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Rh(III)-Catalyzed Domino [4+2] Annulation/aza-Michael Addition of N-(pivaloyloxy)benzamides with 1,5-Enynes via C-H Activation: Synthesis of Functionalised Aromathecins

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Rh(III)-Catalyzed Domino [4+2] Annulation/aza-Michael Addition of *N*-(pivaloyloxy)benzamides with 1,5-Enynes *via* C-H Activation: Synthesis of Functionalised Aromathecins

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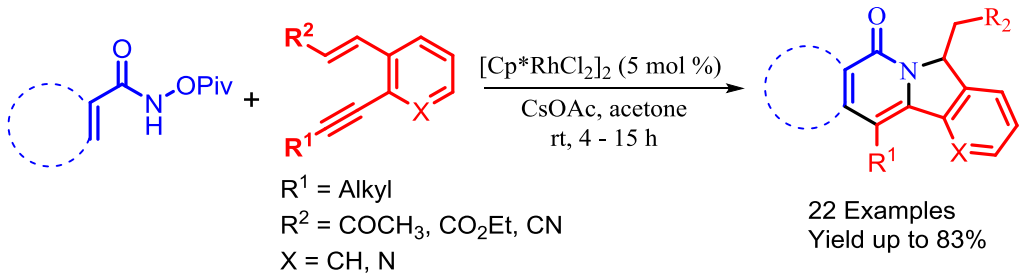


ABSTRACT: Reported herein is the Rh(III)-catalyzed cascade annulation reactions of *N*-(pivaloyloxy)benzamides with 1,5-enynes to access diversely substituted aromathecin derivatives involving C-H activation. The developed procedure offers an efficient synthetic tool for the assembly of a wide range of *N*-(pivaloyloxy)benzamides and 1,5-enynes with good atom-economy and functional group tolerance. The key reactions involved in this annulation are alkyne insertion and *aza*-Michael addition under oxidant-free mild reaction conditions.

KEYWORDS: [4+2]-Annulation, C-H activation, *N*-(pivaloyloxy)benzamide, aromathecin derivatives, 1,5-enyne, cascade annulation

INTRODUCTION

Activation of arene C-H bond *via* transition metal catalysis is considered to be a very powerful tool to form the carbon-carbon or carbon-heteroatom bonds for the synthesis of various complex molecules due to its excellent selectivity as well as atom and step economy.[1] Over the past decade, directing group (DG) assisted Rh-catalyzed C-H activation followed by the annulation with unsaturated bonds played a significant role in the synthesis of hetero and carbocycles.[2] Recently in rhodium catalysis, N-O bond containing DGs were used to make the reaction redox-neutral where the N-O bond assists for the catalyst turnover without an external oxidant and also facilitates the further cyclisation after the alkyne insertion.[3] Despite these advantages, the use of N-O bond containing DGs in tandem annulation reactions are less explored. For example, in the year 2014, Tian and Lin research group reported an interesting rhodium-catalyzed dual annulation reaction of *N*-(pivaloyloxy)benzamides with 1,6-enynes for the first time.[4] This work paved a way for the development of few other rhodium-catalysed cascade reactions.[5] These reports along with the advantage of the aforementioned directing groups inspired us to develop a rhodium-catalyzed cascade reaction for the synthesis of aromathicin derivatives from *N*-(pivaloyloxy)arylamides with 1,5-enynes.

