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Microwave assisted $[RuCl_2(p\text{-cymene})_2]_2$ catalyzed regioselective *endo*-tandem cyclization involving imine and alkyne activation: an approach to benzo[4,5]imidazo[2,1-*a*]pyridine scaffold†

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A microwave assisted efficient route to the synthesis of benzimidazole fused heterocycles through metal catalyzed *endo*-cyclization strategy involving imine and alkyne activation has been developed. In the presence of $[RuCl_2(p\text{-cymene})_2]_2$, a variety of 2-ethynyl aldehydes underwent cascade cyclization with substituted benzenediamines to afford the corresponding benzo[4,5]imidazo[2,1-*a*] pyridine scaffold in moderate to good yields.

Introduction

A wide array of medicinally important natural and synthetic molecules contain isoquinoline or heterocycles fused to isoquinoline core.[1] Thus development of new synthetic strategies for the quick assembly of these heterocyclic scaffolds has been of crucial importance to the synthetic community. Benzimidazole fused heterocyclic frameworks are an important class of pharmacophores displaying an extensive range of therapeutical and biological activities, such as anti-HIV-1, antimicrobial, antifungal and anticancer properties.[2] Furthermore, a number of bioactive heterocycles containing this scaffold show a prominent growth inhibitory effect, inhibit topoisomerase II and also, induce strong G2/M arrest of the cell cycle followed by drastic apoptosis, which is in accordance with the DNA intercalative binding mode (Fig. 1).[3] Therefore, this scaffold containing molecule has been the focus of attention of medicinal chemists as well as synthetic organic chemists and thus much effort has been devoted to develop methods for the synthesis of benzimidazole fused heterocycle ring systems. The most common strategy to access these types of scaffolds is the cascade cyclization of 2-ethynyl aldehydes with benzenediamines.[4] C–C bond formation *via* tandem nucleophilic addition and electrophilic cyclization of various *ortho*-alkynyl aldehydes, amines and various carbon based pronucleophiles in the presence or absence of various alkynophilic Lewis acid catalysts also give these types of scaffolds.[5,6] Copper-catalyzed tandem process,[7] palladium-catalyzed cross-coupling protocols,[8] rhodium-catalyzed dual C–H bond activation,[9] and various multistep routes[10] can be employed to synthesize these types of scaffolds.

Result and discussion

Sequential reactions in one-pot have played a leading role in the synthesis of both natural as well as synthetic molecules.[11] To the best of our knowledge, tandem synthesis of benzimidazole fused derivatives through $[RuCl_2(p\text{-cymene})_2]_2$ catalyzed *endo*-cyclization strategy from *ortho*-alkynyl aldehydes has not yet been explored. This cascade strategy involves the formation of three new N–C bonds and thereby leading to the formation of two heterocyclic rings in fused polycyclic heterocycles. We are interested in developing new synthetic methodologies for the synthesis and bioevaluation of small but smart heterocycles[12] and we report here microwave (MW) assisted metal catalyzed

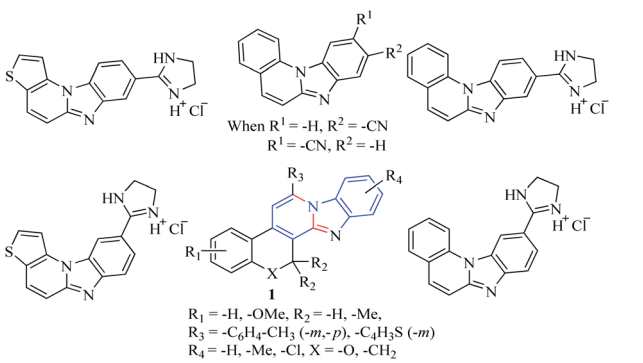

Fig. 1 Representative biologically important benzimidazoles and our target **1**.

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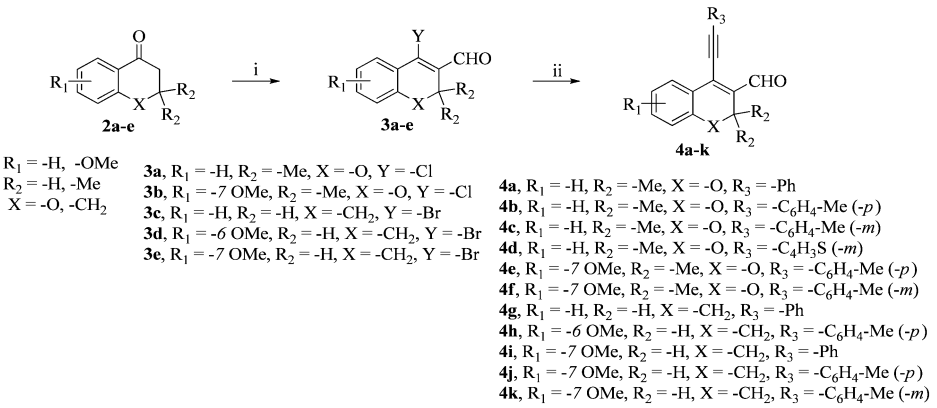
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c4ra02581d



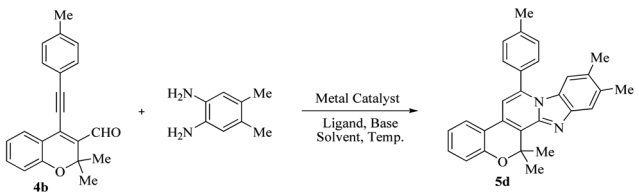
Scheme 1 Synthesis of substituted *ortho*-alkynyl aldehydes (**4a–k**). *Reagents and conditions*: (i) $POCl_3$ (or PBr_3, $CHCl_3$), dry DMF, 0 °C-rt, 8–9 h, 68–79%; (ii) $Pd(PPh_3)_2Cl_2$, CuI, Alkynes, DMF, 5–30 min, rt, 63–85%.

regioselective *endo*-tandem cyclization involving alkyne activation for fused benzimidazole derivatives.

First, the synthesis of *ortho*-alkynyl aldehydes was undertaken. All of them were prepared from different substituted chromanones and tetralones following two synthetic steps, involving Vilsmeier–Haack–Arnold[13] reaction and Sonogashira[14] coupling (Scheme 1). Now with the *ortho*-alkynyl aldehydes (**4a–k**) in hand (Table 2), the stage was set to implement the crucial catalytic N–C bond formation towards domino cyclization.

In order to optimise the desired reaction conditions, at first we used 2,2-dimethyl-4-(*p*-tolylethynyl)-2*H*-chromene-3-carbaldehyde **4b** as a model substrate with different Ru-metal sources, solvents and bases at a variety of temperatures (Table 1). When 10 mol% of $RuCl_3 \cdot 3H_2O$ was used as catalyst in presence of K_2CO_3 and DMF, there was no reaction (entry 1, Table 1). Similar results were obtained when *tert*-butylammonium bromide (TBAB) as additive, PPh_3 as ligand and also other solvents DMSO were used for 15 h (entries 2 & 3, Table 1). When

Table 1 Optimization studies for the synthesis of benzimidazoles fused derivatives



Entry	Catalysts	Additive	Solvents	Bases	Ligands	T/°C	Yield[a](%)
1	$RuCl_3 \cdot 3H_2O$ (10 mol%)	—	DMF	K_2CO_3	—	110	NR
2	$RuCl_3 \cdot 3H_2O$ (10 mol%)	—	DMF	K_2CO_3	PPh_3	110	NR
3	$RuCl_3 \cdot 3H_2O$ (10 mol%)	TBAB	DMSO	K_2CO_3	PPh_3	110	NR
4	$[RuCl_2(p\text{-cymene})_2]_2$ (10 mol%)	TBAB	DMF	K_2CO_3	—	110	Trace
5	$[RuCl_2(p\text{-cymene})_2]_2$ (10 mol%)	TBAB	DMF	K_2CO_3	PPh_3	110	54
6	$[RuCl_2(p\text{-cymene})_2]_2$ (10 mol%)	—	DMF	K_2CO_3	PPh_3	110	32
7	$[RuCl_2(p\text{-cymene})_2]_2$ (10 mol%)	—	DMF	—	PPh_3	110	NR[b]
8	$[RuCl_2(p\text{-cymene})_2]_2$ (10 mol%)	TBAB	DMF	Cs_2CO_3	PPh_3	110	78(69[c])
9	$[RuCl_2(p\text{-cymene})_2]_2$ (10 mol%)	TBAB	DMSO	Cs_2CO_3	PPh_3	110	46
10	$[RuCl_2(p\text{-cymene})_2]_2$ (10 mol%)	TBAB	MeCN	Cs_2CO_3	PPh_3	110	NR
11	$[RuCl_2(p\text{-cymene})_2]_2$ (10 mol%)	TBAB	DMF	Cs_2CO_3	PCy_3	110	35
12	$[RuCl_2(p\text{-cymene})_2]_2$ (10 mol%)	TBAB	DMF	K_3PO_4	PPh_3	110	23
13	$[RuCl_2(p\text{-cymene})_2]_2$ (15 mol%)	TBAB	DMF	Cs_2CO_3	PPh_3	110	78
14	—	TBAB	DMF	Cs_2CO_3	PPh_3	110	NR
15	—	TBAB	DMF	Cs_2CO_3	—	110	NR
16	$[RuCl_2(p\text{-cymene})_2]_2$ (10 mol%)	TBAB	DMF	Cs_2CO_3	PPh_3	110 (MW)	65[d]
17	$[RuCl_2(p\text{-cymene})_2]_2$ (10 mol%)	TBAB	DMF	Cs_2CO_3	PPh_3	130 (MW)	78[e]

[a] Isolated yield after column chromatography as well as preparative TLC. [b] Starting consumed but no desired product *i.e.*, enamine product formed before alkyne activation (**U**, Fig. 2). [c] 5 mol% of $[RuCl_2(p\text{-cymene})_2]_2$, 10 mol% of PPh_3. All reaction carried out 20–30 h except (entries 15 & 16). [d] Starting not fully consumed within 1 h and extended 0.5 h but no fruitful result obtained. [e] Reaction time 1.5 h. NR = no reaction.

