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ARTICLE

One-Pot Synthesis of Indolo[2,1-*b*]quinazoline-6,12-diones under Aerobic Conditions

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ABSTRACT

An efficient approach for the formation of biologically important indolo[2,1-*b*]quinazoline-6,12-diones in good to moderate yields has been accomplished from 2-haloacetophenones and anthranilamides employing I_2/DMSO/CuI under aerobic conditions. This tandem process is believed to proceed *via* iodination of 2-haloacetophenone followed by Kornblum oxidation and copper-catalyzed intramolecular *N*-arylation. This method adopts five reactions such as α-halogenation, oxidation, condensation, aromatization and heteroaryl coupling in a single step which makes it as an attractive and useful for the synthesis of indolo[2,1-*b*]quinazoline-6,12-diones.

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KEYWORDS

Indolo[2,1-*b*]quinazoline-6,12-diones, *N*-arylation, Oxidative cyclization, Kornblum oxidation, Quinazolinone.

INTRODUCTION

Tryptanthrin (indolo[2,1-*b*]quinazoline-6,12-dione) is an alkaloid comprising quinazoline ring fused to an indole moiety with carbonyl groups at 6- and 12-positions and has emerged as a potential therapeutic agent [1]. Nitrogen containing fused polyheteroarenes are often found as structural frameworks in natural products and pharmaceutically active compounds [2,3]. In particular, the indole fused quinazolinone is a core structure of diverse alkaloids with a broad spectrum of biological activities [4-9]. Furthermore, indolo[2,1-*b*]quinazolinones are found to exhibit intriguing biological properties such as antitumor activity against leukemia U937, breast MCF-7, glioma U251, colon SW620 and lung H522 cancer cell lines [10], antituberculosis [11,12], antiprotozoal, antioxidant, antibacterial [13-15], anti-parasitic and anti-inflammatory activities [16]. More specifically, the fused quinazolinone natural products such as asperlicins, circumdatins, benzomalvins, tryptanthrin and its analogues phaitanthrins A-E, methylisatoid, candidine, *etc.* (Fig. 1) were isolated from particular orchid, *Phaius mishmensis*. They play an important role in medicinal chemistry due to their structure and promising bioactivity [17,18].

In view of the importance of these heterocycles, diverse synthetic methods have been developed for the synthesis of indolo[2,1-*b*]quinazolines. Among them, condensation between isatoic anhydrides and isatins in the presence of triethylamine

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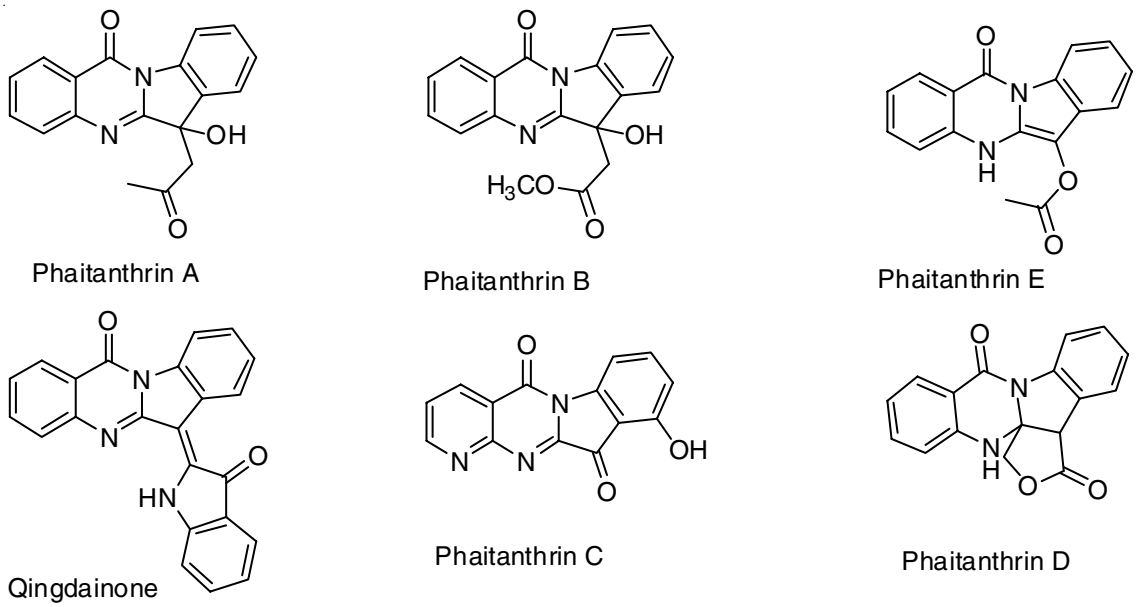


Fig. 1. Examples of biologically active quinazoline natural alkaloids

or in aqueous β-cyclodextrin solution has been studied [19]. Recently, tryptanthrin has been synthesized from quinazolines esters with aryl TMS triflates in one step reaction [20]. An alternative method of condensation between *o*-aminobenzoic acid and isatin in the presence of $SOCl_2$ has been reported [21,22].

However, most of these approaches still suffer from drawbacks such as harsh reaction conditions, prolonged reaction times, poor substrate scope and utilizing step-by-step synthetic strategy. Therefore, the development of a simple and convenient methodology under mild conditions is highly desirable for the synthesis of indolo[2,1-*b*]quinazoline-6,12-diones.

Direct transformations of inert chemical bonds particularly sp^3 C-H bond functionalization for the formation of C-C and C-N bonds have become an imperative synthetic strategy in sustainable chemistry [23-26]. However, most of these reactions require costly reagents like Ru-, Rh-, Ir- and Pd-complexes as catalysts [27-29] and consequent functionalization of sp^3 and sp^2 C-H bonds, which directly fix main functional groups to enhance the structural complexity of simply prepared substrates (Fig. 2) [30-32].