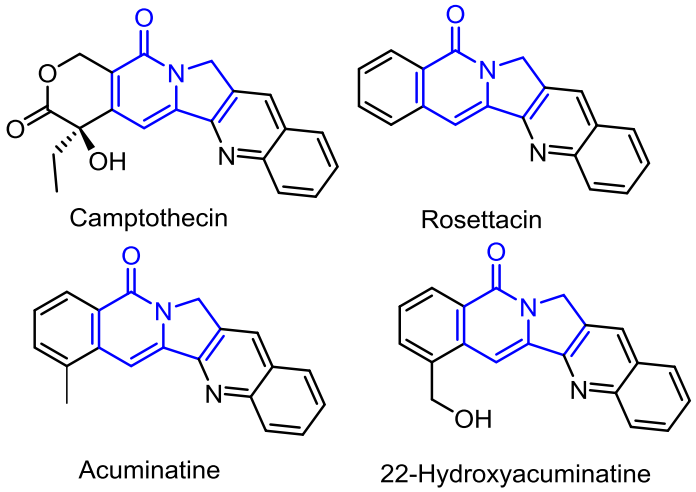
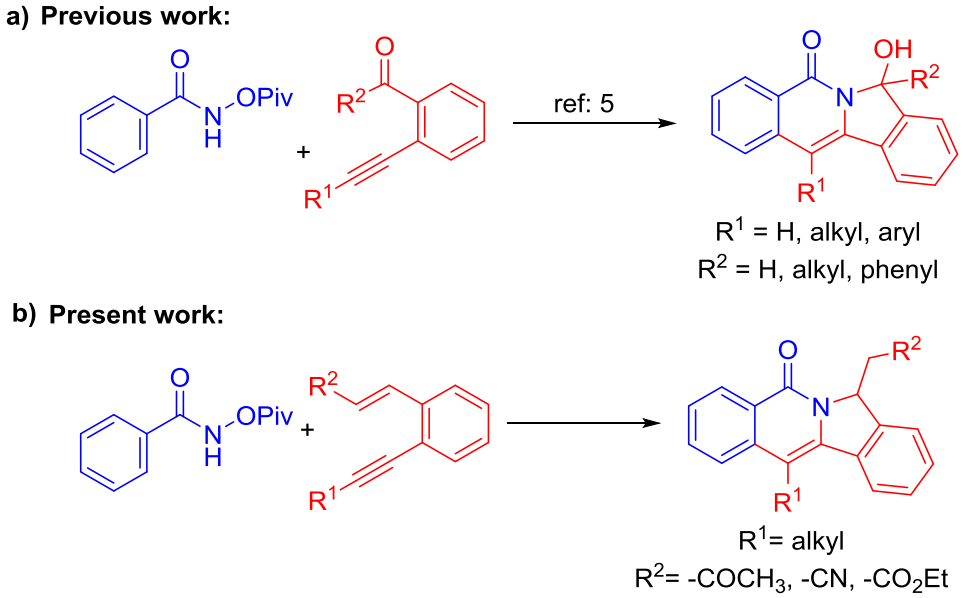


Figure 1. Representative Structures of Camptothecin and Aromathecins

Aromathecins are hybrid molecules of camptothecin (a topoisomerase inhibitor) which were designed to overcome the limitations of camptothecin derivatives such as limited solubility, dose-limiting toxicities and the *in vivo* formation of corresponding secoacid by the hydrolysis of lactone ring.[6]. The requirement of potential topoisomerase inhibitor encouraged the researchers to develop the new synthetic methods to acquire diversely functionalised aromathecins. Rosettacin, acuminatine and 22-hydroxyacuminatine are the few examples of previously synthesised aromathecins (Figure-1).[7] Recently, we have developed a facile method for the synthesis of aromathecins through rhodium-catalysed cascade reaction of *N*-(pivaloyloxy)benzamides with 2-alkynyl aldehydes, wherein the 1,2-addition of the amide N-H to the aldehyde group facilitated the second cyclisation to generate the hydroxyl functionality on the formed five membered ring (**Scheme 1a**).[5a] During the same time, Erik and co-workers reported the similar results wherein the chemoselectivity of the reaction was also studied with sterically hindered diaryl-substituted alkynes (**Scheme 1a**).[5b] These results combined with our interest on enyne-assisted annulations[8] encouraged us to explore the 1,4-addition of the amide