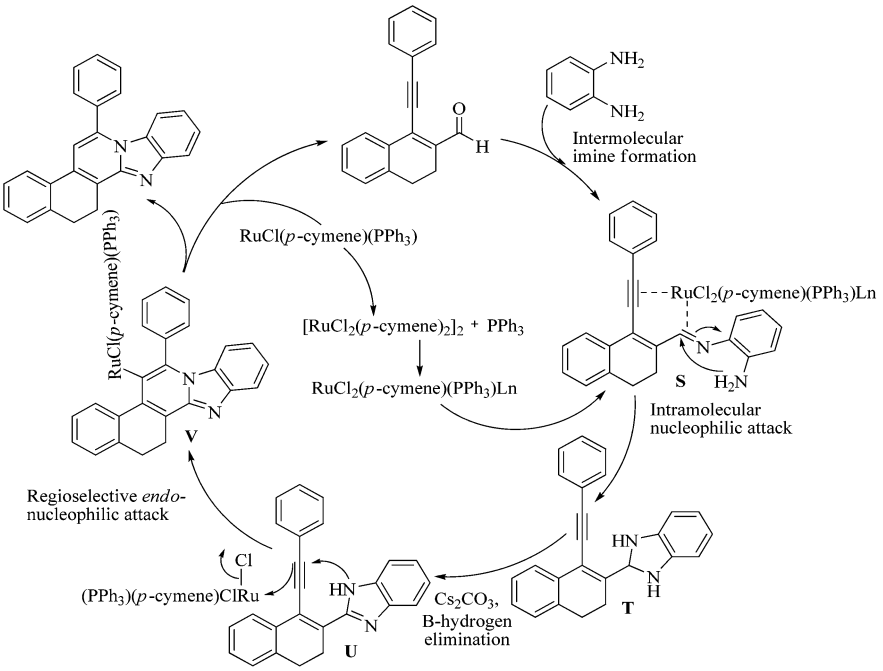


Fig. 2 Proposed mechanistic pathway for the synthesis of benzimidazole fused heterocycles.

$[RuCl_2(p\text{-cymene})_2]_2$ (10 mol%) was used, it provided the product **5d** in trace amount only in presence of base and solvent (entry 4, Table 1).

Delightfully, we obtained the desired benzimidazole derivative **5d** in 54% yield after 15 h stirring with dry DMF at 110 °C temperatures (entry 5, Table 1). This observation encouraged us to find the optimal catalytic conditions for the regioselective *endo*-tandem strategy. Upon using reaction conditions similar to (entry 5, Table 1) but in the absence of TBAB additive, a significant decrease in reaction yield to 32% was observed (entry 6, Table 1). This particular result demonstrates that the additive is not necessary but the reaction outcome is additive dependent. However, we also implemented this reaction in absence of base, but didn't get any desired product except benzimidazole intermediate (**U**, Fig. 2, see ESI†). However, the yield of **5d** was further increased to 78% when the substrate was stirred with 10 mol% $[RuCl_2(p\text{-cymene})_2]_2$ and 2 equiv Cs_2CO_3 in DMF at 110 °C under argon atmosphere (entry 8, Table 1). Subsequently, various other solvent, base and catalytic combination were screened, which are summarized in Table 1 (entries 9–12).

It was noticed that when the reaction time was increased from 20 to 30 h and also catalyst $[RuCl_2(p\text{-cymene})_2]_2$ loading from 10 to 15 mol% in dry DMF, no effect on the yield of the product **5d** (entry 13, Table 1) was observed. However, in the absence of catalyst, reactants remain unchanged during the course of the reaction (entries 14 & 15, Table 1). After successful reaction condition scanning for the synthesis of benzimidazoles, we turned our attention to reducing the reaction time. Using microwave heating allowed the reaction to be completed within 1.5 h with no change in reaction yield (entries 16 & 17, Table 1).

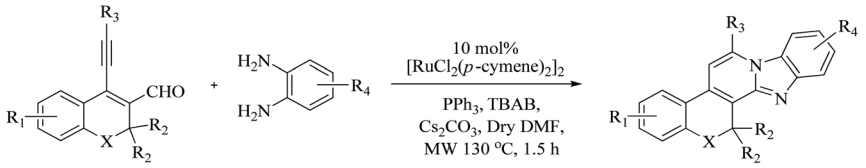
With the optimized reaction condition (DMF as the solvent, $[RuCl_2(p\text{-cymene})_2]_2$ (10 mol%) as the catalyst and Cs_2CO_3 (2 equiv) as base at 130 °C in presence of PPh_3 (15 mol%) as ligand and TBAB as additive for 1.5 h microwave irradiation under argon atmosphere) we then explored the scope and generality of the present process. We were pleased to find that this current methodology was successful with a variety of substituent on both the *ortho*-alkynyl aldehydes (**4a–k**) as well as the benzenediamines, affording the polycyclic heteroaromatic products (**5a–s**) in moderate to good yields (38–78%, Table 2). Mostly we used symmetrically substituted benzenediamines to avoid regioisomeric products. For example, when we used 4-methylbenzene-1,2-diamine, as expected we got mixture (1 : 1) of product (**5e**, Table 2).

All the final molecules were characterized by ^1H, ^{13}C, ESI-MS, HRMS and IR analysis. The final molecules (**5d**, **5g**) were confirmed by on the basis of the DEPT, HSQC, HMBC and COSY spectroscopic analysis (see ESI†). With these observations, a plausible mechanism is proposed in Fig. 2.

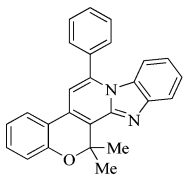
Conclusion

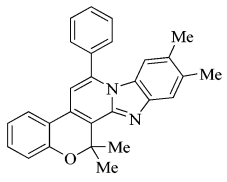
In summary, we have developed an efficient protocol for the synthesis of benzimidazole fused derivatives in moderate to good yields with high regioselectivity. These atom economic transformations are based on nucleophilic addition of *ortho*-alkynyl aldehydes and benzenediamines involving dichloro(*p*-cymene)ruthenium(II) dimer catalyzed tandem cyclization followed by formation of three new N–C bonds and two heterocyclic rings in one-pot giving fused polycyclic heterocycles. Further investigations are underway in order to expand the applicability of this process as well as building blocks for material science and pharmaceutical importance.

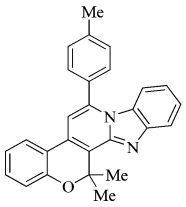
Table 2 Synthesis of benzimidazole fused derivatives (5a–s)

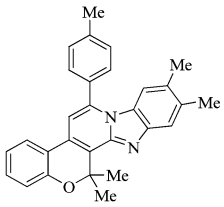


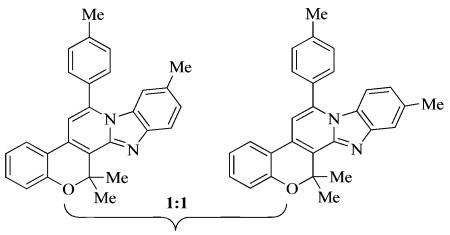
R_1 = -H, -OMe, R_2 = -H, -Me,
R_3 = -C_6H_4-Me (-*m*,-*p*), -C_4H_3S (-*m*)
R_4 = -H, -Me, -Cl, X = -O, -CH_2

