2–MeOH, 9.5:0.5, v/v); IR (KBr) ν: 1726, 1266, 1096, 703 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=5.92 (d, 1H, J=8.5 Hz, ArH), 6.13–3.38 (m, 5H, ArH), 6.41 (d, 1H, J=1.7 Hz, ArH), 6.72–6.77 (m, 1H, ArH), 6.88 (s, 1H, ArH), 6.96–7.02 (m, 3H, ArH), 7.77 (s, 1H, ArH); ^{13}C NMR (75 MHz, DMSO): δ (ppm)=91.6, 121.2, 124.2, 128.4(2C), 128.5(3C), 129.8(2C), 130.1, 130.6, 131.4, 131.7, 132.6, 133.8, 135.8, 136.7, 137.3, 141.8, 145.8, 162.7. MS (ESI+): m/z=530.1. ESI-HRMS calculated for $C_{22}H_{13}INO_2$ $[MH]^+$: 529.9253, found: 529.9248.

*4.2.5. 4-Chloro-17-iodo-18-phenyl-9-oxa-1-azatetracyclo [8.8.0.0^{2,7}.0^{11,16}]octadeca-2,4,6,11,13,15,17-heptaen-8-one (**3aAe**).* Yield: 90% (0.87 g from 0.42 g) as a white solid, mp: 198–200 °C; R_f=0.65 (CH_2Cl_2–MeOH, 9.5:0.5, v/v); IR (KBr) ν: 1725, 1591, 1424, 1262, 1088, 705 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=6.43 (d, 1H, J=1.1 Hz, ArH), 6.93 (s, 1H, CH), 7.12–7.15 (m, 3H, ArH), 7.34–7.45 (m, 5H, ArH), 7.59 (t, 1H, J=7.2 Hz, ArH), 7.76 (d, 1H, J=7.9 Hz, ArH), 7.98 (d, 1H, J=8.4 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=90.2, 121.6, 122.7(2C), 126.7, 128.3, 128.6(4C), 130.5(2C), 131.2, 131.7(2C), 133.2, 138.2, 139.2, 139.4, 141.7, 144.8, 162.7. MS (ESI+): m/z=486.1. ESI-HRMS calculated for $C_{22}H_{13}ClINO_2$ $[MH]^+$: 485.9758, found: 485.9740. The details of the crystal structure investigation of this compound can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK vide CCDC no. 956063.

*4.2.6. 18-(4-tert-Butylphenyl)-4-fluoro-17-iodo-9-oxa-1-azatetracyclo[8.8.0.0^{2,7}.0^{11,16}]octadeca-2,4,6,11,13,15,17-heptaen-8-one (**3aBb**).* Yield: 88% (0.93 g from 0.53 g) as a brown solid, mp: 151–153 °C; R_f=0.68 (CH_2Cl_2–MeOH, 9.5:0.5, v/v); IR (KBr) ν: 1720, 1425, 723 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=1.29 (s, 9H, 3×CH_3), 6.21 (d, 1H, J=9.1 Hz, ArH), 6.87 (t, 1H, J=7.2 Hz, ArH), 7.04 (d, 1H, J=7.3 Hz, ArH), 7.32 (d, 2H, J=7.7 Hz, ArH), 7.39 (s, 1H, ArH), 7.51 (t, 1H, J=7.1 Hz, ArH), 7.61–7.71 (m, 2H, ArH), 7.85 (d, 1H, J=7.8 Hz, ArH), 8.05 (s, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=31.4(3C), 35.0, 90.6, 100.8, 103.9, 112.4 (d, J=25.5 Hz), 114.5 (d, J=22.5 Hz), 123.3, 125.6(2C), 128.7, 129.2, 130.2(2C), 131.6, 132.8, 134.7 (d, J=30.7 Hz), 142.9, 145.6, 151.7, 153.2, 153.5, 158.5, 162.9. MS (ESI+): m/z=526.1. ESI-HRMS calculated for $C_{26}H_{21}FINO_2$ $[MH]^+$: 526.0679, found: 526.0692.

*4.2.7. 18-(4-tert-Butylphenyl)-4-chloro-17-iodo-9-oxa-1-azatetracyclo[8.8.0.0^{2,7}.0^{11,16}]octadeca-2,4,6,11,13,15,17-heptaen-8-one (**3aBe**).* Yield: 78% (0.84 g from 0.53 g) as a white solid, mp: 180–182 °C; R_f=0.66 (CH_2Cl_2–MeOH, 9.5:0.5, v/v); IR (KBr) ν: 1718, 1265, 736 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=1.32 (s, 9H, 3×CH_3), 6.29 (s, 1H, CH), 6.88–7.01 (m, 3H, ArH), 7.11 (d, 1H, J=8.2 Hz, ArH), 7.33–7.43 (m, 4H, ArH), 7.57 (s, 1H, ArH), 7.74 (d, 1H, J=7.5 Hz, ArH), 7.98 (d, 1H, J=8.3 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=31.7(3C), 35.3, 90.1, 122.8, 124.9, 125.5, 126.6, 128.3, 128.8, 130.3, 130.8, 130.9, 131.2, 131.4, 132.1, 133.1, 133.5, 134.9, 135.5, 138.9, 144.7, 153.1, 155.4, 163.1. MS (ESI+): m/z=541.8. ESI-HRMS calculated for $C_{26}H_{21}ClINO_2$ $[MH]^+$: 541.0305, found: 541.0309.