Scheme 1. Rh (III)-Catalyzed Cascade Reactions



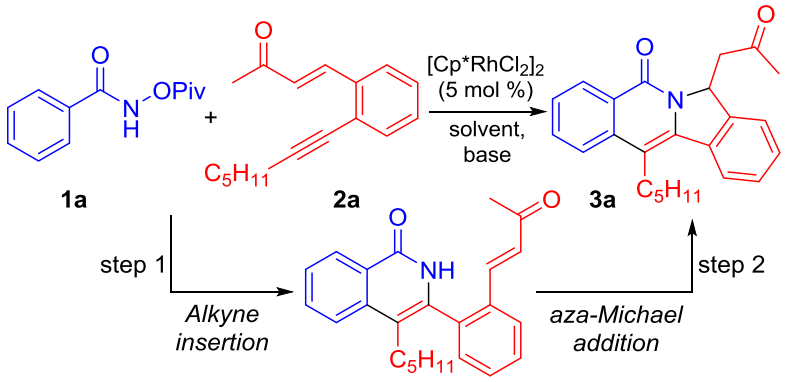
N-H bond to the activated olefins (aza-Michael addition) in rhodium(III)-catalyzed cascade reaction of *N*-(pivaloyloxy)benzamides with 2-alkynyl benzylidenes to yield the functionalized aromathecins.

RESULTS AND DISCUSSION

To implement our assumption, *N*-(pivaloyloxy)benzamide **1a** and (*E*)-4-(2-(hept-1-yn-1-yl)phenyl)but-3-en-2-one (**2a)** were taken as the starting materials for the rhodium-catalyzed cascade annulation reactions. Initially, the reaction was performed between 0.3 mmol of **1a** and 0.2 mmol of **2a** in the presence of 5 mol % of rhodium catalyst and 200 mol % of CsOAc in 2 mL of acetone at room temperature for 12 h, after completion of the reaction (monitored by the TLC) the desired product **3a** was isolated in 80% yield (Table 1 entries 1). Among the other solvents used such as *tert*-butanol, methanol, acetonitrile and dimethylformamide, no solvent was found to be the better than that of acetone for this reaction (Table 1 entries 2-5). Next, the effect of the base on the yield of the product **3a** was studied, by replacing CsOAc with NaOAc, KOAc, Cs_2CO_3, K_2CO_3 and Na_2CO_3 (Table 1 entries 6-10). From this study, it is understood that

the base CsOAc gave the maximum yield of the product **3a** (Table 1, entry 1) in the present rhodium-catalysed cascade reaction.

Table 1. Optimization of Reaction Conditions for the Synthesis of **3a**[a]

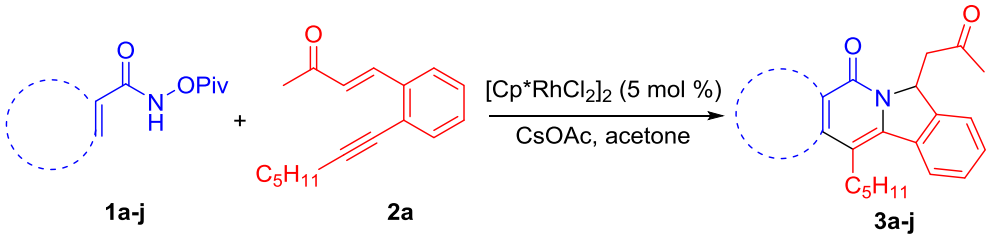


entry	solvent	base	yield of **3a** (%)
1	**Acetone**	**CsOAc**	**80**
2	*tert*-Butanol	CsOAc	52
3	MeOH	CsOAc	48
4	CH_3CN	CsOAc	75
5	DMF	CsOAc	5
6	Acetone	NaOAc	22
7	Acetone	KOAc	53
8	Acetone	Cs_2CO_3	51
9	Acetone	K_2CO_3	18
10	Acetone	Na_2CO_3	44