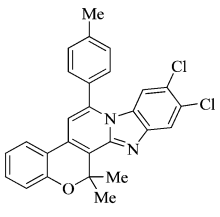

5a, 53%

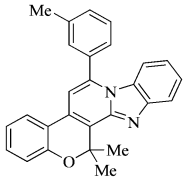

5b, 64%

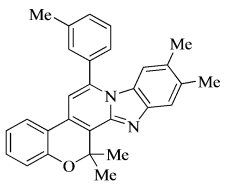

5c, 75%

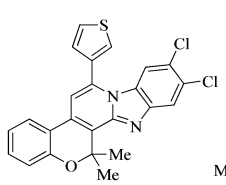

5d, 78%

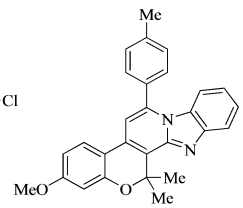

5e, 77%

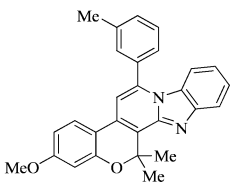

5f, 74%

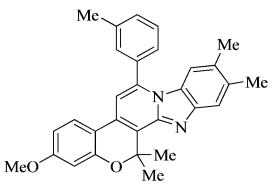

5g, 75%

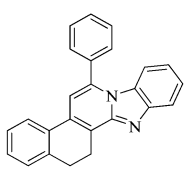

5h, 48%

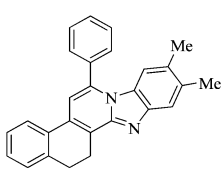

5i, 63%

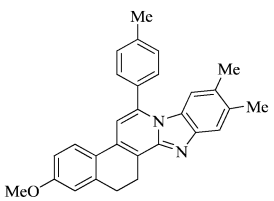

5j, 63%

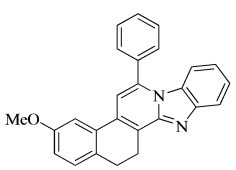

5k, 67%

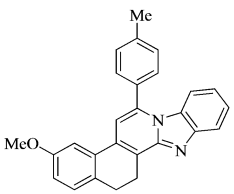

5l, 65%

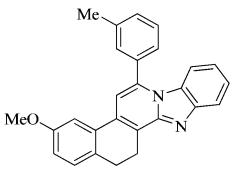

5m, 65%

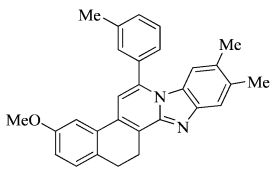

5n, 57%


5o, 38%


5p, 34%


5q, 73%


5r, 64%


5s, 35%

Experimental section

General remarks

All dry reactions were carried out under argon atmosphere in oven-dried glassware using standard gas-light syringes, cannulas, septa and also microwave crimp top. All reagents and solvents were purchased from commercial sources and used without further purification. Organic solvents were dried by reported standard methods. Analytical TLC was performed using 2.5 × 5 cm aluminum plates coated with a 0.25 mm thickness of silica gel (60F-254), visualization was accomplished with iodine and under UV lamp. Column chromatography was performed using silica gel (60–120 and 100–200 mesh). Some cases, preparative thin layer chromatography were performed on GF254 silica by using requisite distilled solvent system as mentioned below. ^{1}H NMR spectra were recorded on 300 and 400 MHz spectrometer in $CDCl_3$ (all signals are reported in ppm with the internal chloroform signal at 7.26 ppm as standard) at 25 °C. ^{13}C NMR spectra were recorded on 75 and 100 MHz spectrometer in $CDCl_3$ (all signals are reported in ppm with the internal chloroform signal at 77.00 ppm as standard) at 25 °C. In a few cases tetramethylsilane (TMS) at 0.00 ppm was used as the reference standard. ^{1}H NMR multiplicities are reported as follows: singlet (s), doublet (d), double doublet (dd), triplet (t), quartet (q) or multiplet (m). The HRMS spectra were recorded as EI-HRMS on Q-TOF mass spectrometer. IR spectra were recorded using a FTIR spectrophotometer in cm^{-1}. Biotage® Initiator Classic was used for measuring reaction mixture temperatures during microwave heating with external sensor type method.

Typical procedure and spectral data of few compounds (**3a** and **3c–e**) were already reported.[12g,15–17]

Experimental procedures and characterization data

4-Chloro-7-methoxy-2,2-dimethyl-2*H*-chromene-3-carbaldehyde (3b). Light greenish oily liquid, yield = 78% (2.124 g). R_f = 0.5 (1% EtOAc–hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 10.18 (s, 1H), 7.58 (d, J = 7.2 Hz, 1H), 6.54 (dd, J_1 = 1.3, J_2 = 8.9 Hz, 1H), 6.36 (d, J = 2.3 Hz, 1H), 3.82 (s, 3H), 1.62 (s, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 188.5, 164.9, 156.4, 144.6, 129.3, 127.5, 112.8, 108.8, 101.5, 80.9, 55.6, 26.4 ppm. IR (neat, cm^{-1}): 3041, 2335, 1232, 1043, 764, 661. Mass (ESI-MS): m/z 253.3 (100, $[M + H]^+$). ESI-HRMS: m/z $[M + H]^+$ calcd for $C_{13}H_{14}ClO_3$ 253.0631, found 253.0635.

General experimental procedure of Sonogashira coupling for the synthesis of 2-ethynylaldehydes (4a–k)

The halogenated aldehyde (1 equiv, 4.21 mmol) was dissolved in dry DMF (5 mL) and added $Pd(PPh_3)_2Cl_2$ (0.03 equiv, 0.13 mmol), CuI (0.07 equiv, 0.30 mmol), and was stirred for 10 min at room temperature under nitrogen atmosphere. After 10 min substituted alkyne (1.5 equiv, 6.32 mmol) and triethylamine (2.70 equiv, 11.38 mmol) were added and the reaction mixture was monitored by TLC. Within 5–15 min reaction was completed. After completion of the reaction, the mixture was diluted with saturated aqueous ammonium chloride and the product was extracted with ethyl acetate and water. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography eluting with 1–2% ethyl acetate in hexane.

2,2-Dimethyl-4-(phenylethynyl)-2*H*-chromene-3-carbaldehyde (4a). Greenish oily liquid, yield = 81% (0.278 g). R_f = 0.80 (2% EtOAc–hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ_H 10.39 (s, 1H), 7.77 (d, J = 6.9 Hz, 1H), 7.62–7.59 (m, 2H), 7.44–7.33 (m, 4H), 7.01 (t, J = 6.9 Hz, 1H), 6.85 (d, J = 7.9 Hz, 1H), 1.66 (s, 6H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ_C 190.4, 153.9, 139.4, 133.4, 131.9, 129.8, 128.6, 127.0, 121.7, 121.3, 119.9, 117.2, 103.2, 81.1, 78.4, 26.4 ppm. IR (neat, cm^{-1}): 3419, 3022, 2934, 2430, 2198, 1654, 1621, 1525, 1355, 1269, 1213, 977, 776, 664. Mass (ESI-MS): m/z 289.3 (100, $[M + H]^+$). ESI-HRMS: m/z $[M + H]^+$ calcd for $C_{20}H_{17}O_2$ 289.1229, found 289.1230.

2,2-Dimethyl-4-(*p*-tolylethynyl)-2*H*-chromene-3-carbaldehyde (4b). Light brownish oily liquid, yield = 69% (0.468 g). R_f = 0.87 (2% EtOAc–hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ_H 10.37 (s, 1H), 7.75 (d, J = 7.7 Hz, 1H), 7.48 (d, J = 7.7 Hz, 2H), 7.35–7.30 (m, 1H), 7.22 (t, J = 8.3 Hz, 2H), 6.99 (d, J = 7.7 Hz, 1H), 6.83 (d, J = 8.3 Hz, 1H), 2.40 (s, 3H), 1.64 (s, 6H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ_C 190.5, 153.8, 140.3, 139.0, 133.9, 133.4, 131.8, 129.4, 127.0, 121.3, 120.0, 118.6, 117.1, 103.6, 80.6, 78.4, 26.4, 21.6 ppm. IR (neat, cm^{-1}): 3433, 3027, 2925, 2430, 2202, 1659, 1619, 1530, 1355, 1266, 1213, 975, 776, 665. Mass (ESI-MS): m/z 303.2 (100, $[M + H]^+$). ESI-HRMS: m/z $[M + H]^+$ calcd for $C_{21}H_{19}O_2$ 303.1385, found 303.1385.

2,2-Dimethyl-4-(*m*-tolylethynyl)-2*H*-chromene-3-carbaldehyde (4c). Light brownish oily liquid, yield = 78% (0.311 g). R_f = 0.86 (2% EtOAc–hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ_H 10.37 (s, 1H), 7.75 (d, J = 7.7 Hz, 1H), 7.48 (d, J = 7.7 Hz, 2H), 7.35–7.30 (m, 1H), 7.22 (t, J = 8.3 Hz, 2H), 6.99 (d, J = 7.7 Hz, 1H), 6.83 (d, J = 8.3 Hz, 1H), 2.40 (s, 3H), 1.64 (s, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ_C 190.4, 153.8, 139.3, 138.5, 133.7, 133.4, 132.4, 130.7, 129.0, 128.5, 127.0, 121.5, 121.3, 119.9, 117.1, 103.5, 80.8, 78.4, 26.4, 21.2 ppm. IR (neat, cm^{-1}): 3429, 3022, 2928, 2430, 2202, 1659, 1621, 1527, 1355, 1269, 1213, 973, 776, 661. Mass (ESI-MS): m/z 303.2 (100, $[M + H]^+$). ESI-HRMS: m/z $[M + H]^+$ calcd for $C_{21}H_{19}O_2$ 303.1385, found 303.1384.