In current years, as per the requirement of green chemistry on synthetic efficiency and atom economy, the construction

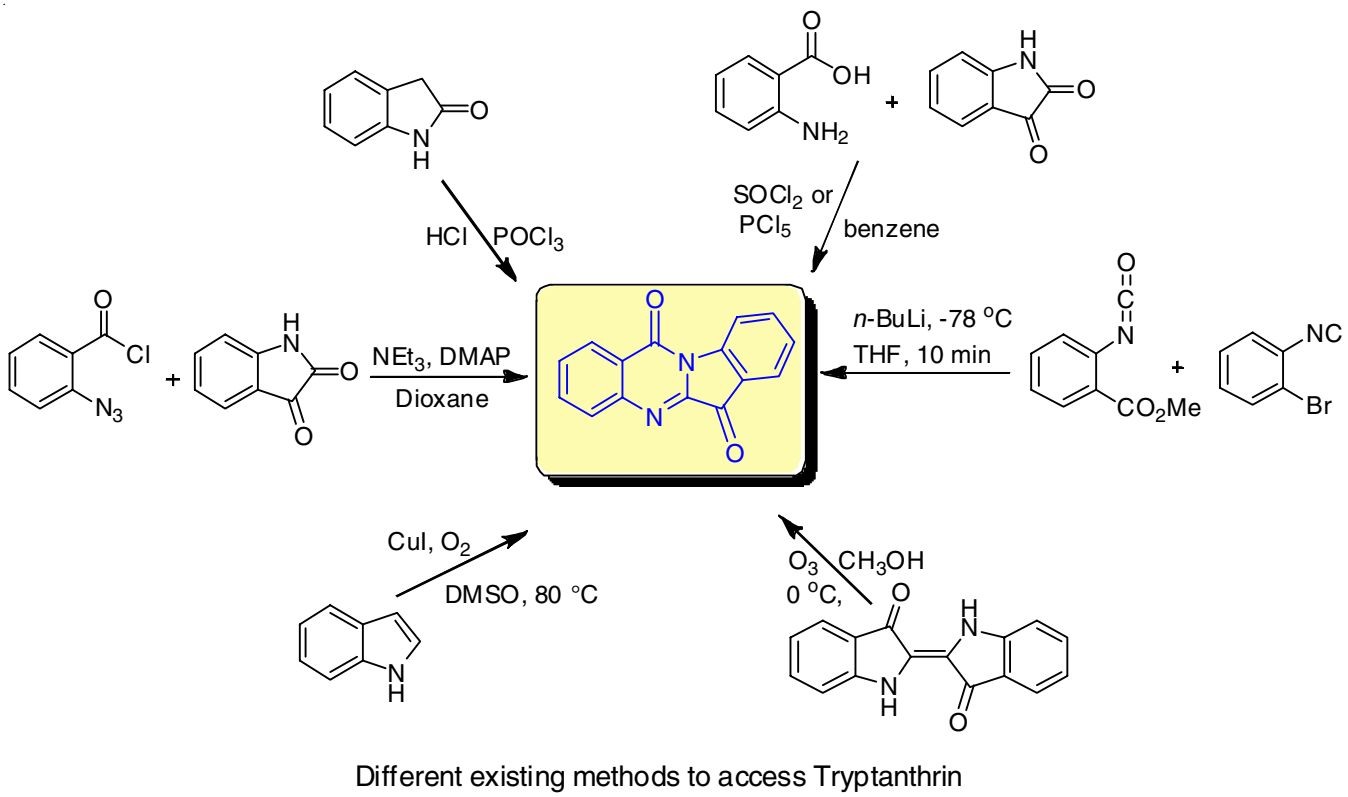


Fig. 2. Different approaches for the synthesis of indolo[2,1-*b*]quinazoline-6,12-diones

of quinazolinone core structure through direct sp^3 C–H bond functionalization has become a much more ideal approach [33,34]. In this context, recently I_2-promoted C–H functionalization reactions have gained increasing attention in organic synthesis as a promising strategy due to their cost efficiency, low toxicity, availability and broad functional group tolerance [35-40]. In this communication, an I_2-promoted sp^3 C-H functionalization and aerobic copper catalyzed reaction system for the formation of new C–C and C–N bonds for accessing indolo[2,1-*b*]quinazo-line-6-12-diones is illustrated.

EXPERIMENTAL

One-pot synthesis of indolo[2,1-*b*]quinazoline-6,12-dione congeners (3a-n): To a stirred solution of compound **1** (1 mmol) in DMSO (5 mL), 2-bromo acetophenone (**2**, 1 mmol) and I_2 (1.5 equiv) was added at room temperature. The resulting mixture was stirred at 100 ºC in open air condition for about 4 h. After that the reaction mixture was cooled to room temperature and CuI (0.3 equiv.) and Cs_2CO_3 (1 equiv.) was added. Then reaction was allowed to stir at 100 ºC for 2 h and the progress of the reaction was monitored by checking TLC. After completion of the reaction, the reaction mixture was quenched with saturated sodium thiosulfate solution (2 mL) and extracted with dichloromethane (3 × 2.5 mL). The organic layers were combined, washed with brine (3-5 mL), dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting crude product was purified by silica gel column chromatography (100-200 mesh) with ethyl acetate/hexane as eluent to afford the pure desired products (**Scheme-I**).