*4.2.8. 17-Iodo-13,14-dimethoxy-18-phenyl-9-oxa-1-azatetracyclo [8.8.0.0^{2,7}.0^{11,16}]octadeca-2,4,6,11,13,15,17-heptaen-8-one (**3bAa**).* Yield: 92% (0.94 g from 0.53 g) as a gray solid, mp: 200–202 °C; R_f=0.70 (CH_2Cl_2–MeOH, 9.5:0.5, v/v); IR (KBr) ν: 1710, 1596, 1241, cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=3.49 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.43 (s, 1H, ArH), 7.02 (s, 1H, CH), 7.22–7.35 (m, 4H, ArH), 7.46 (s, 1H, ArH), 7.56–7.65 (m, 3H, ArH), 8.13 (d, 1H, J=7.6 Hz, ArH), 8.29 (d, 1H, J=7.6 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=55.8, 56.6, 96.1, 105.8, 108.3, 116.4, 121.6, 121.7, 122.9, 124.8, 125.6, 129.0, 129.1, 130.9(2C), 132.8, 133.3, 133.6, 134.1, 135.7, 137.3, 151.2, 153.7, 162.1. MS (ESI+): m/z=512.1. ESI-HRMS calculated for $C_{24}H_{18}INO_4$ $[MH]^+$: 512.059, found: 512.0352.

*4.2.9. 4-Bromo-17-iodo-13,14-dimethoxy-18-phenyl-9-oxa-1-azatetracyclo[8.8.0.0^{2,7}.0^{11,16}]octadeca-2,4,6,11,13,15,17-heptaen-8-one (**3bAc**).* Yield: 86% (1.02 g from 0.53 g) as a yellow solid; mp: 193–195 °C; R_f=0.71 (CH_2Cl_2–MeOH, 9.5:0.5, v/v); IR (KBr) ν: 1705, 1595, 1461, 1233, 763 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 3.58 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.51 (s, 1H, ArH), 7.02 (s, 1H, CH), 7.38–7.53 (m, 4H, ArH), 7.66 (t, 2H, J=7.4 Hz, ArH), 7.97 (d, 1H, J=8.5 Hz, ArH), 8.13 (d, 1H, J=8.4 Hz, ArH), 8.26 (s, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=56.6, 56.7, 84.5, 106.1, 119.3, 198.9, 122.5, 123.8, 128.6, 129.1, 129.2, 129.4, 129.6, 130.1, 130.3, 130.9, 131.3, 131.7, 132.4, 132.9, 133.6, 133.9, 151.9, 154.6. MS (ESI+): m/z=590.1. ESI-HRMS calculated for $C_{24}H_{17}BrINO_4$ $[MH]^+$: 589.9464, found: 589.9471.

*4.2.10. 5-Bromo-17-iodo-13,14-dimethoxy-18-phenyl-9-oxa-1-azatetracyclo[8.8.0.0^{2,7}.0^{11,16}]octadeca-2,4,6,11,13,15,17-heptaen-8-one (**3bAd**).* Yield: 89% (1.05 g from 0.53 g) as a yellow solid, mp: 202–204 °C; R_f=0.70 (CH_2Cl_2–MeOH, 9.5:0.5, v/v); IR (KBr) ν: 1707, 1586, 1462, 1240, 765 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 4.05 (s, 6H, 2×OCH_3), 6.58 (s, 1H, ArH), 7.37 (d, 2H, J=7.9 Hz, ArH), 7.49–7.53 (m, 4H, ArH), 7.76 (t, 2H, J=7.5 Hz, ArH), 8.23 (d, 2H, J=7.6 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=56.6(2C), 57.2, 99.8, 104.7, 112.6(2C), 116.8(2C), 124.5, 127.1(2C), 128.6(2C), 128.7(3C), 136.7(2C), 146.7, 151.4, 157.6(2C), 159.4. MS (ESI+): m/z=590.1. ESI-HRMS calculated for $C_{24}H_{17}BrINO_4$ $[MH]^+$: 589.9464, found: 589.9469.