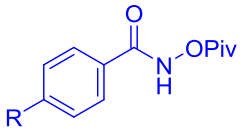
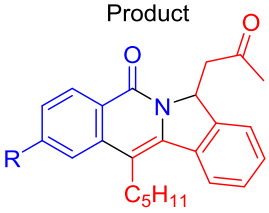
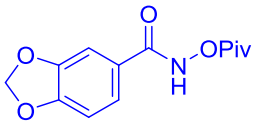
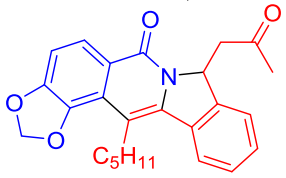
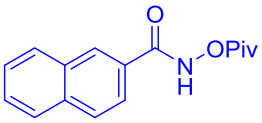
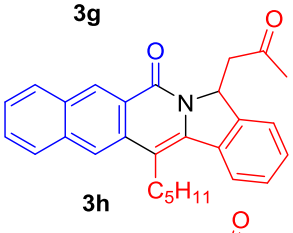
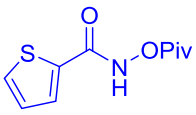
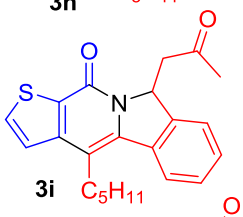
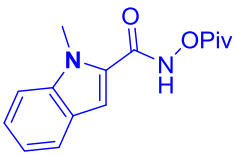
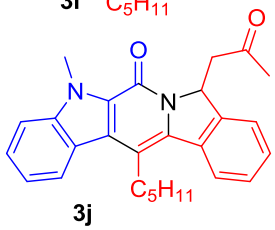
[a] Reaction conditions; all the reactions were performed using 0.3 mmol of **1a** with 0.2 mmol of **2a** in 2 mL of solvent, 5 mol % $[Cp^*RhCl_2]_2$ catalyst and 200 mol % of base in a round bottom flask at room temperature.

With the optimised conditions, the substrate scope of the reaction has been studied to validate the generality of the present reaction. Initially, the annulations of different electronically substituted benzamides **1** with **2a** were examined (Table 2)**.** Irrespective of the nature of the substituent (withdrawing or donating group) present on the aromatic ring of *N*-(pivaloyloxy)benzamide**,** the reaction proceeded efficiently to offer the good yield of the products (**3b**-**3j**). Benzamides with electron-withdrawing groups Br, Cl and NO_2 on phenyl ring (**1b**, **1c** and **1d**) were well reacted

Table 2. Reaction of **2a** with Various *N*-(Pivaloyloxy)benzamides[a]



1a-j **2a** **3a-j**

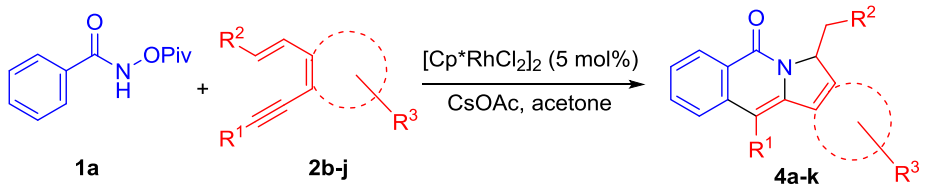
Entry	N-(Pivaloyloxy)amide	time (h)	Product	yield (%)
1[b]		12		80 (76)[b]
	R = H, **1a**		R = H, **3a**	
2	R = Br, **1b**	12	R = Br, **3b**	76
3	R = Cl, **1c**	12	R = Cl, **3c**	72
4	R = NO_2, **1d**	14	R = NO_2, **3d**	75
5	R = Me, **1e**	12	R = Me, **3e**	72
6	R = OMe, **1f**	15	R = OMe, **3f**	68
7	 **1g**	15	 **3g**	73
8	 **1h**	13	 **3h**	70
9	 **1i**	15	 **3i**	69
10	 **1j**	14	 **3j**	74

[a]*Reaction conditions:* All the reactions were performed using 0.3 mmol of **1**, 0.2 mmol of **2**, 5 mol % [Cp*RhCl$_2$]$_2$ catalyst, 200 mol % of CsOAc and 2 mL of acetone in a round bottom flask at room temperature under N_2 atmosphere. [b]Reaction was performed using 6.2 mmols of **1a,** 4.16 mmol of 2**a,** 0.2 mmols of catalyst and 8.32 mmols of base in 25 mL acetone for 24 h and **3a** was isolated.