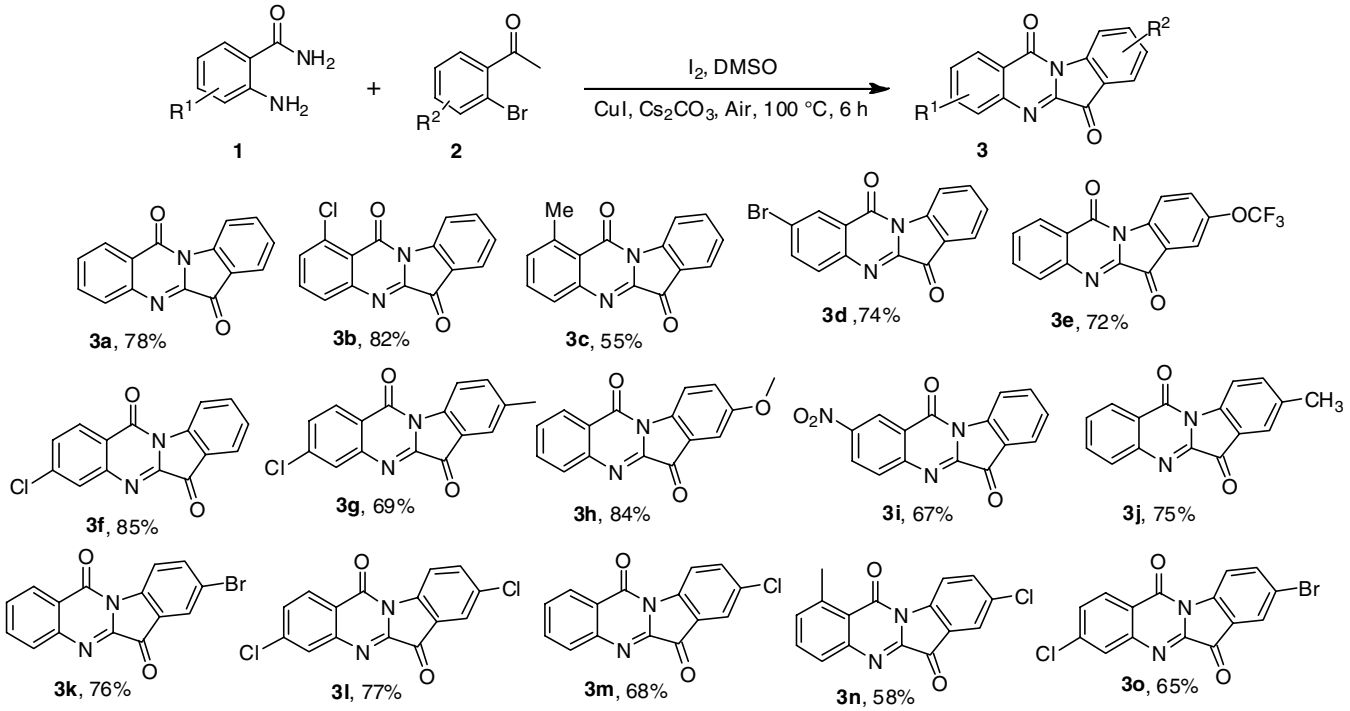
Indolo[2,1-*b*]quinazoline-6,12-dione (3a): Yield: 78%; yellow solid; m.p.: 266-268 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.64 (d, *J* = 7.5 Hz, 1H), 8.45 (d, *J* = 7.5 Hz, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.95 - 7.76 (m, 3H), 7.69 (t, *J* = 8.3 Hz, 1H) 7.44 (t, 1H, *J* = 7.1 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 183.0, 160.0, 146.6, 145.3, 134.6, 133.2, 130.0, 129.7, 126.3, 125, 120.6, 117.2 ppm; MS (EI): *m/z* calcd. for $C_{15}H_8N_2O_2$: 248, Found: 249(M^+); HRMS (ESI): *m/z* calcd. for $C_{15}H_8N_2O_2$: 248.0586; found: 248.0584.

1-Chloroindolo[2,1-*b*]quinazoline-6,12-dione (3b): Yield: 82%; orange solid; m.p.: 282-285 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.63 (d, *J* = 8.7 Hz, 1H), 8.34 (d, *J* = 7.7 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.83-7.77 (m, 2H), 7.72-7.64 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 181.1, 158.2, 157.1, 147.4, 145.6, 140.6, 134.7, 130.7, 130.3, 127.6, 125.5, 123.2, 122.5, 119.3, 108.3 ppm; MS (EI): *m/z* ([M]$^+$): 282; HRMS (EI): *m/z* calcd. for $C_{15}H_7ClN_2O_2$: 282.0196; found: 282.0194.

1-Methylindolo[2,1-*b*]quinazoline-6,12-dione (3c): Yield: 55%; yellow solid; m.p.: 192-194 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.62 (d, *J* = 7.8 Hz, 1H), 7.94 (t, *J* = 7.2 Hz, 2H), 7.80-7.75 (m, 2H), 7.60-7.46 (m, 3H), 2.5 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 180.0, 164.3, 156.8, 142.6, 138.1, 134.1, 133.2, 129.1, 126.8, 125.2, 121.9, 117.9, 23.07 ppm; MS (EI): *m/z* ([M]$^+$): 262; HRMS (EI): *m/z* calcd. for $C_{16}H_{10}N_2O_2$: 262.0742; found: 262.0738.

2-Bromoindolo[2,1-*b*]quinazoline-6,12-dione (3d): Yield: 74%; pale yellow solid, m.p.: 254-250 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 8.7 Hz, 1H), 7.61-7.54 (m, 2H), 7.43 (m, 1H), 6.78 (s, 1H), 6.67 (dd, *J* = 1.7, *J* = 8.7 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 180.0, 146.4, 138.5, 136.3, 129.3, 128.5, 127.1, 124.6, 124.1, 115.4, 115.2, 113.8 ppm; MS (EI): *m/z* ([M]$^+$): 325; HRMS (EI): *m/z* calcd. for $C_{15}H_7BrN_2O_2$: 325.9691; found: 325.9697.

8-(Trifluoromethoxy)indolo[2,1-*b*]quinazoline-6,12-dione (3e): Yield: 72%; yellow solid, m.p.: 238-236 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.74 (d, *J* = 8.7 Hz, 1H), 8.45 (d, *J* = 8.9 Hz, 1H),8.06 (d, *J* = 7.6 Hz, 1H), 7.84 (dt, *J* = 1.4, J = 8.5 Hz, 1H), 7.77-7.64 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 180.6, 157.2, 147.1, 145.9, 143.7, 143.6, 134.4, 130.8, 130.5,



Scheme-I: Substrate scope of various indolo [2,1-*b*]quinazoline-6,12-diones; Reactions were performed using **1a** (1 mmol), **2a** (1 mmol), I_2 (1.5 eq), CuI (30 mol%), Cs_2CO_3 (1 equiv) DMSO (5 mL) at 100 °C for 6 h

130.2, 127.2, 123.1, 122.7, 119.1, 117.3 ppm; MS (EI): *m/z* ([M]$^+$): 332; HRMS (EI): *m/z* calcd. for $C_{16}H_7F_3N_2O_3$: 332.0409; found: 332.0408.

3-Chloroindolo[2,1-*b*]quinazoline-6,12-dione (3f): Yield: 84%; pale yellow solid, m.p.: 286-288 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.58 (d, *J* = 8.0 Hz, 1H), 8.35 (d, *J* = 8.4 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 8.02-8.01 (m, 1H), 7.94 (d, *J* = 7.5 Hz, 1H), 7.83 (dt, *J* = 1.3, *J* = 8.0 Hz, 1H), 7.66-7.57 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 166.3, 145.3, 143.5, 139.6, 131.5, 129.8, 128.5, 128.1, 127.3, 126.7, 126.5, 122.3, 119.4 ppm; MS (EI): *m/z* ([M]$^+$): 282; HRMS (EI): *m/z* calcd. for $C_{15}H_7ClN_2O_2$: 282.0196; found: 282.0194.