*4.2.11. 4-Chloro-17-iodo-13,14-dimethoxy-18-phenyl-9-oxa-1-azatetracyclo[8.8.0.0^{2,7}.0^{11,16}]octadeca-2,4,6,11,13,15,17-heptaen-8-one (**3bAe**).* Yield: 91% (0.99 g from 0.53 g) as a white solid, mp: 195–197 °C; R_f=0.69 (CH_2Cl_2–MeOH, 9.5:0.5, v/v); IR (KBr) ν: 1712, 1577, 1268, 723 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=3.54 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 7.01 (s, 1H, CH), 7.15–7.26 (m, 2H, ArH), 7.35–7.43 (m, 3H, ArH), 7.68 (d, 2H, J=7.6 Hz, ArH), 8.04 (d, 1H, J=8.5 Hz, ArH), 8.17 (d, 2H, J=9.8 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=55.8, 56.6, 96.1, 105.9, 107.9, 114.2, 114.6, 115.9, 119.7, 121.4, 122.6, 126.1, 129.1, 129.4, 132.0, 133.1, 133.3, 134.1, 134.2, 138.5, 139.4, 141.9, 151.4, 153.7. MS (ESI+): m/z=546.1. ESI-HRMS calculated for $C_{24}H_{17}ClINO_4$ $[MH]^+$: 545.9969, found: 545.9972.

*4.2.12. 13-Fluoro-17-iodo-18-phenyl-9-oxa-1-azatetracyclo [8.8.0.0^{2,7}.0^{11,16}]octadeca-2,4,6,11,13,15,17-heptaen-8-one (**3cAa**).* Yield: 93% (0.87 g from 0.45 g) as a light yellow solid, mp: 138–140 °C; R_f=0.65 (CH_2Cl_2–MeOH, 9.5:0.5, v/v); IR (KBr) ν: 1722, 1592, 1243, 765 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=6.48 (d, 1H, J=7.5 Hz, ArH), 7.09–7.24 (m, 4H, ArH), 7.26–7.42 (m, 6H, ArH), 7.79 (d, 1H, J_1=5.5 Hz, J_2=8.5 Hz, ArH), 8.05 (d, 1H, J=6.8 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=91.9, 114.5 (d, J=30.7 Hz), 120.5, 123.9, 124.9, 126.5, 128.5, 128.8 (d, J=27 Hz), 129.2, 129.3, 129.6, 130.3 (d, J=24.7 Hz), 131.1, 132.9, 133.5 (d, J=6.0 Hz), 136.4, 138.5, 141.9, 143.6, 151.4, 160.3, 163.6. MS (ESI+): m/z=470.0. ESI-HRMS calculated for $C_{22}H_{13}FINO_2$ $[MH]^+$: 470.0053, found: 470.0063.

*4.2.13. 13-Fluoro-17-iodo-4,5-dimethoxy-18-phenyl-9-oxa-1-azatetracyclo[8.8.0.0^{2,7}.0^{11,16}]octadeca-2,4,6,11,13,15,17-heptaen-8-one (**3cAh**).* Yield: 80% (0.85 g from 0.45 g) as a gray solid, mp:

172–174 °C; R_f=0.74 (CH_2Cl_2–MeOH, 9.5:0.5, v/v); IR (KBr) ν: 1713, 1586, 1232, 746 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=3.42 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 5.88 (s, 1H, ArH), 6.95 (s, 1H, CH), 7.11–7.15 (m, 2H, ArH), 7.27–7.40 (m, 5H, ArH), 7.43 (s, 1H, ArH), 7.76 (dd, 1H, J_1=5.4 Hz, J_2=8.3 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=56.2, 56.3, 90.5, 107.6, 110.3, 114.7 (d, J=22.5 Hz), 115.2, 118.8 (d, J=22.5 Hz), 124.1 (d, J=33.0 Hz), 128.6, 129.2, 129.9, 130.5, 130.6, 132.2, 132.3, 133.4 (d, J=8.3 Hz), 138.8 (d, J=51.0 Hz), 141.9, 147.6, 152.9, 160.3, 163.1, 163.6. MS (ESI+): m/z=530.0. ESI-HRMS calculated for $C_{24}H_{17}FINO_4$ $[MH]^+$: 530.0265, found: 530.00268.

*4.2.14. 13-Fluoro-17-iodo-18-(4-methylphenyl)-9-oxa-1-azatetracyclo[8.8.0.0^{2,7}.0^{11,16}]octadeca-2,4,6,11,13,15,17-heptaen-8-one (**3cCa**).* Yield: 91% (0.88 g from 0.47 g); a white solid; mp: 208–210 °C; R_f=0.66 (CH_2Cl_2–MeOH, 9.5:0.5, v/v); IR (KBr) ν: 1724, 1593, 1237, 1114, 881 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)= 2.33 (s, 3H, CH_3), 6.44 (d, 1H, J=8.2 Hz, ArH), 6.81 (s, 1H, CH), 6.95 (s, 2H, ArH), 7.08 (d, 2H, J=7.9 Hz, ArH), 7.13–7.22 (m, 3H, ArH), 7.24–7.27 (m, 1H, ArH), 7.74 (dd, 1H, J_1=5.2 Hz, J_2=8.8 Hz, ArH), 8.06 (dd, 1H, J_1=2.1 Hz, J_2=7.6 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=21.5, 87.9, 114.6 (d, J=23.4 Hz), 118.4 (d, J=21.7 Hz), 123.1, 123.7, 123.8, 124.7, 126.1, 129.2, 129.8 (2C), 130.0, 130.4, 133.3 (d, J=8.3 Hz), 133.4, 135.5, 139.2, 141.8, 144.1, 160.3, 163.2, 163.5. MS (ESI+): m/z=484.2. ESI-HRMS calculated for $C_{23}H_{15}FINO_2$ $[MH]^+$: 484.0210, found: 484.0200.