2,2-Dimethyl-4-(thiophen-3-ylethynyl)-2*H*-chromene-3-carbaldehyde (4d). Brownish oily liquid, yield = 82% (0.176 g). R_f = 0.81 (2% EtOAc–hexane). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 11.01 (s, 1H), 8.39 (dd, J_1 = 1.5, J_2 = 7.7 Hz, 1H), 8.34 (dd, J_1 = 1.1, J_2 = 2.9 Hz, 1H), 8.05–7.98 (m, 2H), 7.92–7.91 (m, 1H), 7.69–7.65 (m, 1H), 7.51 (d, J = 8.1 Hz, 1H), 2.31 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 190.4, 153.8, 139.2, 133.6, 133.4, 130.6, 129.6, 127.0, 126.1, 121.7, 120.7, 119.8, 117.2, 98.4, 80.9, 78.4, 26.4 ppm. IR (neat, cm^{-1}): 3428, 3019, 2928, 2411, 2202, 1651, 1607, 1541, 1355, 1250, 1213, 973, 759, 664. Mass (ESI-MS): m/z 295.1 (100, $[M + H]^+$). ESI-HRMS: m/z $[M + H]^+$ calcd for $C_{18}H_{15}O_2S$ 295.0793, found 295.0789.

7-Methoxy-2,2-dimethyl-4-(*p*-tolylethynyl)-2*H*-chromene-3-carbaldehyde (4e). Light greenish oily liquid, yield = 74% (0.238 g). R_f = 0.82 (2% EtOAc–hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ_H 10.31 (s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.47 (d, J = 7.5 Hz, 2H), 7.21 (d, J = 7.5 Hz, 2H), 6.57 (d, J = 8.4 Hz, 1H), 6.38 (s, 1H), 3.82 (s, 3H), 2.40 (s, 3H), 1.64 (s, 6H) ppm. ^{13}C NMR

(75 MHz, $CDCl_3$, 25 °C): δ_C 190.1, 164.4, 156.6, 140.2, 136.3, 134.0, 131.8, 129.4, 128.5, 118.7, 113.3, 108.6, 103.2, 101.5, 80.9, 78.9, 55.5, 26.5, 21.6 ppm. IR (neat, cm^{-1}): 3417, 3019, 2928, 2421, 2202, 1662, 1607, 1544, 1355, 1267, 1213, 983, 769, 665. Mass (ESI-MS): *m*/*z* 333.3 (100, $[M + H]^+$). ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{21}O_3$ 333.1491, found 333.1492.

7-Methoxy-2,2-dimethyl-4-(*m*-tolylethynyl)-2*H*-chromene-3-carbaldehyde (4f). Light brownish oily liquid, yield = 85% (0.298 g). R_f = 0.87 (2% EtOAc–hexane). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 10.23 (s, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.32 (d, J = 9.6 Hz, 2H), 7.21 (t, J = 8.1 Hz, 1H), 7.17–7.14 (m, 1H), 6.48 (dd, J_1 = 2.4, J_2 = 8.8 Hz, 1H), 6.30 (d, J = 2.4 Hz, 1H), 3.74 (s, 3H), 2.30 (s, 3H), 1.56 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 190.1, 164.4, 155.6, 138.4, 136.5, 133.9, 132.4, 130.6, 128.9, 128.5, 128.4, 121.5, 113.3, 108.6, 103.1, 101.5, 80.9, 78.9, 55.5, 26.4, 21.2 ppm. IR (neat, cm^{-1}): 3427, 3019, 2928, 2401, 2202, 1659, 1607, 1541, 1355, 1280, 1213, 983, 759, 669. Mass (ESI-MS): *m*/*z* 333.3 (100, $[M + H]^+$). ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{21}O_3$ 333.1491, found 333.1492.

1-(Phenylethynyl)-3,4-dihydronaphthalene-2-carbaldehyde (4g). Light brownish oily liquid, yield = 68% (0.295 g). R_f = 0.82 (2% EtOAc–hexane). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ_H 10.51 (s, 1H), 7.95–7.92 (m, 1H), 7.61–7.58 (m, 2H), 7.41–7.40 (m, 3H), 7.36–7.33 (m, 2H), 7.25–7.20 (m, 1H), 2.85 (t, J = 7.5 Hz, 2H), 2.64 (d, J = 8.6 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 192.2, 140.2, 137.6, 135.9, 132.1, 131.8, 130.7, 129.4, 128.6, 127.8, 127.2, 126.9, 122.0, 101.1, 82.9, 26.7, 19.9. IR (neat, cm^{-1}): 3019, 2205, 1659, 1406, 1215, 757, 669. Mass (ESI-MS): *m*/*z* 259.0 (100, $[M + H]^+$). ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{15}O$ 259.1123, found 259.1121.

6-Methoxy-1-(*p*-tolylethynyl)-3,4-dihydronaphthalene-2-carbaldehyde (4h). Light brownish oily liquid, yield = 81% (0.310 g). R_f = 0.81 (2% EtOAc–hexane). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ_H 10.45 (s, 1H), 7.86 (d, J = 8.3 Hz, 1H), 7.48 (d, J = 7.6 Hz, 2H), 7.20 (d, J = 6.9 Hz, 2H), 6.85 (d, J = 7.6 Hz, 1H), 6.75 (s, 1H), 3.85 (s, 3H), 2.82 (t, J = 6.6 Hz, 2H), 2.63 (t, J = 7.7 Hz, 2H), 2.39 (s, 3H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ_C 192.0, 161.6, 139.9, 139.7, 137.7, 136.2, 131.7, 129.3, 129.1, 125.3, 119.0, 113.5, 112.0, 101.1, 82.6, 77.6, 55.3, 27.3, 21.6, 19.8 ppm. IR (neat, cm^{-1}): 3429, 3020, 2206, 1603, 1428, 1368, 1216, 759, 670. Mass (ESI-MS): *m*/*z* 303.1 (100, $[M + H]^+$). ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{19}O_2$ 303.1385, found 303.1386.

7-Methoxy-1-(phenylethynyl)-3,4-dihydronaphthalene-2-carbaldehyde (4i). Brownish oily liquid, yield = 63% (0.346 g). R_f = 0.82 (2% EtOAc–hexane). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ_H 10.51 (s, 1H), 7.60–7.59 (m, 2H), 7.51 (s, 1H), 7.42–7.40 (m, 3H), 7.14 (d, J = 8.2 Hz, 1H), 6.91 (d, J = 8.2 Hz, 2H), 3.86 (s, 3H), 2.79 (t, J = 7.8 Hz, 2H), 2.63 (t, J = 7.9 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 192.3, 158.5, 140.7, 135.9, 133.2, 131.8, 129.8, 129.4, 128.6, 122.0, 115.9, 112.8, 101.1, 82.9, 55.4, 25.9, 20.3 ppm. IR (neat, cm^{-1}): 3426, 3019, 2216, 1603, 1432, 1368, 1215, 759, 667. Mass (ESI-MS): *m*/*z* 289.3 (100, $[M + H]^+$). ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{17}O_2$ 289.1229, found 289.1227.

7-Methoxy-1-(*p*-tolylethynyl)-3,4-dihydronaphthalene-2-carbaldehyde (4j). Brownish oily liquid, yield = 73% (0.413 g). R_f = 0.85 (2% EtOAc–hexane). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 10.49 (s, 1H), 7.50 (d, J = 2.7 Hz, 1H), 7.47 (d, J = 7.9 Hz, 2H), 7.20 (d, J = 7.9 Hz, 2H), 7.12 (d, J = 7.9 Hz, 1H), 6.89 (dd, J_1 = 2.7, J_2 = 8.4 Hz, 1H), 3.85 (s, 3H), 2.77 (t, J = 7.9 Hz, 2H), 2.61 (t, J = 8.3 Hz, 2H), 2.39 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ_C 192.3, 158.5, 140.3, 139.8, 136.1, 133.2, 131.7, 129.7, 129.3, 128.5, 118.9, 115.9, 112.8, 101.5, 82.4, 55.3, 25.8, 21.5, 20.2 ppm. IR (neat, cm^{-1}): 3428, 3020, 2930, 2408, 2201, 1652, 1604, 1317, 1368, 1215, 1034 760, 670. Mass (ESI-MS): *m*/*z* 303.6 (100, $[M + H]^+$). ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{19}O_2$ 303.1385, found 303.1385.