3-Chloro-8-methylindolo[2,1-*b*]quinazoline-6,12-dione (3g): Yield: 69%; yellow solid, m.p.: 268-270 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.63 (d, *J* = 8.6 Hz, 1H), 7.88-7.86 (m, 1H), 7.75-7.67 (m, 2H), 7.54-7.55 (m, 1H), 7.47 (d, *J* = 7.5 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.6, 169.7, 147.4, 145.5, 142.8, 137.3, 134.9, 133.5, 130.7, 130.3, 129.6, 128.5, 125.1, 122.3, 119.5, 23.6 ppm; MS (EI): *m/z* ([M]$^+$): 296; HRMS (EI): *m/z* calcd. for $C_{16}H_9ClN_2O_2$: 296.0353; found: 296.0355.

8-Methoxyindolo[2,1-*b*]quinazoline-6,12-dione (3h): Yield: 69%; yellow solid, m.p.: 278-282 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.57 (d, *J* = 8.7 Hz, 1H), 8.46 (dd, *J* = 1.4, *J* = 8.1 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.86 (dt, *J* = 1.8, *J* = 8.5 Hz, 1H), 7.73-7.66 (m, 1H), 7.38 (d, *J* = 3.9, 1H), 7.35 (dd, *J* = 2.8, *J* = 8.8 Hz, 1H), 3.7 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.7, 158.1, 156.3, 146.5, 144.7, 139.1, 134.3, 130.5, 129.9, 127.2, 124.3, 123.6, 122.3, 118.8, 108.1, 56.1 ppm; MS (EI): *m/z* ([M]$^+$): 278. HRMS (EI): *m/z* calcd. for $C_{16}H_{10}N_2O_3$: 278.0691; found: 278.0693.

2-Nitroindolo[2,1-*b*]quinazoline-6,12-dione (3i): Yield: 67%; yellow solid, m.p.: 250-252 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (d, *J* = 8.4 Hz, 1H), 7.98 (d, *J* = 8.7 Hz, 1H), 7.73-7.66 (m, 1H), 7.58 (s, 1H), 7.52-7.50 (m, 1H), 7.45 (dd, *J* = 1.9, *J* = 8.4 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.3, 157.5, 157.2, 149.3, 146.5, 131.6, 130.2, 130.3, 129.5, 128.3, 127.6, 125.4, 116.3, 115.6 ppm; MS (EI): *m/z* ([M]$^+$): 293.

8-Methyl indolo[2,1-*b*]quinazoline-6,12-dione (3j): Yield: 75%; yellow solid, m.p.: 276-274 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.92 (dd, *J* = 8.2, *J* = 13.9 Hz, 1H), 8.64-8.50 (m, 1H), 8.30-8.13 (m, 1H), 7.88-7.35 (m, 2H), 7.34-7.29 (m, 1H), 3.03 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 181.6, 167.4, 147.6, 146.2, 143.5, 138.4, 134.3, 131.6, 129.7, 127.1, 126.3, 117.2, 116.8, 116.1, 25.2 ppm; MS (EI): *m/z* ([M]$^+$): 262; HRMS (EI): *m/z* calcd. for $C_{16}H_{10}N_2O_2$: 262.0742; found: 262.0746.

8-Bromoindolo[2,1-*b*]quinazoline-6,12-dione (3k): Yield: 76%; cream colour solid, m.p.: 294-296 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.5-8.41 (m, 3H), 7.75-7.67 (m, 2H), 7.40 (t, *J* = 7.7 Hz, 1H), 7.14 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.2, 155.3, 154.3, 137.5, 135.3, 134.9, 134.8, 131.3, 129.7, 125.4, 124.7, 113.3, 113.0, 112.7 ppm; MS (EI): *m/z* ([M]$^+$): 325; HRMS (EI): *m/z* calcd. for $C_{15}H_7BrN_2O_2$: 325.9691; found: 325.9697.

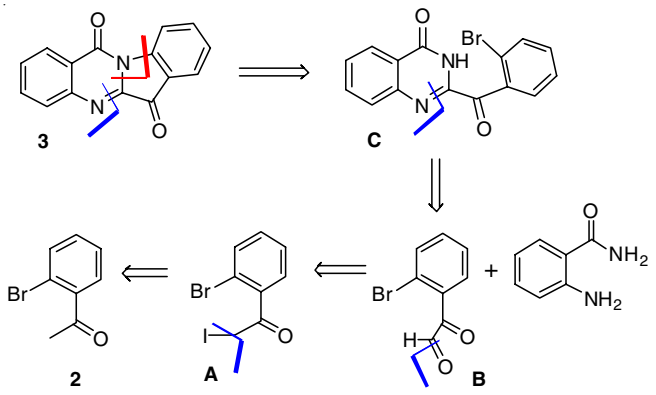
3,8-Dichloroindolo[2,1-*b*]quinazoline-6,12-dione (3l): Yield: 76%; yellow solid; m.p.: 286-288 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.3 Hz, 1H), 7.97 (d, *J* = 8.7 Hz, 1H), 7.69-7.67 (m, 1H), 7.54 (s, 1H), 7.50-7.48 (m, 1H) 7.41 (dd, *J* = 1.9, *J* = 8.4 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 181.1, 157.5, 157.1, 149.6, 146.3, 131.9, 130.8, 130.3, 129.2, 128.4, 127.7, 125.3, 116.7, 115.6 ppm; MS (EI): *m/z* ([M]$^+$): 315; HRMS (EI): *m/z* calcd. for $C_{15}H_6Cl_2N_2O_2$: 315.9806; found: 315.9816.

8-Chloroindolo[2,1-*b*]quinazoline-6,12-dione (3m): Yield: 68%; yellow solid; m.p.: 289-291 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.52 (d, *J* = 8.6 Hz, 1H), 8.37 (d, *J* = 7.6 Hz,1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.82-7.78 (m, 2H), 7.69-7.59 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 181.1, 158.5, 157.1, 146.6, 144.3, 140.1, 134.8, 130.5, 127.4, 125.2, 123.7, 122.5, 119.0, 108.3 ppm; MS (EI): *m/z* ([M]$^+$): 282; HRMS (EI): *m/z* calcd. for $C_{15}H_7ClN_2O_2$: 282.0196; found: 282.0198.

8-Chloro-1-methyl indolo[2,1-*b*]quinazoline-6,12-dione (3n): Yield: 58%; yellow solid; m.p.: 263-265 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.63 (d, *J* = 8.6 Hz, 1H), 7.86-7.84 (m, 1H), 7.75-7.68 (m, 2H), 7.56-7.54 (m, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 3.03 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.6, 169.4, 147.6, 145.2, 142.5, 137.4, 134.2, 133.4, 130.7, 127.1, 126.3, 125.2, 122.7, 119.3, 24.1 ppm; MS (EI): *m/z* ([M]$^+$): 296; HRMS (EI): *m/z* calcd. for $C_{16}H_9ClN_2O_2$: 296.0353; found: 296.0354.