*4.2.15. 4,13-Difluoro-17-iodo-18-(4-methylphenyl)-9-oxa-1-azatetracyclo[8.8.0.0^{2,7}.0^{11,16}]octadeca-2,4,6,11,13,15,17-heptaen-8-one (**3cCb**).* Yield: 84% (0.84 g from 0.47 g) as a gray solid, mp: 135–137 °C; R_f=0.67 (CH_2Cl_2–MeOH, 9.5:0.5, v/v); IR (KBr) ν: 1717, 1374, 1257 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=2.35 (s, 3H, CH_3), 6.36 (d, 1H, J=9.3 Hz, ArH), 6.93–7.06 (m, 3H, ArH), 7.13 (d, 2H, J=7.3 Hz, ArH), 7.37–7.42 (m, 3H, ArH), 7.88 (dd, 1H, J_1=5.3 Hz, J_2=8.2 Hz, ArH), 8.07 (t, 1H, J_1=5.2 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=21.4, 91.3, 112.5 (d, J=24.7 Hz), 114.2, 114.5, 114.6, 114.8, 114.9, 120.6 (d, J=23.3 Hz), 124.4 (d, J=9.0 Hz), 126.3 (d, J=27.7 Hz), 129.4, 130.2, 134.0, 134.1, 134.6, 139.4, 139.8, 160.4, 162.7, 163.7, 166.2, 171.3. MS (ESI+): m/z=502.2. ESI-HRMS calculated for $C_{23}H_{14}F_2INO_2$ $[MH]^+$: 502.0116, found: 502.0091.

*4.2.16. 13-Fluoro-17-iodo-6-methyl-18-(4-methylphenyl)-9-oxa-1-azatetracyclo[8.8.0.0^{2,7}.0^{11,16}]octadeca-2,4,6,11,13,15,17-heptaen-8-one (**3cCi**).* Yield: 79% (0.78 g from 0.47 g) as a pale yellow solid, mp: 144–146 °C; R_f=0.64 (CH_2Cl_2–MeOH, 9.5:0.5, v/v); IR (KBr) ν: 1719, 1473, 1258, 747 (CO_2Me), 3441 (OH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=2.38 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 6.38 (t, 1H, J=4.8 Hz, ArH), 6.76 (s, 1H, CH), 6.99–7.32 (m, 8H, ArH), 7.77 (dd, 1H, J_1=3.6 Hz, J_2=8.8 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=21.5, 21.8, 88.6, 114.6 (d, J=23.4 Hz), 118.6 (d, J=21.0 Hz), 122.7, 122.8, 123.8, 128.7, 129.1, 129.4, 130.2, 131.6, 133.2, 133.3 (d, J=8.2 Hz), 139.1, 142.2, 142.4, 144.6, 160.2, 162.7, 163.5. MS (ESI+): m/z=498.1. ESI-HRMS calculated for $C_{24}H_{17}FINO_2$ $[MH]^+$: 498.0366, found: 498.0371.

*4.2.17. 18-(Cyclohex-1-en-1-yl)-17-iodo-13-methoxy-9-oxa-1-azatetracyclo[8.8.0.0^{2,7}.0^{11,16}]octadeca-2,4,6,11,13,15,17-heptaen-8-one (**3dDa**).* Yield: 83% (0.84 g from 0.48 g) as a brown solid, mp: 180–182 °C; R_f=0.62 (CH_2Cl_2–MeOH, 9.5:0.5, v/v); IR (KBr) ν: 1701, 1473, 1371, 1295, 757 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)= 1.51 (br s, 4H, 2×CH_2), 1.92–2.24 (m, 4H, 2×CH_2), 3.56 (s, 3H, OCH_3), 6.51 (s, 1H, ArH), 7.09 (d, 1H, J=8.2 Hz, ArH), 7.17 (s, 1H, CH), 7.28–7.33 (m, 1H, ArH), 7.49 (s, 2H, ArH), 7.53 (d, 1H, J=7.3 Hz, ArH), 7.66 (s, 1H, ArH), 8.12 (d, 1H, J=7.5 Hz, ArH), 8.27 (d, 1H, J=7.6 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=21.1, 21.8, 24.4, 26.5, 55.8, 96.8, 111.4, 116.5, 119.8, 121.6, 122.7, 125.1, 125.2(2C), 125.8, 130.7, 131.1, 131.9, 132.9, 133.6, 135.8, 137.7, 161.5. MS (ESI+): m/z=486.1. ESI-HRMS calculated for $C_{23}H_{20}INO_3$ [M+Na]: 508.0386, found: 508.0390.