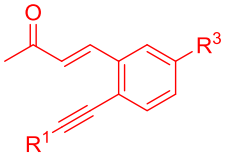
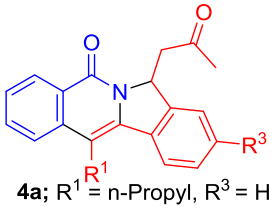
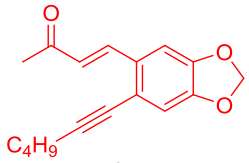
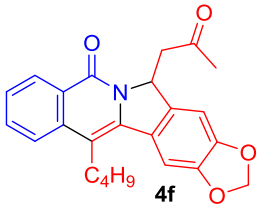
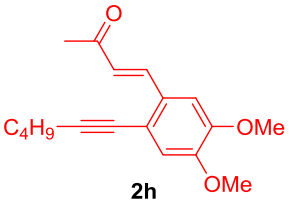
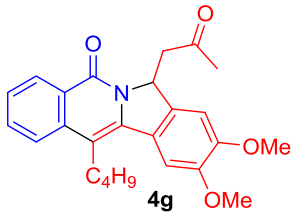
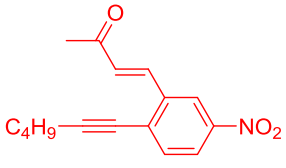
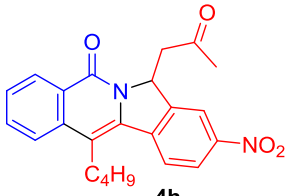
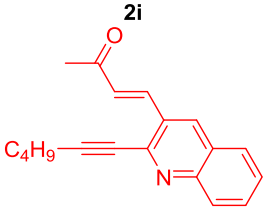
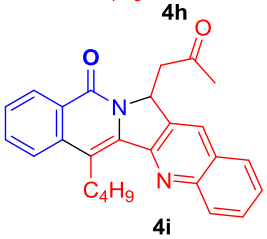
with **2a** to provide the corresponding annulated products **3b, 3c** and **3d** in good yield (entries 2 to 4, Table 2). Substrates containing donating groups –Me, -OMe and methlenedioxy (**1e**, **1f** and **1g)** also participated in the rhodium-catalyzed cascade reaction with **2a** to afford the products **3e**, **3f** and **3g** in 72, 68 and 73% yields, respectively (entries 5 to 7, Table 2). Notably, *N*-(pivaloyloxy)-2-naphthamide (**1h**), heterocyclic amides such as *N*-(pivaloyloxy)thiophene-2-carboxamide (**1i**) and 1-methyl-*N*-(pivaloyloxy)-1*H*-indole-2-carboxamide (**1j**) were all capable of proceeding to the cyclised products **3h**, **3i** and **3j** in 70, 69 and 74% of the yield (entries 8 to 10, Table 2). The efficiency of this rhodium-catalyzed domino [4+2] annulation/aza-Michael addition was further demonstrated by doing a gram-scale reaction of **1a** with **2a** and the required annulated product **3a** was afforded in 76% of the yield.

Subsequently, the feasibility of the various 1,5-enynes (**2)** was tested for the rhodium-catalysed annulation reaction (**Table 3**). Substrates with alkyl groups such as *n*-propyl (**2b**), *n*-butyl (**2c**), cyclohexyl (**2d**) and -CH_2OH (**2e**) tethered to alkyne were found to be suitable in the cascade reactions with **1a** under the present reaction conditions to deliver the corresponding products **4a**, **4b**, **4c** and **4d** in good to excellent yield (entries 1 to 4, Table 3). 1,5-enynes with donating groups on aromatic ring underwent the reaction smoothly and delivered the products **4e**, **4f** and **4g** in 82, 83 and 76% yields, respectively (entries 5 to 7, Table 3). Nitro derivative, (*E*)-4-(2-(hept-1-yn-1-yl)-5-nitrophenyl)but-3-en-2-one (**2i**), was compatible with the reaction conditions and affording the required product **4h** in 82% yield (entry 8, Table 3). Gratifyingly, the reaction of **1a** with heteroaryl-1,5-enyne, (*E*)-4-(2-(hept-1-yn-1-yl)quinolin-3-yl)but-3-en-2-one (**2j**) led to the formation of Rosettacin analogue **4i** in 76% yield (entry 9, Table 3).