7-Methoxy-1-(*m*-tolylethynyl)-3,4-dihydronaphthalene-2-carbaldehyde (4k). Light brownish oily liquid, yield = 67% (0.530 g). R_f = 0.82 (2% EtOAc–hexane). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 10.43 (s, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.32 (d, J = 8.9 Hz, 2H), 7.21 (d, J = 7.5 Hz, 1H), 7.15 (d, J = 7.5 Hz, 1H), 7.07 (d, J = 8.3 Hz, 1H), 6.83 (dd, J_1 = 2.8, J_2 = 8.3 Hz, 1H), 3.79 (s, 3H), 2.71 (t, J = 7.5 Hz, 2H), 2.55 (t, J = 8.8 Hz, 2H), 2.31 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ_C 192.4, 158.5, 140.6, 138.41, 136.0, 133.2, 132.3, 130.4, 129.8, 128.9, 128.6, 128.5, 121.9, 115.9, 112.9, 101.4, 82.6, 55.4, 31.9, 25.9, 21.2, 20.3 ppm. IR (neat, cm^{-1}): 3426, 3022, 2918, 2401, 2202, 1613, 1659, 1532, 1355, 1283, 1213, 983, 775, 664. Mass (ESI-MS): *m*/*z* 303.1 (100, $[M + H]^+$). ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{19}O_2$ 303.1385, found 303.1388.

General procedure for synthesis of benzimidazole fused heterocycles (5a–s)

A microwave crimp top vial equipped with a stir bar was charged with *ortho*-alkynylaldehydes (**4a–k**) (1.0 equiv, 0.16 mmol), substituted benzenediamines (1.2 equiv, 0.20 mmol), and Cs_2CO_3 (2.0 equiv, 0.33 mmol). To this mixture catalytic amount of TBAB was added followed by 1 mL of dry DMF at room temperature. Then 10 mol% of $[RuCl_2(p\text{-cymene})_2]_2$, 15 mol% of PPh_3, DMF (1 mL) were added under argon atmosphere. The reaction mixture was stirred at 130 °C for 1.5 h. Finally, after completion of the reaction (as monitored by TLC), the mixture was cooled to room temperature, diluted with ethyl acetate (10 mL) and filtered through celite bed. The filtrate was then mixed with water, and extracted with (2 × 10 mL) ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography as well as preparative thin layer chromatography, eluting with 1–3% ethyl acetate in hexane.

1,1-Dimethyl-8-phenyl-1*H*-benzo[4,5]imidazo[1,2-*a*]chromeno-[3,4-*c*]pyridine (5a). Light greenish oily liquid, yield = 53% (0.050 g). R_f = 0.76 (2% EtOAc–hexane). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 7.94 (d, J = 6.86 Hz, 1H), 7.68–7.58 (m, 6H), 7.39 (d, J = 7.50 Hz, 1H), 7.32–7.28 (m, 1H), 7.05 (s, 1H), 7.01 (t, J = 7.5 Hz, 2H), 6.95 (t, J = 7.8 Hz, 1H), 6.50 (d, J = 7.9 Hz, 1H), 2.13 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 153.4, 140.5, 134.5, 131.0, 130.1, 129.1, 129.0, 125.1, 124.4, 123.5, 121.4, 120.6, 119.8, 119.6, 118.0, 114.4, 107.4, 78.4, 27.1 ppm. IR (neat, cm^{-1}): 3423, 3050, 2962, 1745, 1631, 1420, 1319, 1235, 1055, 765, 665. Mass (ESI-MS): *m*/*z* 377.5 (100, $[M + H]^+$). ESI-

HRMS: m/z $[M + H]^+$ calcd for $C_{26}H_{21}N_2O$ 377.1654, found 377.1656.

1,1,11,12-Tetramethyl-8-phenyl-1*H*-benzo[4,5]imidazo[1,2-*a*]-chromeno[3,4-*c*]pyridine (5b). Light greenish oily liquid, yield = 64% (0.063 g). $R_f = 0.72$ (2% EtOAc–hexane). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 7.67–7.66 (m, 1H), 7.65–7.63 (m, 1H), 7.61 (s, 2H), 7.59–7.57 (m, 3H), 7.30–7.28 (m, 1H), 7.01–6.98 (m, 3H), 6.23 (s, 1H), 2.36 (s, 3H), 2.12 (s, 3H), 2.11 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 153.3, 140.2, 134.7, 134.5, 130.8, 129.9, 129.1, 129.0, 128.1, 127.6, 124.3, 123.4, 121.3, 120.0, 119.4, 117.9, 114.4, 106.8, 78.4, 27.07, 20.7, 20.4 ppm. IR (neat, cm^{-1}): 3417, 3028, 2927, 1635, 1424, 1331, 1225, 762, 661. Mass (ESI-MS): m/z 405.1 (100, $[M + H]^+$). ESI-HRMS: m/z $[M + H]^+$ calcd for $C_{28}H_{25}N_2O$ 405.1967, found 405.1964.

1,1-Dimethyl-8-(*p*-tolyl)-1*H*-benzo[4,5]imidazo[1,2-*a*]chromeno-[3,4-*c*]pyridine (5c). Light greenish oily liquid, yield = 75% (0.051 g). R_f = 0.72 (2% EtOAc–hexane). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 7.89 (d, J = 8.2 Hz, 1H), 7.59 (d, J = 7.2 Hz, 1H), 7.47 (d, J = 8.2 Hz, 2H), 7.42–7.35 (m, 3H), 7.30–7.26 (m, 1H), 7.01–6.93 (m, 4H), 6.60 (s, 1H), 2.54 (s, 3H), 2.12 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 153.4, 146.7, 145.1, 140.6, 140.1, 131.7, 130.9, 129.8, 129.3, 128.9, 128.7, 124.9, 124.3, 123.5, 121.3, 120.4, 119.9, 119.7, 117.9, 114.5, 107.1, 78.5, 27.0, 21.6 ppm. IR (neat, cm^{-1}): 3425, 3020, 2927, 1631, 1404, 1318, 1215, 758, 669. Mass (ESI-MS): m/z 391.1 (100, $[M + H]^+$). ESI-HRMS: m/z $[M + H]^+$ calcd for $C_{27}H_{23}N_2O$ 391.1810, found 391.1809.

1,1,11,12-Tetramethyl-8-(*p*-tolyl)-1H-benzo[4,5]imidazo[1,2-*a*]-chromeno[3,4-*c*]pyridine (5d). Greenish oily liquid, yield = 78% (0.059 g). R_f = 0.71 (2% EtOAc–hexane). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 7.67 (s, 1H), 7.61–7.58 (m, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 7.7 Hz, 2H), 7.28 (dd, J_1 = 1.4, J_2 = 7.7 Hz, 1H), 7.01–6.96 (m, 3H), 6.33 (s, 1H), 2.55 (s, 3H), 2.36 (s, 3H), 2.14 (s, 3H), 2.11 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 153.3, 146.2, 143.9, 140.3, 139.9, 134.2, 131.9, 130.6, 129.6, 128.9, 127.9, 127.7, 124.2, 123.4, 121.3, 120.1, 119.5, 117.9, 114.5, 106.7, 78.4, 27.0, 21.5, 20.7, 20.4 ppm. IR (neat, cm^{-1}): 3427, 3028, 2932, 1625, 1424, 1323, 1225, 772, 664. Mass (ESI-MS): m/z 419.6 (100, $[M + H]^+$). ESI-HRMS: m/z $[M + H]^+$ calcd for $C_{29}H_{27}N_2O$ 419.2123, found 419.2122.

Mixture (1 : 1) of 1,1,12-trimethyl-8-(*p*-tolyl)-1*H*-benzo[4,5] imidazo[1,2-*a*]chromeno[3,4-*c*]pyridine and 1,1,11-trimethyl-8-(*p*-tolyl)-1H-benzo[4,5]imidazo[1,2-*a*]chromeno[3,4-*c*]pyridine (5e). Light greenish oily liquid, yield = 77% (0.066 g). R_f = 0.79 (2% EtOAc–hexane). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 7.78 (d, J = 8.2 Hz, 1H), 7.72–7.69 (m, 2H), 7.61–7.59 (m, 2H), 7.53 (dd, J_1 = 3.4, J_2 = 5.7 Hz, 1H), 7.48–7.46 (m, 4H), 7.43–7.40 (m, 4H), 7.30–7.26 (m, 2H), 7.21 (dd, J_1 = 1.2, J_2 = 8.4 Hz, 1H), 7.00–6.97 (m, 4H), 6.78 (dd, J_1 = 1.4, J_2 = 8.6 Hz, 1H), 6.46 (d, J = 8.6 Hz, 1H), 6.36 (s, 1H), 2.55 (s, 3H), 2.54 (s, 3H), 2.46 (s, 3H), 2.26 (s, 3H), 2.11 (s, 12H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 167.7, 153.3, 146.7, 146.4, 145.5, 143.2, 140.4, 140.0, 134.8, 132.4, 132.3, 131.8, 131.7, 130.9, 130.8, 130.7, 130.1, 129.7, 129.6, 129.4, 128.9, 128.8, 128.7, 128.5, 128.1, 127.4, 126.6, 124.3, 124.2, 123.4, 122.0, 121.3, 120.0, 119.2, 119.1, 117.9, 114.3, 113.9, 106.9, 106.6, 78.4, 27.0, 21.9, 21.6, 21.5 ppm. IR (neat, cm^{-1}): 3423, 3028, 2944, 1635, 1427, 1333, 1271, 773, 666. Mass (ESI-MS): m/z 405.6 (100, $[M + H]^+$). ESI-HRMS: m/z $[M + H]^+$ calcd for $C_{28}H_{25}N_2O$ 405.1967, found 405.1968.