*4.2.18. 4-Bromo-18-(cyclohex-1-en-1-yl)-17-iodo-13-methoxy-9-oxa-1-azatetracyclo[8.8.0.0^{2,7}.0^{11,16}]octadeca-2,4,6,11,13,15,17-heptaen-8-one (**3dDc**).* Yield: 84% (0.94 g from 0.48 g) as a brown solid, mp: 210–212 °C; R_f=0.64 (CH_2Cl_2–MeOH, 9.5:0.5, v/v); IR (KBr) ν: 1714, 1601, 1383, 1252, 836 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=1.38–1.56 (m, 6H, 3×CH_2), 1.71–1.86 (m, 2H, CH_2), 3.80 (s, 3H, OCH_3), 5.14 (s, 1H, ArH), 7.15 (s, 1H, CH), 7.24 (d, 1H, J=9.0 Hz, ArH), 7.44–7.62 (m, 3H, ArH), 7.76 (d, 1H, J=9.0 Hz, ArH), 7.95 (d, 1H, J=9.0 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 21.4, 22.1, 25.3, 27.7, 56.1, 95.3, 111.2, 120.9, 124.5, 125.8, 128.6(2C), 131.1, 131.9(2C), 133.1(2C), 135.5, 136.7(2C), 143.3, 159.8, 163.8. MS (ESI+): m/z=564.1. ESI-HRMS calculated for $C_{23}H_{19}BrINO_3$ $[MH]^+$: 563.9671, found: 565.9653.

4.3. General procedure for the iodine-mediated reaction of 2-alkynylbenzaldehydes (1) and 2-aminobenzamides (4) as exemplified by the preparation of 5aA1

To a stirred solution of **1aA** (0.42 g, 2.0 mmol), **41** (0.272 g, 2.0 mmol) in MeCN (15 mL) were added I_2 (0.762 g, 3.0 mmol), K_2CO_3 (0.414 g, 3.0 mmol) and anhydrous Na_2SO_4 (0.289 g, 2.0 mmol) at room temperature. The reaction was allowed to proceed at room temperature until complete consumption of starting material as monitored by TLC (ca. 3 h). Thereafter saturated $Na_2S_2O_3$ aqueous solution was added; the solid precipitate was filtered and dried to give **5aA1**.

*4.3.1. 13-Iodo-12-phenyl-6H-isoquinolino[2,1-a]quinazolin-6-one (**5aA1**).* Yield: 92% (0.83 g from 0.42 g) as a gray solid, mp: 200–202 °C; R_f=0.53 (hexanes–EtOAc, 7:3, v/v); IR (KBr) ν: 1687, 1501, 1138, 756 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm)=7.02 (d, 1H, J=8.6 Hz, ArH), 7.16 (t, 1H, J=7.7 Hz, ArH), 7.33 (t, 1H, J=7.4 Hz, ArH) 7.41 (br s, 5H, ArH), 7.66 (t, 1H, J=7.6 Hz, ArH), 7.83 (t, 1H, J=7.4 Hz, ArH), 8.07 (d, 1H, J=8.2 Hz, ArH), 8.26 (d, 1H, J=7.7 Hz, ArH), 8.92 (d, 1H, J=8.0 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm)=91.5, 121.9, 122.6, 126.3, 126.8, 127.5, 127.9, 128.7, 129.7, 129.8, 130.8, 131.5, 132.8, 134.3, 135.8, 139.3, 139.5, 139.8, 153.7. MS (ESI+): m/z=449.1. ESI-HRMS calculated for $C_{22}H_{13}N_2O$ $[MH]^+$: 449.0151, found: 449.0157.