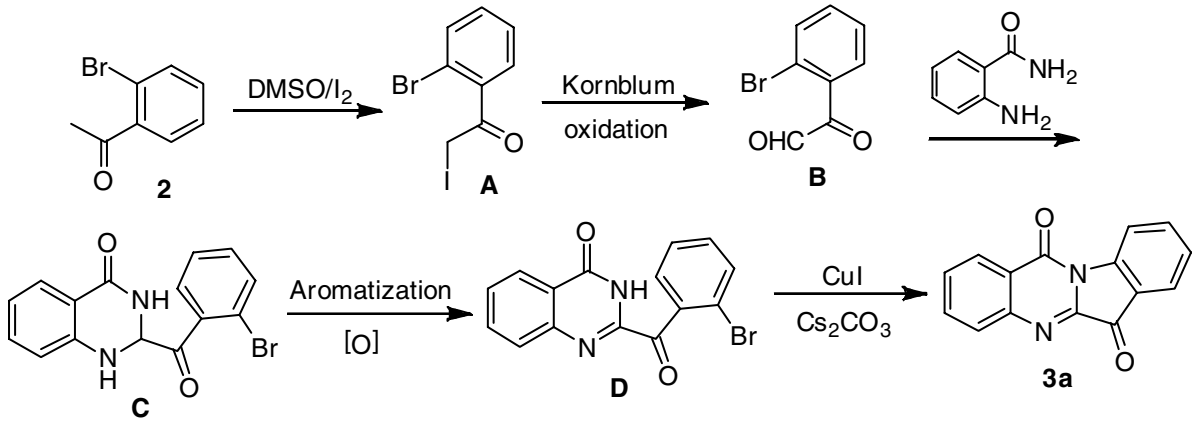
RESULTS AND DISCUSSION

Initially, retrosynthetically was envisioned that indolo-[2,1-*b*]quinazoline-6,12-dione could be achieved from compounds **1** & **2** assembling four reactions in one pot while aldehyde B might be furnished from the α-bromo ketone **2** through Kornblum oxidation. It was also thought that **B** could easily cyclized to **C** and **3** furnished *via* intramolecular hetero aryl coupling of **C** (**Scheme-II**).

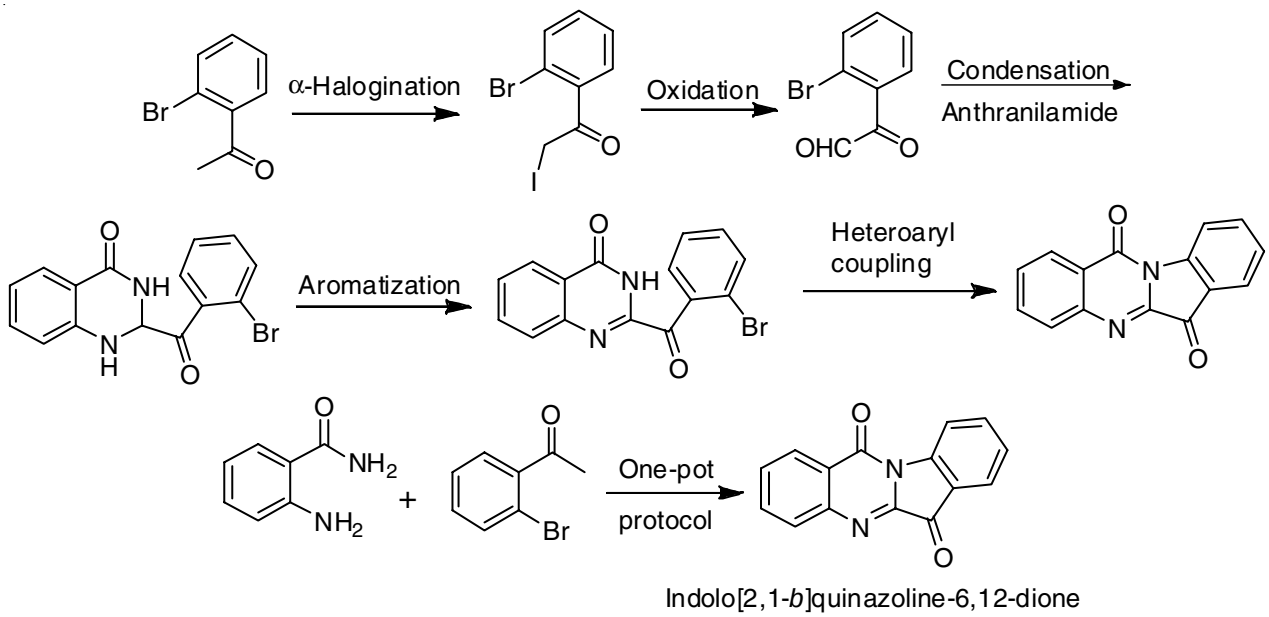


Scheme-II: Retrosynthetic analysis

Afterward, many approaches for the synthesis of indolo-[2,1-*b*]quinazoline-6,12-dione have been developed which consist of α-iodination, Kornblum oxidation, intermolecular condensation, aromatization and hetero arylation reaction sequence as shown in **Scheme-IV**. However, it remains scarce to apply these reactions to construct *N*-heterocycles. In this context, herein, we wished to check whether it would be workable to extend a one-pot protocol for the synthesis of indolo-[2,1-*b*]quinazoline-6-12-dione conjugates, which can be synthesized in a straightforward oxidative cyclization reaction of anthranilamide with 2-bromo acetophenone, wherein five reactions would self-sequentially take place in one-pot (**Scheme-IV**).