11,12-Dichloro-1,1-dimethyl-8-(*p*-tolyl)-1*H*-benzo[4,5]imidazo-[1,2-*a*]chromeno[3,4-*c*]pyridine (5f). Greenish oily liquid, yield = 74% (0.041 g). R_f = 0.75 (2% EtOAc–hexane). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 7.96 (s, 1H), 7.60 (dd, J_1 = 1.4, J_2 = 7.6 Hz, 1H), 7.45 (s, 4H), 7.33–7.29 (m, 1H), 7.04 (s, 1H), 7.03–6.99 (m, 2H), 6.64 (s, 1H), 2.56 (s, 3H), 2.08 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 153.5, 148.1, 144.3, 140.8, 140.5, 131.3, 130.7, 130.0, 129.9, 129.0, 128.8, 128.7, 128.3, 124.3, 123.8, 123.6, 121.5, 120.4, 119.6, 118.0, 115.6, 107.8, 78.3, 26.9, 21.6 ppm. IR (neat, cm^{-1}): 3430, 3048, 2962, 2416, 1623, 1421, 1236, 1055, 767, 664. Mass (ESI-MS): m/z 459.3 (100, $[M + H]^+$). ESI-HRMS: m/z $[M + H]^+$ calcd for $C_{27}H_{21}Cl_2N_2O$ 459.1031, found 459.1030.

1,1-Dimethyl-8-(*m*-tolyl)-1*H*-benzo[4,5]imidazo[1,2-*a*]chromeno-[3,4-*c*]pyridine (5g). Light greenish oily liquid, yield = 75% (0.055 g). R_f = 0.71 (2% EtOAc–hexane). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 8.04 (dd, J_1 = 1.1, J_2 = 7.7 Hz, 1H), 7.86–7.83 (m, 2H), 7.53–7.48 (m, 1H), 7.49–7.42 (m, 3H), 7.29–7.24 (m, 2H), 6.99–6.92 (m, 2H), 6.40–6.36 (m, 1H), 5.96 (s, 1H), 2.23 (s, 3H), 1.66 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 155.2, 152.6, 139.0, 138.4, 135.8, 133.1, 130.1, 130.0, 129.9, 128.7, 128.4, 127.7, 127.1, 126.8, 126.1, 125.2, 120.6, 120.0, 119.2, 117.8, 113.4, 113.3, 107.9, 75.3, 27.9, 21.2 ppm. IR (neat, cm^{-1}): 3430, 3019, 1655, 1404, 1215, 1130, 756, 668. Mass (ESI-MS): m/z 391.1 (100, $[M + H]^+$). ESI-HRMS: m/z $[M + H]^+$ calcd for $C_{27}H_{23}N_2O$ 391.1810, found 391.1807.

1,1,11,12-Tetramethyl-8-(*m*-tolyl)-1*H*-benzo[4,5]imidazo[1,2-*a*]-chromeno[3,4-*c*]pyridine (5h). Brownish oily liquid, yield = 48% (0.051 g). R_f = 0.77 (2% EtOAc–hexane). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 7.61 (d, J = 6.9 Hz, 1H), 7.52–7.46 (m, 2H), 7.40–7.37 (m, 2H), 7.31–7.27 (m, 1H), 7.04–6.98 (m, 4H), 6.28 (s, 1H), 2.49 (s, 3H), 2.36 (s, 3H), 2.14 (s, 6H), 2.13 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ_C 153.5, 140.6, 139.0, 134.0, 131.3, 130.9, 129.6, 128.9, 128.8, 128.0, 126.1, 123.6, 121.5, 119.7, 118.8, 118.0, 114.6, 78.2, 26.9, 21.4, 20.7, 20.3 ppm. IR (neat, cm^{-1}): 3431, 3049, 2962, 2406, 1623, 1420, 1236, 1055, 757, 661. Mass (ESI-MS): m/z 419.7 (100, $[M + H]^+$). ESI-HRMS: m/z $[M + H]^+$ calcd for $C_{29}H_{27}N_2O$ 419.2123, found 419.2118.

11,12-Dichloro-1,1-dimethyl-8-(thiophen-3-yl)-1*H*-benzo[4,5]-imidazo[1,2-*a*]chromeno[3,4-*c*]pyridine (5i). Light brownish oily liquid, yield = 63% (0.071 g). R_f = 0.74 (2% EtOAc–hexane). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 7.97 (s, 1H), 7.28–7.69 (m, 2H), 7.68–7.65 (m, 1H), 7.54–7.51 (m, 2H), 7.12 (s, 1H), 7.04–6.98 (m, 2H), 6.66 (s, 1H), 2.07 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 167.7, 153.5, 145.0, 135.4, 132.4, 131.4, 130.9, 129.8, 128.8, 128.2, 127.8, 126.6, 124.2, 123.6, 121.5, 120.5, 118.1, 115.2, 108.3, 78.3, 26.9 ppm. IR (neat, cm^{-1}): 3427, 3018, 2932, 1632, 1421, 1323, 1232, 772, 665. Mass (ESI-MS): m/z 451.3 (100, $[M + H]^+$). ESI-HRMS: m/z $[M + H]^+$ calcd for $C_{24}H_{17}C_{12}N_2OS$ 451.0439, found 451.0441.

4-methoxy-1,1-Dimethyl-8-(*p*-tolyl)-1*H*-benzo[4,5]imidazo[1,2-*a*]-chromeno[3,4-*c*]pyridine (5j). Light greenish oily liquid, yield = 63% (0.067 g). R_f = 0.69 (2% EtOAc–hexane). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 7.87 (d, J = 8.5 Hz, 1H), 7.51–7.45 (m, 3H), 7.41–7.34 (m, 3H), 6.94–6.90 (m, 2H), 6.57 (s, 1H), 6.55 (s, 2H), 3.84 (s, 3H), 2.54 (s, 3H), 2.11 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$,

25 °C): δ_C 162.3, 154.9, 146.9, 145.1, 140.5, 140.0, 131.8, 129.7, 129.0, 128.9, 124.8, 124.5, 122.1, 120.1, 119.5, 114.4, 112.9, 108.3, 107.0, 102.5, 78.9, 55.4, 27.1, 21.5 ppm. IR (neat, cm^{-1}): 3402, 3023, 2919, 1625, 1424, 1323, 1255, 767, 660. Mass (ESI-MS): *m*/*z* 421.2 (100, $[M + H]^+$). ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{28}H_{25}N_2O_2$ 421.1916, found 421.1913.

4-Methoxy-1,1-dimethyl-8-(*m*-tolyl)-1*H*-benzo[4,5]imidazo[1,2-*a*]chromeno[3,4-*c*]pyridine (5k). Light greenish oily liquid, yield = 67% (0.039 g). R_f = 0.76 (2% EtOAc–hexane). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 8.02 (s, 1H), 7.53–7.46 (m, 3H), 7.40–7.37 (m, 3H), 7.03 (s, 1H), 6.96 (t, *J* = 7.9 Hz, 1H), 6.57–6.56 (m, 2H), 6.50 (d, *J* = 8.6 Hz, 1H), 3.84 (s, 3H), 2.48 (s, 3H), 2.15 (s, 3H), 2.14 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 163.0, 155.3, 141.0, 139.3, 131.1, 129.5, 129.2, 128.5, 126.0, 124.9, 121.4, 118.7, 114.5, 108.9, 102.6, 78.6, 55.5, 26.9, 21.5 ppm. IR (neat, cm^{-1}): 3431, 3019, 2406, 1613, 1404, 1216, 757, 669. Mass (ESI-MS): *m*/*z* 421.5 (100, $[M + H]^+$). ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{28}H_{25}N_2O_2$ 421.1916, found 421.1913.

4-Methoxy-1,1,11,12-tetramethyl-8-(*m*-tolyl)-1*H*-benzo[4,5]-imidazo[1,2-*a*]chromeno[3,4-*c*]pyridine (5l). Greenish oily liquid, yield = 65% (0.047 g). R_f = 0.72 (2% EtOAc–hexane). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 7.64 (s, 1H), 7.51–7.44 (m, 3H), 7.39–7.36 (m, 2H), 6.90 (s, 1H), 6.57–6.55 (m, 2H), 6.26 (s, 1H), 3.83 (s, 3H), 2.47 (s, 3H), 2.35 (s, 3H), 2.12 (s, 3H), 2.09 (d, *J* = 4.6 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 162.0, 154.8, 140.3, 138.8, 134.7, 134.1, 130.5, 129.6, 128.8, 127.8, 126.1, 124.4, 119.3, 114.4, 113.1, 108.2, 106.4, 102.5, 78.9, 55.4, 27.0, 21.4, 20.6, 20.4 ppm. IR (neat, cm^{-1}): 3423, 3019, 2402, 1613, 1515, 1406, 1215, 928, 756, 669. Mass (ESI-MS): *m*/*z* 449.7 (100, $[M + H]^+$). ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{30}H_{29}N_2O_2$ 449.2229, found 449.2225.