*4.3.2. 12-(4-tert-Butylphenyl)-13-iodo-6H-isoquinolino[2,1-a]quinazolin-6-one (**5aB1**).* Yield: 88% (0.88 g 0.53 g) as a yellow solid; mp: 220–222 °C; R_f=0.49 (hexanes–EtOAc, 7:3, v/v); IR (KBr) ν: 1683, 1469, 1119 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=1.34 (s, 9H, 3×CH_3), 7.12 (dt, 1H, J_1=1.5 Hz, J_2=8.7 Hz, ArH), 7.09–7.15 (m, 1H, ArH), 7.29–7.42 (m, 5H, ArH), 7.65 (t, 1H, J=7.3 Hz, ArH), 7.79–785 (m, 1H, ArH), 8.07 (d, 1H, J=8.1 Hz, ArH), 8.26 (dd, 1H, J_1=1.4 Hz, J_2=7.8, Hz, ArH), 8.93 (d, 1H, J=8.1 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=31.3(3C), 34.9, 91.2, 121.9, 122.5, 125.5(2C), 126.2, 126.7, 127.3, 127.8, 129.4, 130.5, 131.1(2C), 132.7, 134.2, 135.8, 136.4, 139.3, 139.9, 153.3, 153.6, 167.8. MS (ESI+): m/z=505.1. ESI-HRMS calculated for $C_{26}H_{21}IN_2O$ $[MH]^+$: 505.0777, found: 505.0783.

*4.3.3. 12-(4-tert-Butylphenyl)-13-iodo-9-nitro-6H-isoquinolino[2,1-a]quinazolin-6-one (**5aB2**).* Yield: 90% (0.98 g from 0.53 g) as a yellow solid, mp: 230–232 °C; R_f=0.46 (hexanes–EtOAc, 7:3, v/v); IR (KBr) ν: 1692, 1456, 1213, 756 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=1.35 (s, 9H, 3×CH_3), 7.19 (d, 1H, J=9.4 Hz, ArH), 7.36 (d, 2H, J=8.4 Hz, ArH), 7.45 (d, 2H, J=8.4 Hz, ArH), 7.69 (t, 1H, J=7.4 Hz, ArH), 7.85–7.95 (m, 2H, ArH), 8.11 (d, 1H, J=8.1 Hz, ArH), 8.89 (d, 1H, J=7.6 Hz, ArH), 9.09 (d, 1H, J=2.6 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=31.4(3C), 35.3, 92.9, 122.9, 123.2, 123.6, 124.6, 125.8, 126.1, 128.3(2C), 130.1, 131.1(2C), 133.1, 135.1, 135.8, 136.1,

139.3, 142.9, 145.5, 154.2, 154.7, 166.4. MS (ESI+): *m/z*=550.1. ESI-HRMS calculated for $C_{26}H_{20}IN_3O_3$ $[MH]^+$: 550.0628, found: 550.0620. The details of the crystal structure investigation of this compound can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK vide CCDC no. 956064.

*4.3.4. 13-Iodo-2,3-dimethoxy-12-phenyl-6H-isoquinolino[2,1-a]quinazolin-6-one (**5bA1**).* Yield: 86% (0.87 g from 0.53 g) as a gray solid, mp: 180–182 °C; R_f=0.56 (hexanes–EtOAc, 7:3, v/v); IR (KBr) ν: 1665, 1498, 1123, 726 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=4.11 (s, 6H, OCH_3), 7.04–7.12 (m, 3H, ArH), 7.16 (d, 1H, *J*=9.0 Hz, ArH), 7.30–7.41 (m, 4H, ArH), 7.52 (s, 1H, ArH), 8.27 (d, 1H, *J*=9.0 Hz, ArH), 8.36 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm)=56.5, 57.1, 91.5, 107.9, 114.1, 119.9, 122.1(2C), 122.6, 126.7, 127.5, 128.7(2C), 129.7, 130.6, 131.6(2C), 138.8, 139.4, 139.8, 151.1, 153.2, 155.0, 168.1. MS (ESI+): *m/z*=509.1. ESI-HRMS calculated for $C_{24}H_{17}IN_2O_3$ $[MH]^+$: 509.0362, found: 509.0348.

*4.3.5. 3-Fluoro-13-iodo-12-phenyl-6H-isoquinolino[2,1-a]quinazolin-6-one (**5cA1**).* Yield: 85% (0.79 g from 0.45 g) as a gray solid, mp: 198–200 °C; R_f=0.49 (hexanes–EtOAc, 7:3, v/v); IR (KBr) ν: 1686, 1518, 1338, 1136, 963, 761 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.03 (d, 1H, *J*=7.8 Hz, ArH), 7.17 (s, 1H, ArH), 7.28–7.52 (m, 7H, ArH), 8.08 (s, 1H, ArH), 8.23 (d, 1H, *J*=6.6 Hz, ArH), 8.58 (d, 1H, *J*=7.6 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=90.3, 113.2 (d, *J*=24.0 Hz), 121.9, 122.4, 122.6, 122.6, 127.1, 127.4, 127.8, 127.9, 128.7, 128.9, 129.9, 130.9, 131.4, 132.4, 135.6 (d, *J*=8.3 Hz), 139.3 (d, *J*=9.7 Hz), 152.7, 161.3, 164.6, 167.7. MS (ESI+): *m/z*=467.1. ESI-HRMS calculated for $C_{22}H_{12}FIN_2O$ $[MH]^+$: 467.0057, found: 467.0048.