Scheme-III: A plausible reaction mechanism



Scheme-IV: Synthesis of indolo[2,1-*b*]quinazoline-6,12-dione

Present preliminary investigation started with a model reaction in one pot, the condensation of anthranilamide (**1a**) and 2-bromo acetophenone (**2a)** using I_2 under solvent free conditions at room temperature for 24 h for the synthesis of indolo[2,1-*b*]quinazoline-6,12-diones, no reaction (entry 1, Table-1) was observed even after prolonged time. Next, we performed this reaction using DMSO as a solvent at room temperature, we observed the required product in traces (entry 2, Table-1). Interestingly, we carried out the same reaction at 100 ºC for 12 h, formation of product (**3a**) in 15% yield was observed (entry 3, Table-1). Encouraged by the above results, we performed further optimization for improving the yield of the product, by altering the reaction conditions using various catalysts, oxidants, solvents. The poor yield of the product could be due to inadequate catalytic efficiency and low solubility of the reactants, With a view to further improve the yield, the reaction was screened using various catalysts such as copper catalysts along with different concentrations of oxidants in various solvents were investigated (entries 4-17). Lower yield was obtained when the reaction was conducted without base, so different bases such as Na_2CO_3, K_2CO_3, $K_3PO_4{\cdot}3H_2O$, Cs_2CO_3 were examined (entries 6-17). Among all, Cs_2CO_3 was found to be effective. Thereafter, various oxidants with different iodine sources like phenyliodonium diacetate (PIDA), tetrabutylammonium iodide (TBAI), *N*-iodosuccinimide (NIS) along with molecular iodine (I_2) were investigated (entries 15-17), it was observed that PIDA and TBAI were ineffective for this transformation, whereas NIS has shown little conversion yielding traces of required product (**3a**). This observation confirmed that molecular iodine is necessary oxidant for the success of this transformation. Additionally, the reaction with various equivalents of I_2 from 0.3-2.2 equivalents (entries 3-14) was also studied. No effect on the yield as well as reaction time (entry 14, Table-1) was observed even by increasing the oxidant to stoichiometric ratio. Furthermore, the experimental results showed that copper reagents could catalyze the transformation, so we screened various copper salts, including $CuBr_2$, $CuCl_2$, $Cu(OAc)_2$, $Cu(NO_3)_2$, $Cu(OTf)_2$, CuCl, CuI (entries 4-16).

Screening of copper salts revealed that CuI is a suitable catalyst for the reaction and yielded the product **3a** in good yield (78%, entry 13, Table-1). Lower yield was obtained when the reaction was conducted under an argon or N_2 atmosphere. In order to improve the yield of the reaction, the effect of solvents were investigated using other solvents such as EtOAc, CH_3CN,

TABLE-1
OPTIMIZATION OF REACTION CONDITIONS FOR THE SYNTHESIS OF INDOLO[2,1-*b*]QUINAZOLINE-6,12-DIONES

Entry	Oxidant	Cu source	Base	Solvent	Temp. (°C)	Yield[b] (%)
1	I_2 (0.3 eq)	–	–	Neat	RT	NR[c]
2	I_2 (0.3 eq)	–	–	DMSO	RT	Trace
3	I_2 (0.3 eq)	–	–	DMSO	100	15
4	I_2 (0.3 eq)	$CuBr_2$	–	EtOAc	70	22
5	I_2 (0.5 eq)	$CuCl_2$	–	CH_3CN	80	36
6	I_2 (0.8 eq)	$Cu(OAc)_2$	Na_2CO_3	CH_2Cl_2	30	33
7	I_2 (1 eq)	$Cu(OTf)_2$	K_2CO_3	iPrOH	80	48
8	I_2 (1.1 eq)	$Cu(OTf)_2$	$K_3PO_4 \cdot 3H_2O$	Toluene	80	28
9	I_2 (1.2 eq)	CuCl	Cs_2CO_3	DMF	80	45
10	I_2 (1.3 eq)	CuI[d]	Cs_2CO_3	DCE	80	60
11	I_2 (1.5 eq)	CuI	Cs_2CO_3	Anisole	90	56
12	I_2 (1.5 eq)	CuI	Cs_2CO_3	DMSO	100	79
13	I_2 (2.2 eq)	CuI	Cs_2CO_3	DMSO	100	82
14	PIDA (2 eq)	CuI	Cs_2CO_3	DMSO	100	NR
15	NIS (2 eq)	CuI	Cs_2CO_3	DMSO	100	Trace
17	TBAI (2 eq)	CuI	Cs_2CO_3	DMSO	100	NR

[a]Reactions were performed using **1a** (1 mmol), **2a** (1 mmol), I_2 (1.5 eq), CuI (30 mol%), Cs_2CO_3 (1 equiv) DMSO (5 mL) at 100 °C for 6 h. [b]Isolated yields. [c]No reaction. [d]0.3 equiv of CuI.

DCM, THF, ^{i}PrOH, toluene, DMF, DCE, anisole, DMSO (entries 2-13). Among these, most of the solvents resulted in lower yields (entries 4-12), compared to DMSO which could imply that the DMSO may act as a supplementary oxidant for the oxidation of C(sp^3)-H bond. After systematic optimization of reaction revealed that the best optimization conditions were I_2 (1.5 equiv.), CuI (0.3 equiv.) and Cs_2CO_3 (1 equiv.) in DMSO at 100 ºC for 6h (entry 13, Table-1).

With the established optimized conditions in hand then investigated the reaction scope and generality of this protocol was further illustrated towards the synthesis of various indolo-[2,1-*b*]quinazoline-6,12-diones, which are biologically important heterocycles in medicinal chemistry. We then explored the scope of the oxidative cyclization to various substituted anthranilamides such as methyl, bromo, nitro and chloro. Similarly, this protocol works well with 2-bromo acetophenones bearing different substitutions such as alkyl and halo. In case of halogen substituted substrates, the corresponding substituted quinazoline derivative was obtained slightly in higher yields. To our delight, in all cases, the desired condensed corresponding quinazoline derivatives afforded in good to moderate yields are shown in **Scheme-I**.

On the basis of experimental results, a tentative mechanism for this conversion is briefly outlined in **Scheme-III**. Initially, **2a** was α-iodination to A, which reacts with DMSO to provide aldehyde B *via* Kornblum oxidation then, B converts into cyclized intermediate **C**, followed by subsequent further aromatization to give the intermediate D and finally after intramolecular hetero aryl coupling of D afforded the corresponding desired product **3a**.

Conclusion

A highly versatile and straightforward tandem protocol for the construction of biologically important indolo[2,1-*b*]-quinazoline-6,12-diones from readily available starting materials was reported. The cascade process is believed to involve iodine mediated aerobic oxidation, iminium formation, oxidative aromatization and intramolecular hetero aryl coupling. The significant features of this methodology involves the usage of inexpensive, non-toxic I_2 and air as an eco friendly oxidant with broad range of substrate scope makes this protocol economical, which is superior over the previous reports.