8-Phenyl-1,2-dihydrobenzo[*f*]benzo[4,5]imidazo[2,1-*a*]isoquinoline (5m). Brownish oily liquid, yield = 65% (0.061 g). R_f = 0.78 (2% EtOAc–hexane). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 8.04 (d, *J* = 7.6 Hz, 1H), 7.93 (s, 1H), 7.86 (d, *J* = 8.7 Hz, 1H), 7.62 (d, *J* = 7.3 Hz, 2H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.38 (d, *J* = 7.1 Hz, 1H), 7.33–7.25 (m, 2H), 7.20 (d, *J* = 7.3 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.60 (t, *J* = 7.7 Hz, 1H), 6.19 (s, 1H), 2.94–2.88 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ_C 154.7, 139.5, 137.1, 135.9, 130.7, 129.9, 129.3, 129.1, 128.9, 128.6, 128.4, 127.6, 127.3, 126.8, 125.3, 124.8, 119.6, 119.4, 113.3, 110.7, 30.9, 21.7 ppm. IR (neat, cm^{-1}): 3423, 3049, 2946, 1613, 1433, 1215, 942, 768, 660. Mass (ESI-MS): *m*/*z* 347.3 (100, $[M + H]^+$). ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{19}N_2$ 347.1548, found 347.1547.

11,12-Dimethyl-8-phenyl-1,2-dihydrobenzo[*f*]benzo[4,5]imidazo[2,1-*a*]isoquinoline (5n). Light yellowish oily liquid, yield = 57% (0.044 g). R_f = 0.77 (2% EtOAc–hexane). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 8.00 (s, 1H), 7.67 (d, *J* = 9.4 Hz, 3H), 7.44 (t, *J* = 5.9 Hz, 1H), 7.34 (t, *J* = 7.1 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 1H), 6.96 (t, *J* = 8.3 Hz, 1H), 5.59 (t, *J* = 8.6 Hz, 1H), 6.14 (s, 1H), 2.95–2.93 (m, 2H), 2.89–2.86 (m, 2H), 2.48 (s, 3H), 2.42 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 152.1, 138.1, 137.3, 130.7, 129.9, 129.8, 129.1, 128.9, 128.7, 128.4, 127.6, 126.2, 125.5, 124.4, 118.8, 113.9, 30.6, 21.6, 20.5, 19.6 ppm. IR (neat, cm^{-1}): 3442, 3059, 2961, 1653, 1403, 1219, 914, 758, 654. Mass (ESI-MS): *m*/*z* 375.3 (100, $[M + H]^+$). ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{23}N_2$ 375.1861, found 375.1858.

4-Methoxy-11,12-dimethyl-8-(*p*-tolyl)-1,2-dihydrobenzo[*f*]benzo-[4,5]imidazo[2,1-*a*]-isoquinoline (5o). Brownish oily liquid, yield = 38% (0.027 g). R_f = 0.72 (2% EtOAc–hexane). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 8.00 (d, *J* = 8.5 Hz, 1H), 7.84 (s, 1H), 7.77 (s, 1H), 7.60 (s, 1H), 7.84 (d, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 2H), 6.77 (s, 1H), 6.18–6.09 (m, 2H), 3.74 (s, 3H), 2.89–2.86 (m, 4H), 2.46 (s, 3H), 2.39 (s, 3H), 2.37(s, 3H) ppm. IR (neat, cm^{-1}): 3403, 3021, 2961, 1653, 1409, 1205, 929, 775, 676. Mass (ESI-MS): *m*/*z* 419.8 (100, $[M + H]^+$). ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{29}H_{27}N_2O$ 419.2123, found 419.2125.

5-Methoxy-8-phenyl-1,2-dihydrobenzo[*f*]benzo[4,5]imidazo-[2,1-*a*]isoquinoline (5p). Light yellowish oily liquid, yield = 34% (0.016 g). R_f = 0.70 (2% EtOAc–hexane). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 8.04 (dd, J_1 = 1.2, J_2 = 7.99 Hz, 1H), 7.95 (s, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.73–7.71 (m, 2H), 7.54–7.50 (m, 1H), 7.46–7.39 (m, 2H), 7.36–7.32 (m, 2H), 7.12 (d, *J* = 8.2 Hz, 1H), 6.56 (dd, J_1 = 2.7, J_2 = 8.4 Hz, 1H), 5.90 (s, 1H), 3.18 (s, 3H), 2.91–2.85 (m, 4H) ppm. IR (neat, cm^{-1}): 3419, 3025, 2962, 1703, 1420, 1235, 1055, 929, 758, 664. Mass (ESI-MS): *m*/*z* 377.3 (100, $[M + H]^+$). ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{21}N_2O$ 377.1654, found 377.1649.

5-Methoxy-8-(*p*-tolyl)-1,2-dihydrobenzo[*f*]benzo[4,5]imidazo-[2,1-*a*]isoquinoline (5q). Light greenish oily liquid, yield = 73% (0.051 g). R_f = 0.69 (2% EtOAc–hexane). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 8.02 (dd, J_1 = 1.4, J_2 = 7.8 Hz, 1H), 7.92 (s, 1H), 7.85–7.83 (m, 1H), 7.60 (d, *J* = 7.8 Hz, 2H), 7.57–7.48 (m, 1H), 7.45–7.41 (m, 1H), 7.15 (d, *J* = 7.8 Hz, 2H), 7.12 (d, *J* = 8.3 Hz, 1H), 6.56 (dd, J_1 = 2.7, J_2 = 8.3 Hz, 1H), 5.92 (s, 1H), 3.19 (s, 3H), 2.91–2.83 (m, 4H), 2.37 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ_C157.1, 154.3, 139.6, 136.8, 135.9, 131.7, 129.9, 129.4, 129.0, 128.8, 128.0, 127.5, 126.6, 124.8, 119.6, 119.5, 113.9, 112.8, 113.2, 110.7, 54.5, 30.0, 22.1, 21.3 ppm. IR (neat, cm^{-1}): 3402, 3023, 2949, 1745, 1620, 1424, 1323, 1255, 765, 652. Mass (ESI-MS): *m*/*z* 391.3 (100, $[M + H]^+$). ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{23}N_2O$ 391.1810, found 391.1811.

5-Methoxy-8-(*m*-tolyl)-1,2-dihydrobenzo[*f*]benzo[4,5]imidazo-[2,1-*a*]isoquinoline (5r). Light brownish oily liquid, yield = 64% (0.054 g). R_f = 0.80 (2% EtOAc–hexane). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 8.04 (d, *J* = 7.7 Hz, 1H), 7.93 (s, 1H), 7.85 (d, *J* = 7.7 Hz, 1H), 7.55 (s, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.45–7.41 (m, 2H), 7.20 (s, 2H), 7.11 (d, *J* = 8.1 Hz, 1H), 6.57 (d, *J* = 8.1 Hz, 1H), 5.89 (s, 1H), 3.19 (s, 3H), 2.87 (s, 4H), 2.25 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ_C 157.0, 154.4, 139.2, 138.1, 135.9, 131.7, 130.3, 130.0, 129.9, 129.4, 128.8, 128.3, 128.0, 127.6, 126.7, 126.6, 124.8, 119.7, 119.4, 113.5, 113.3, 113.0, 110.7, 54.6, 30.0, 22.1, 21.2 ppm. IR (neat, cm^{-1}): 3416, 3025, 2927, 1635, 1441, 1330, 1225, 1054, 772, 662. Mass (ESI-MS): *m*/*z* 391.3 (100, $[M + H]^+$). ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{23}N_2O$ 391.1810, found 391.1811.

5-Methoxy-11,12-dimethyl-8-(*m*-tolyl)-1,2-dihydrobenzo[*f*]-benzo[4,5]imidazo[2,1-*a*]isoquinoline (5s). Light brownish oily liquid, yield = 35% (0.021 g). R_f = 0.77 (2% EtOAc–hexane). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H 8.03 (s, 1H), 7.65 (s, 1H), 7.59 (s, 1H), 7.54 (d, *J* = 10.7 Hz, 1H), 7.27–7.26 (m, 3H), 7.11 (t, *J* = 8.0 Hz, 1H), 6.61–6.59 (m, 1H), 5.82 (s, 1H), 3.20 (s, 3H),

2.89–2.88 (m, 4H), 2.49 (s, 3H), 2.43 (s, 3H), 2.25 (s, 3H) ppm. IR (neat, cm^{-1}): 3423, 3019, 2961, 1613, 1403, 1215, 929, 758, 669. Mass (ESI-MS): *m*/*z* 419.5 (100, $[M + H]^+$). ESI-HRMS: *m*/*z* $[M + H]^+$calcd for $C_{29}H_{27}N_2O$ 419.2123, found 419.2121.