*4.3.6. 13-Iodo-3-methoxy-12-phenyl-6H-isoquinolino[2,1-a]quinazolin-6-one (**5dA1**).* Yield: 88% (0.86 g from 0.47 g) as a yellow solid, mp: 232–235 °C; R_f=0.51 (hexanes–EtOAc, 7:3, v/v); IR (KBr) ν: 1678, 1512, 1235, 763 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=4.01 (s, 3H, OCH_3), 7.05 (d, 1H, *J*=8.7 Hz, ArH), 7.16 (dd, 1H, J_1=1.2 Hz, J_2=8.2 Hz, ArH), 7.32–739 (m, 7H, ArH), 7.99 (d, 1H, *J*=9.0 Hz, ArH), 8.25 (d, 1H, *J*=7.8 Hz, ArH), 8.32 (d, 1H, *J*=2.4 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=56.4, 91.6, 107.7, 122.1, 122.5, 124.5, 126.8, 127.4, 127.5, 128.6, 129.6, 129.8, 130.8, 131.5, 134.6, 137.6, 139.3, 139.5, 153.4, 160.7, 168.2. MS (ESI+): *m/z*=479.0. ESI-HRMS calculated for $C_{23}H_{15}IN_2O_2$ $[MH]^+$: 479.0256, found: 479.0268.

*4.3.7. 13-Iodo-3-methoxy-12-p-tolyl-6H-isoquinolino[2,1-a]quinazolin-6-one (**5dC1**).* Yield: 93% (0.91 g from 0.5 g) as a yellow solid, mp: 219–221 °C; R_f=0.51 (hexanes–EtOAc, 7:3, v/v); IR (KBr) ν: 1683, 1443, 1201, 937, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm)=2.39 (s, 3H, CH_3), 4.02 (s, 3H, OCH_3), 7.08 (d, 1H, *J*=8.7 Hz, ArH), 7.16–7.19 (m, 3H, ArH), 7.27–7.39 (m, 4H, ArH), 7.99 (d, 1H, *J*=8.9 Hz, ArH), 8.26 (d, 1H, *J*=7.7 Hz, ArH), 8.34 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$:CD_3OD): δ (ppm)=21.2, 55.9, 91.9, 107.6, 121.8, 122.2, 124.3, 126.7, 126.8, 126.9, 129.1, 121.9, 131.1, 131.1, 134.6, 136.4, 137.6, 139.3, 139.8, 153.4, 160.5, 168.6. MS (ESI+): *m/z*=493.1. ESI-HRMS calculated for $C_{24}H_{17}IN_2O$ $[MH]^+$: 493.0413, found: 493.0416.

4.4. General procedure for the Sonogashira coupling, as exemplified for the preparation of 7

A mixture of aryl iodide **3aAa** (0.5 g, 1.1 mmol), phenylacetylene (0.15 mL, 1.32 mmol), $Pd(PPh_3)_2Cl_2$ (0.031 g, 0.11 mmol), CuI (0.005 g, 0.033 mmol) and Et_3N (0.46 mL, 3.3 mmol) was added to a sealed tube in DMF (8 mL) under an atmosphere of N_2 and stirred at rt for 12 h. After complete consumption of the starting material as monitored by TLC, to the reaction mixture 25 mL of water was added and the reaction mixture was extracted with EtOAc (3×20 mL). The organic layers were combined, dried and evaporated to afford a residue, which upon purification via silica gel column chromatography (hexane–EtOAc, 70/30, v/v) afforded the product **7** (0.367 g, 78%) as a light brown solid.

*4.4.1. 18-Phenyl-17-(2-phenylethynyl)-9-oxa-1-azatetracyclo[8.8.0.0^{2,7}.0^{11,16}]octadeca-2,4,6,11(16),12,14,17-heptaen-8-one (**7**).* Mp: 192–194 °C; R_f=0.32 (CH_2Cl_2–MeOH, 9.5:0.5, v/v); IR (KBr) ν: 1724, 1601, 1286, 768 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=6.42 (d, 1H, *J*=7.8 Hz, ArH), 6.88 (s, 1H, CH), 7.07–7.18 (m, 3H, ArH), 7.25–7.33 (m, 7H, ArH), 7.43–7.58 (m, 5H, ArH), 7.73 (d, 1H, *J*=7.9 Hz, ArH), 8.06 (d, 1H, *J*=7.5 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=77.3, 83.7, 88.6, 122.2, 122.6, 123.3, 124.7, 126.1, 127.9, 128.4(4C), 128.9, 129.1, 130.1, 130.6, 131.1, 131.3, 132.2(4C), 132.9, 133.1, 138.7, 142.2, 144.2, 163.4, 171.3. MS (ESI+): *m/z*=425.2. ESI-HRMS calculated for $C_{30}H_{19}NO_2$ $[MH]^+$: 425.1416, found: 425.1419.