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REFERENCES

1. C.W. Jao, W.-C. Lin, Y.-T. Wu and P.L. Wu, Isolation, Structure Elucidation and Synthesis of Cytotoxic Tryptanthrin Analogues from *Phaius mishmensis*, *J. Nat. Prod.*, **71**, 1275 (2008); https://doi.org/10.1021/np800064w
2. L. Zhang, X.-M. Peng, G.L.V. Damu, R.-X. Geng and C.-H. Zhou, Comprehensive Review in Current Developments of Imidazole-Based Medicinal Chemistry, *Med. Res. Rev.*, **34**, 340 (2014); https://doi.org/10.1002/med.21290
3. J.F. González, I. Ortín, E. de la Cuesta and J.C. Menéndez, Privileged Scaffolds in Synthesis: 2,5-Piperazinediones as Templates for the Preparation of Structurally Diverse Heterocycles, *Chem. Soc. Rev.*, **41**, 6902 (2012); https://doi.org/10.1039/c2cs35158g
4. U.A. Kshirsagar, Recent Developments in the Chemistry of Quinazolinone Alkaloids, *Org. Biomol. Chem.*, **13**, 9336 (2015); https://doi.org/10.1039/C5OB01379H
5. M.M. Kamel, W.A. Zaghary, R.I. Al-Wabli and M.M. Anwar, *Egypt. Pharm. J.*, **15**, 98 (2016); https://doi.org/10.4103/1687-4315.197580
6. F.-D. Kong, S.-L. Zhang, S.-Q. Zhou, Q.-Y. Ma, Q.-Y. Xie, J.-P. Chen, J.-H. Li, L.-M. Zhou, J.-Z. Yuan, Z. Hu, H.-F. Dai, X.-L. Huang and Y.-X. Zhao, *J. Nat. Prod.*, **82**, 3456 (2019); https://doi.org/10.1021/acs.jnatprod.9b00845
7. S. Sinha and M. Srivastava, Biologically Active Quinazolones, *Prog. Drug Res.*, **43**, 143 (1994); https://doi.org/10.1007/978-3-0348-7156-3_5
8. H. Xie, Y. Zhang, S. Zhang, X. Chen and W. Wang, Bifunctional Cinchona Alkaloid Thiourea Catalyzed Highly Efficient, Enantioselective Aza-Henry Reaction of Cyclic Trifluoromethyl Ketimines: Synthesis of Anti-HIV Drug DPC 083, *Angew. Chem. Int. Ed.*, **50**, 11773 (2011); https://doi.org/10.1002/anie.201105970
9. L. Li, J. Ge, H. Wu, Q.-H. Xu and S.Q. Yao, Organelle-Specific Detection of Phosphatase Activities with Two-Photon Fluorogenic Probes in Cells and Tissues, *J. Am. Chem. Soc.*, **134**, 12157 (2012); https://doi.org/10.1021/ja3036256