2-(1-(Phenylethynyl)-3,4-dihydronaphthalen-2-yl)-1*H*-benzo[*d*]-imidazole (U). Light greenish oily liquid, yield = 57% (0.042 g). R_f = 0.27 (10% EtOAc–hexane). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ_H 11.7 (s, 1H), 7.85 (d, J = 6.9 Hz, 2H), 7.66 (t, J = 3.4 Hz, 2H), 7.48–7.42 (m, 4H), 7.35–7.21 (m, 5H), 3.32 (t, J = 8.2 Hz, 2H), 2.97 (t, J = 7.5 Hz, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ_C 150.9, 143.0, 136.1, 133.6, 133.5, 133.1, 131.1, 129.5, 128.9, 128.6, 127.4, 126.8, 126.3, 124.0, 122.7, 122.0, 119.9, 118.8, 110.6, 98.8, 87.9, 27.3, 25.3 ppm. IR (neat, cm^{-1}): 3427, 3023, 2928, 2428, 2202, 1662, 1627, 1544, 1375, 1267, 1213, 984, 769, 660. Mass (ESI-MS): *m*/*z* 347.2 (90, $[M + H]^+$). ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{19}N_2$ 347.1548, found 347.1550.

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References

1 (*a*) R. J. Griffin, G. Fontana, B. T. Golding, S. Guiard, I. R. Hardcastle, J. J. J. Leahy, N. Martin, C. Richardson, L. Rigoreau, M. Stockley and G. C. M. Smith, *J. Med. Chem.*, 2005, **48**, 569; (*b*) K. W. Bentley, *Nat. Prod. Rep.*, 2006, **23**, 444; (*c*) A. D. C. Parenty, L. V. Smith, K. M. Guthrie, D. L. Long, J. Plumb, R. Brown and L. Cronin, *J. Med. Chem.*, 2005, **48**, 4504; (*d*) M. Chrzanowska and M. D. Rozwadowska, *Chem. Rev.*, 2004, **104**, 3341; (*e*) K. W. Bentley, *Nat. Prod. Rep.*, 2005, **22**, 249; (*f*) S. D. Riedl, S. B. Felix, W. J. Houlihan, M. Zafferani, G. Steinhauser, D. Oberberg, H. Kalvelage, R. Busch, J. Rastetterand and W. E. Berdel, *Cancer Res.*, 1991, **51**, 43; (*g*) D. Scholz, H. Schmidt, E. E. Prieschl, R. Csonga, W. Scheirer, V. Weber, A. Lembachner, G. Seidl, G. Werner, P. Mayer and T. Baumruker, *J. Med. Chem.*, 1998, **41**, 1050.

2 (*a*) V. K. Pandey and A. Shukla, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 1999, **38**, 1381; (*b*) S. M. Rida, S. A. M. El-Hawash, H. T. Y. Fahmy, A. A. Hazzaa and M. M. M. El-Meligy, *Arch. Pharmacal Res.*, 2006, **29**, 826; (*c*) R. L. Weinkauf, A. Y. Chen, C. Yu, L. Liu, L. Barrows and E. LaVoie, *Bioorg. Med. Chem.*, 1994, **2**, 781; (*d*) L. W. Deady, T. Rodemann, G. J. Finlay, B. C. Baguley and W. A. Denny, *Anti-Cancer Drug Des.*, 2001, **15**, 339.

3 (*a*) M. Hranjec, M. Kralj, I. Piantanida, M. Sedić, L. Sÿuman, K. Pavelić and G. Karminski-Zamola, *J. Med. Chem.*, 2007, **50**, 5696; (*b*) M. Hranjec, I. Piantanida, M. Kralj, L. Suman, K. Pavelić and G. Karminski-Zamola, *J. Med. Chem.*, 2008, **51**, 4899.

4 (*a*) Q. Sun and E. J. LaVoie, *Heterocycles*, 1996, **43**, 737; (*b*) H.-C. Ouyang, R.-Y. Tang, P. Zhong, X.-G. Zhang and J.-H. Li, *J. Org. Chem.*, 2011, **76**, 223; (*c*) Y. Ohta, Y. Kubota, T. Watabe, H. Chiba, S. Oishi, N. Fujii and H. Ohno, *J. Org. Chem.*, 2009, **74**, 6299; (*d*) G. Dyker, W. Stirner and G. Henkel, *Eur. J. Org. Chem.*, 2000, **8**, 1433; (*e*) T. K. Chaitanya, K. S. Prakash and R. Nagarajan, *Tetrahedron*, 2011, **67**, 6934; (*f*) N. Rustagi, T. Aggarwal and A. K. Verma, *Green Chem.*, 2011, **13**, 1640; (*g*) N. Okamoto, K. Sakurai, M. Ishikur, K. Takeda and R. Yanada, *Tetrahedron Lett.*, 2009, **50**, 4167; (*h*) S. K. Manna, S. K. Mondal, A. Ahmed, A. Mandal, A. Jana, M. Ikbal, S. Samanta and J. K. Ray, *RSC Adv.*, 2014, **4**, 2474; (*i*) V. Rustagi, R. Tiwari and A. K. Verma, *Eur. J. Org. Chem.*, 2012, **24**, 4590; (*j*) N. T. Patil, A. Konala, S. Sravanti, A. Singh, R. Ummanni and B. Sridhar, *Chem. Commun.*, 2013, **49**, 10109.

5 N. Asao, K. Iso and S. S. Yudha, *Org. Lett.*, 2006, **8**, 4149.

6 (*a*) H. Gao and J. Zhang, *Adv. Synth. Catal.*, 2009, **351**, 85; (*b*) S. Obika, H. Kono, Y. Yasui, R. Yanada and Y. Takemoto, *J. Org. Chem.*, 2007, **72**, 4462; (*c*) H. Zhou, H. Jin, S. Ye, X. He and J. Wu, *Tetrahedron Lett.*, 2009, **50**, 4616; (*d*) Q. Ding, B. Wang and J. Wu, *Tetrahedron*, 2007, **63**, 12166; (*e*) R. Yanada, S. Obika, H. Kono and Y. Takemoto, *Angew. Chem., Int. Ed.*, 2006, **45**, 3822; (*f*) N. Asao, Y. S. Salprima, T. Nogami and Y. Yamamoto, *Angew. Chem., Int. Ed.*, 2005, **44**, 5526; (*g*) Y. Ye, Q. Ding and J. Wu, *Tetrahedron*, 2008, **64**, 1378; (*h*) M. Yu, Y. Wang, C.-J. Li and X. Yao, *Tetrahedron Lett.*, 2009, **50**, 6791; (*i*) K. Gao and J. Wu, *J. Org. Chem.*, 2007, **72**, 8611.

7 A. K. Verma, R. R. Jha, R. Chaudhary, R. Tiwari, K. S. K. Reddy and A. Danodia, *J. Org. Chem.*, 2012, **77**, 8191.

8 (*a*) I. Cerňa, R. Pohl, B. Klepetárová and M. Hocek, *J. Org. Chem.*, 2010, **75**, 2302; (*b*) S. Philipp, H. Holger, J. Dominik, P. Christof, G. Anja and B. Esther, PCT Int. Appl. WO 2010086089, August 5 2010; (*c*) C. Venkatesh, G. S. M. Sundaram, H. Ila and H. Junjappa, *J. Org. Chem.*, 2006, **71**, 1280.

9 J.-R. Huang, L. Dong, B. Han, C. Peng and Y.-C. Chen, *Chem.–Eur. J.*, 2012, **18**, 8896.

10 L. W. Deady and T. Rodemann, *Aust. J. Chem.*, 2001, **54**, 529.

11 D. B. Ramachary and S. Jain, *Org. Biomol. Chem.*, 2011, **9**, 1277.

12 (*a*) R. Singh, M. K. Parai and G. Panda, *Org. Biomol. Chem.*, 2009, **7**, 1858; (*b*) R. Singh and G. Panda, *Org. Biomol. Chem.*, 2010, **8**, 1097; (*c*) R. Singh and G. Panda, *Org. Biomol. Chem.*, 2011, **9**, 4782; (*d*) K. Samanta and G. Panda, *Org. Biomol. Chem.*, 2011, **9**, 7365; (*e*) K. Samanta, N. Srivastava, S. Saha and G. Panda, *Org. Biomol. Chem.*, 2012, **10**, 1553; (*f*) A. K. Jana, S. K. Das and G. Panda, *Tetrahedron*, 2009, **68**, 10114; (*g*) S. K. Manna, M. K. Parai and G. Panda, *Tetrahedron Lett.*, 2011, **52**, 5951; (*h*) S. K. Manna and G. Panda, *RSC Adv.*, 2013, **3**, 18332.

13 (*a*) M. I. Hegab and M. M. Abdulla, *Arch. Pharm. Chem. Life Sci.*, 2006, **339**, 41; (*b*) Z. Arnold and J. Zemlicka, *Collect. Czech. Chem. Commun.*, 1959, **24**, 2385.

14 H. A. Oskooie, M. M. Heravi and K. F. Behbahani, *Molecules*, 2007, **12**, 1438.
15 T. L. Gilchrist and M. A. M. Hearly, *Tetrahedron*, 1993, **49**, 2543.
16 S. S. Moleele, J. P. Michel and C. B. De Koning, *Tetrahedron*, 2006, **62**, 2831.
17 R. Jana, I. Chatterjee, S. Samanta and J. K. Ray, *Org. Lett.*, 2008, **10**, 4795.