*4.4.2. 17,18-Diphenyl-9-oxa-1-azatetracyclo[8.8.0.0^{2,7}.0^{11,16}]octadeca-2,4,6,11(16),12,14,17-heptaen-8-one (**9**).* Yield: 90% (0.127 g from 0.15 g) as a yellow solid, mp: <250 °C; R_f=0.45(CH_2Cl_2–MeOH, 9.5:0.5, v/v); IR (KBr) ν: 1690, 1523, 1142 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.31–7.41 (m, 8H, ArH), 7.51–7.53 (m, 4H, ArH), 7.61–7.67 (m, 3H, ArH), 8.19 (t, 2H, *J*=4.9 Hz, ArH), 8.66 (d, 1H, *J*=4.9 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=83.8, 112.2(2C), 119.5(2C), 120.1, 121.3(2C), 122.1(2C), 122.3, 128.4(4C), 128.9(2C), 129.8(2C), 131.8, 132.3(4C), 135.4, 136.1, 139.7(2C), 141.4, 195.8. MS (ESI+): *m/z*=422.2. ESI-HRMS calculated for $C_{30}H_{18}N_2O$ $[MH]^+$: 422.1419, found: 422.1427.

4.5. General procedure for the Suzuki–Miyaura coupling, as exemplified for the preparation of 8

To a 50 mL two-necked round-bottomed flask charged with degassed dioxane/H_2O (8:2) were added aryl iodide **3aAa** (0.5 g, 1.1 mmol), phenylboronic acid (0.16 g, 1.33 mmol), $Pd(PPh_3)_4$ (0.063 g, 0.11 mmol), Na_2CO_3 (0.35 g, 3.32 mmol) under nitrogen and the mixture was stirred at 100 °C for 6 h. On completion, the reaction mixture was quenched with H_2O (30 mL) and extracted with EtOAc (3×20 mL). The organic layers were pooled, dried (Na_2SO_4) and evaporated to obtain a residue, which upon purification via silica gel column chromatography (hexane–EtOAc, 70/30, v/v) resulted into **8** (0.381 g, 86%) as a yellow solid.

*4.5.1. 18-Phenyl-17-(2-phenylethynyl)-1,9-diazatetracyclo[8.8.0.0^{2,7}.0^{11,16}]octadeca-2,4,6,9,11(16),12,14,17-octaen-8-one (**8**).* Mp: 210–212 °C; R_f=0.38 (CH_2Cl_2–MeOH, 9.5:0.5, v/v); IR (KBr) ν: 1720, 1596 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm)=6.43 (d, 1H, *J*=7.9 Hz, ArH), 6.87 (s, 1H, CH), 7.08–7.17 (m, 4H, ArH), 7.21–7.34 (m, 8H, ArH), 7.38–7.44 (m, 2H, ArH), 7.54–7.57 (m, 1H, ArH), 7.73 (d, 1H, *J*=8.0 Hz, ArH), 8.06 (dd, 1H, J_1=1.4 Hz, J_2=7.6 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm)=88.4, 120.6, 123.2, 124.7, 126.1, 126.4, 127.9, 128.4(3C), 128.7(2C), 129.1, 129.8(3C), 130.0, 130.6, 131.1, 131.3, 132.9, 133.1, 134.4, 138.7, 142.2, 144.2, 163.4, 171.2. MS (ESI+): *m/z*=401.0. ESI-HRMS calculated for $C_{28}H_{19}NO_2$ $[MH]^+$: 401.1416, found: 401.1413.

*4.5.2. 17,18-Diphenyl-1,9-diazatetracyclo[8.8.0.0^{2,7}.0^{11,16}]octadeca-2,4,6,9,11(16),12,14,17-octaen-8-one (**10**).* Yield: 94% (0.198 g from 0.21 g) as a yellow solid, mp: <250 °C; R_f=0.56 (CH_2Cl_2–MeOH, 9.5:0.5, v/v); IR (KBr) ν: 1686, 1519 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.23–7.38 (m, 12H, ArH), 7.57–7.65 (m, 3H, ArH), 8.16 (d, 2H, *J*=5.7 Hz, ArH), 8.64 (d, 1H, *J*=4.9 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=112.2(2C), 119.5(2C), 120.5, 121.3(2C), 122.1(2C), 126.5(2C), 128.7(4C), 129.7, 129.8(4C), 131.8, 134.4, 135.3, 135.9,

139.7(2C), 141.4, 195.7. MS (ESI+): m/z=398.2. ESI-HRMS calculated for $C_{28}H_{18}N_2O$ $[MH]^+$: 398.1419, found: 398.1423.

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Supplementary data

Synthesis of 2-alkynylbenzaldehydes, details for the X-ray data for compounds **3aAe** and **5aB*2*** and copies of ^1H and ^{13}C NMR spectra for all compounds are provided. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.08.086. These data include MOL files and InChiKeys of the most important compounds described in this article.

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