10. A.K. Bhattacharjee, M.G. Hartell, D.A. Nichols, R.P. Hicks, B. Stanton, J.E. van Hamont and W.K. Milhous, Analysis of Stereoelectronic Properties, Mechanism of Action and Pharmacophore of Synthetic Indolo[2,1-*b*]quinazoline-6,12-dione Derivatives in Relation to Antileishmanial Activity using Quantum Chemical, Cyclic Voltammetry and 3-D-QSAR Catalyst Procedures, *Eur. J. Med. Chem.*, **39**, 59 (2004); https://doi.org/10.1016/j.ejmech.2003.10.004
11. J. Scovill, E. Blank, M. Konnick, E. Nenortas and T. Shapiro, Antitrypanosomal Activities of Tryptanthrins, *Antimicrob. Agents Chemother.*, **46**, 882 (2002); https://doi.org/10.1128/AAC.46.3.882-883.2002
12. B. Krivogorsky, P. Grundt, R. Yolken and L. Jones-Brando, Inhibition of Toxoplasma gondii by Indirubin and Tryptanthrin Analogs, *Antimicrob. Agents Chemother.*, **52**, 4466 (2008); https://doi.org/10.1128/AAC.00903-08
13. A.K. Bhattacharjee, D.J. Skanchy, B. Jennings, T.H. Hudson, J.J. Brendle and K.A. Werbovetz, Structure-Activity Relationship Study of Antimalarial Indolo [2,1-*b*]quinazoline-6,12-diones (Tryptanthrins). Three dimensional Pharmacophore Modeling and Identification of New Antimalarial Candidates, *Bioorg. Med. Chem.*, **10**, 1979 (2002); https://doi.org/10.1016/S0968-0896(02)00013-5
14. V.M. Sharma, P. Prasanna, K.V. Adi Seshu, B. Renuka, C.V. Laxman Rao, G. Sunil Kumar, C.P. Narasimhulu, P. Aravind Babu, R.C. Puranik, D. Subramanyam, A. Venkateswarlu, S. Rajagopal, K.B.S. Kumar, C.S. Rao, N.V.S.R. Mamidi, D.S. Deevi, R. Ajaykumar and R. Rajagopalan, *Bioorg. Med. Chem. Lett.*, **12**, 2303 (2002); https://doi.org/10.1016/S0960-894X(02)00431-6
15. T. Motoki, Y. Takami, Y. Yagi, A. Tai, I. Yamamoto and E. Gohda, Inhibition of Hepatocyte Growth Factor Induction in Human Dermal Fibroblasts by Tryptanthrin, *Biol. Pharm. Bull.*, **28**, 260 (2005); https://doi.org/10.1248/bpb.28.260
16. R.P. Hicks, D.A. Nichols, C.A. DiTusa, D.J. Sullivan, M.G. Hartell, B.W. Koser and A.K. Bhattacharjee, Evaluation of 4-Azaindolo[2,1-*b*]-quinazoline–6,12–diones' Interaction with Hemin and Hemozoin: A Spectroscopic, X-ray Crystallographic and Molecular Modeling Study, *Internet Electron. J. Mol. Des.*, **4**, 751 (2005).
17. K. Iwaki, E. Ohashi, N. Arai, K. Kohno, S. Ushio, M. Taniguchi and S. Fukuda, Tryptanthrin Inhibits Th2 Development and IgE-Mediated Degranulation and IL-4 Production by Rat Basophilic Leukemia RBL-2H3 Cells, *J. Ethnopharmacol.*, **134**, 450 (2011); https://doi.org/10.1016/j.jep.2010.12.041
18. M. Sarangapani and V.M. Reddy, Phramacological Evaluation of 1-(*N*,*N*-Disubstituted aminomethyl)-3-imino-(2-phenyl-3,4-dihydro-4-oxo-quinazolin-3-yl)indolin-2-ones, *Indian J. Pharm. Sci.*, **58**, 147 (1996).
19. A. Kumar, V.D. Tripathi and P. Kumar, β-Cyclodextrin Catalysed Synthesis of Tryptanthrin in Water, *Green Chem.*, **13**, 51 (2011); https://doi.org/10.1039/C0GC00523A
20. U.A. Kshirsagar and N.P. Argade, Copper-Catalyzed Intramolecular N-Arylation of Quinazolinones: Facile Convergent Approach to (-)-Circumdatins H and J, *Org. Lett.*, **12**, 3716 (2010); https://doi.org/10.1021/ol101597p
21. K.C. Jahng, S.I. Kim, D.H. Kim, C.S. Seo, J.K. Son, S.H. Lee, E.S. Lee and Y.D. Jahng, One-Pot Synthesis of Simple Alkaloids: 2,3-Polymethylene-4(3H)-quinazolinones, Luotonin A, Tryptanthrin, and Rutaecarpine, *Chem. Pharm. Bull. (Tokyo)*, **56**, 607 (2008); https://doi.org/10.1248/cpb.56.607
22. J.L. Liang, S.-E. Park, Y. Kwon and Y. Jahng, Synthesis of Benzo-annulated Tryptanthrins and their Biological Properties, *Bioorg. Med. Chem.*, **20**, 4962 (2012); https://doi.org/10.1016/j.bmc.2012.06.034
23. F. Diederich and P.J. Stang, Metal-Catalyzed Cross-Coupling Reactions, Wiley-VCH: New York (1998).
24. C.J. Li, Cross-Dehydrogenative Coupling (CDC): Exploring C-C Bond Formations beyond Functional Group Transformations, *Acc. Chem. Res.*, **42**, 335 (2009); https://doi.org/10.1021/ar800164n
25. J.A. Labinger and J.E. Bercaw, Understanding and Exploiting C–H Bond Activation, *Nature*, **417**, 507 (2002); https://doi.org/10.1038/417507a
26. C. He, S. Guo, J. Ke, J. Hao, H. Xu, H.Y. Chen and A.W. Lei, Silver-Mediated Oxidative C–H/C–H Functionalization: A Strategy to Construct Polysubstituted Furans, *J. Am. Chem. Soc.*, **134**, 5766 (2012); https://doi.org/10.1021/ja301153k
27. F. Jia and Z.P. Li, Iron-Catalyzed/Mediated Oxidative Transformation of C–H Bonds, *Org. Chem. Front.*, **1**, 194 (2014); https://doi.org/10.1039/C3QO00087G
28. Y.H. Yan, Y.H. Zhang, C.T. Feng, Z.G. Zha and Z.Y. Wang, Selective Iodine-Catalyzed Intermolecular Oxidative Amination of C(sp^3)–H Bonds with *ortho*-Carbonyl-Substituted Anilines to Give Quinazoline, *Angew. Chem. Int. Ed.*, **51**, 8077 (2012); https://doi.org/10.1002/anie.201203880
29. Z.J. Liu, J. Zhang, S.L. Chen, E.B. Shi, Y. Xu and X.B. Wan, Cross Coupling of Acyl and Aminyl Radicals: Direct Synthesis of Amides Catalyzed by Bu_4NI with TBHP as an Oxidant, *Angew. Chem., Int. Ed.,* **51**, 3231 (2012); https://doi.org/10.1002/anie.201108763
30. F. Collet, C. Lescot and P. Dauban, Catalytic C–H Amination: The Stereoselectivity Issue, *Chem. Soc. Rev.*, **40**, 1926 (2011); https://doi.org/10.1039/c0cs00095g
31. S.H. Cho, J.Y. Kim, J. Kwak and S. Chang, Recent Advances in the Transition Metal-Catalyzed Twofold Oxidative C–H Bond Activation Strategy for C–C and C–N Bond Formation, *Chem. Soc. Rev.*, **40**, 5068 (2011); https://doi.org/10.1039/c1cs15082k
32. W.J. Yoo and C.J. Li, Highly Efficient Oxidative Amidation of Aldehydes with Amine Hydrochloride Salts, *J. Am. Chem. Soc.*, **128**, 13064 (2006); https://doi.org/10.1021/ja064315b
33. R. Vanjari and K.N. Singh, Utilization of Methylarenes as Versatile Building Blocks in Organic Synthesis, *Chem. Soc. Rev.*, **44**, 8062 (2015); https://doi.org/10.1039/C5CS00003C
34. D. Zhao, T. Wang and J.-X. Li, Metal-free Oxidative Synthesis of Quinazolinones *via* Dual Amination of sp^3 C–H Bonds, *Chem. Commun.*, **50**, 6471 (2014); https://doi.org/10.1039/C4CC02648A
35. S.E. Allen, R.R. Walvoord, R. Padilla-Salinas and M.C. Kozlowski, Aerobic Copper-Catalyzed Organic Reactions, *Chem. Rev.*, **113**, 6234 (2013); https://doi.org/10.1021/cr300527g
36. J. Kim, H. Kim and S. Chang, Copper-Mediated Selective Cyanation of Indoles and 2-Phenylpyridines with Ammonium Iodide and DMF, *Org. Lett.*, **14**, 3924 (2012); https://doi.org/10.1021/ol301674m
37. B. Nachtsheim and P. Finkbeiner, *Synthesis*, **45**, 979 (2013); https://doi.org/10.1055/s-0032-1318330
38. H. Huang, X. Ji, W. Wu and H. Jiang, Practical Synthesis of Polysubstituted Imidazoles via Iodine- Catalyzed Aerobic Oxidative Cyclization of Aryl Ketones and Benzylamines, *Adv. Synth. Catal.*, **355**, 170 (2013); https://doi.org/10.1002/adsc.201200582
39. W. Xu, U. Kloeckner and B.J. Nachtsheim, Direct Synthesis of 2,5-Disubstituted Oxazoles through an Iodine-Catalyzed Decarboxylative Domino Reaction, *J. Org. Chem.*, **78**, 6065 (2013); https://doi.org/10.1021/jo400753n
40. W.C. Gao, R.L. Wang and C. Zhang, Practical Oxazole Synthesis Mediated by Iodine from α-Bromoketones and Benzylamine Derivatives, *Org. Biomol. Chem.*, **11**, 7123 (2013); https://doi.org/10.1039/c3ob41566j