Table 3. Reaction of **1a** with Various 1, 5-Enynes[a]



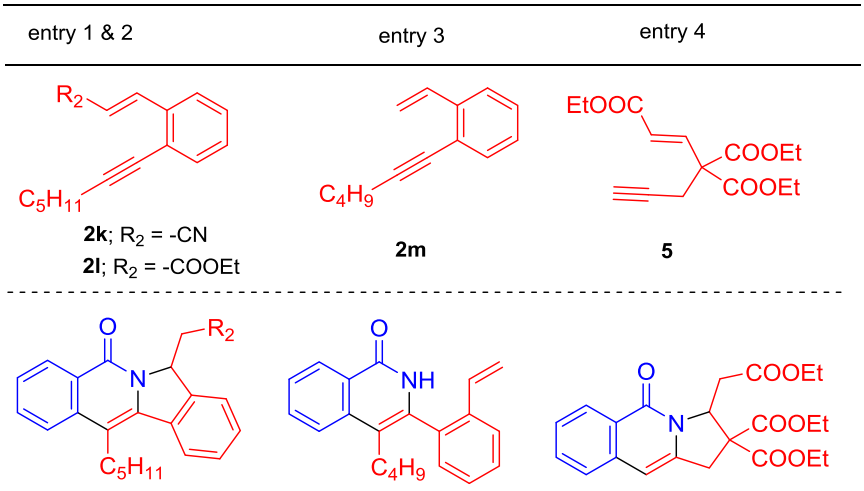
1a **2b-j** **4a-k**

entry	1,5-enyne (**2**)	time (h)	product	yield (%)
1	 **2b;** R^1 = n-Propyl, R^3 = H	12	 **4a;** R^1 = n-Propyl, R^3 = H	79
2	R^1 = n-butyl, **2c**	12	**4b;** R^1 = n-butyl, R^3 = H	81
3	R^1 = Cyclohexyl, **2d**	12	**4c;** R^1 = Cyclohexyl,R^3 = H	78
4	R^1 = -CH_2OH, **2e**	14	**4d:** R^1 = -CH_2OH, R^3 = H	75
5	R^1 = n-butyl, R^3 = -OMe, **2f**	12	**4e:** R^1 = n-butyl, R^3 = -OMe	82
6	 **2g**	12	 **4f**	83
7	 **2h**	12	 **4g**	76
8	 **2i**	14	 **4h**	82
9	 **2j**	15	 **4i**	76

[a]*Reaction conditions:* All the reactions were performed using 0.3 mmol of **1**, 0.2 mmol of **2**, 5 mol % $[Cp^*RhCl_2]_2$ catalyst, 200 mol % of CsOAc and 2 mL of acetone in a round bottom flask at room temperature under N_2 atmosphere.

Further, the effect of diverse functional groups in 1,5-enynes were evaluated in the present annulation reaction with **1a** (Table 4). To our delight, the anticipated transformation was well ensued with 1,5-enynes containing cyano (**2k)** and ester (**2l**) groups on olefin, affording the desired products **4j** and **4k** in 68% and 62% yield, respectively (Table 4, entry 1 and 2). However, the reaction of terminal olefin substrate, 1-(hex-1-yn-1-yl)-2-vinylbenzene (**2m**), failed to give the desired product via the *aza*-Michael addition of N-H to the terminal olefin was not observed under these reaction conditions, instead it gave the mono-annulated product **6** in 54% yield (Table 4, entry 3). It is noteworthy to mention that the reaction between malonate-bridged 1,5-enyne, triethyl (*E*)-hex-1-en-5-yne-1,3,3-tricarboxylate (**5**), and **1a** is successfully delivered the product **7** in 31% yield.

Table 4. Reaction of **1a** with 1,5-Enynes Having Various Functional Groups[a]



[a]*Reaction conditions:* 0.3 mmol of **1a,** 0.2 mmol of 1,5- enyne, 5 mol % $[Cp^*RhCl_2]_2$ catalyst, 200 mol % of CsOAc and 2 mL of acetone in a round bottom flask at room temperature under N_2 atmosphere.

On the basis of the present experimental results and previous reports,[5] a plausible mechanism was proposed (Figure.2). Initially, the activated Rh(III)-catalyst **I** forms a five membered

rhodocycle **II** with **1a** *via* C-H activation. Addition of alkyne **2a** to the rhodocycle **II** leads to the intermediate **IV** through C-C bond formation. Next, the C-N bond formation involving reductive

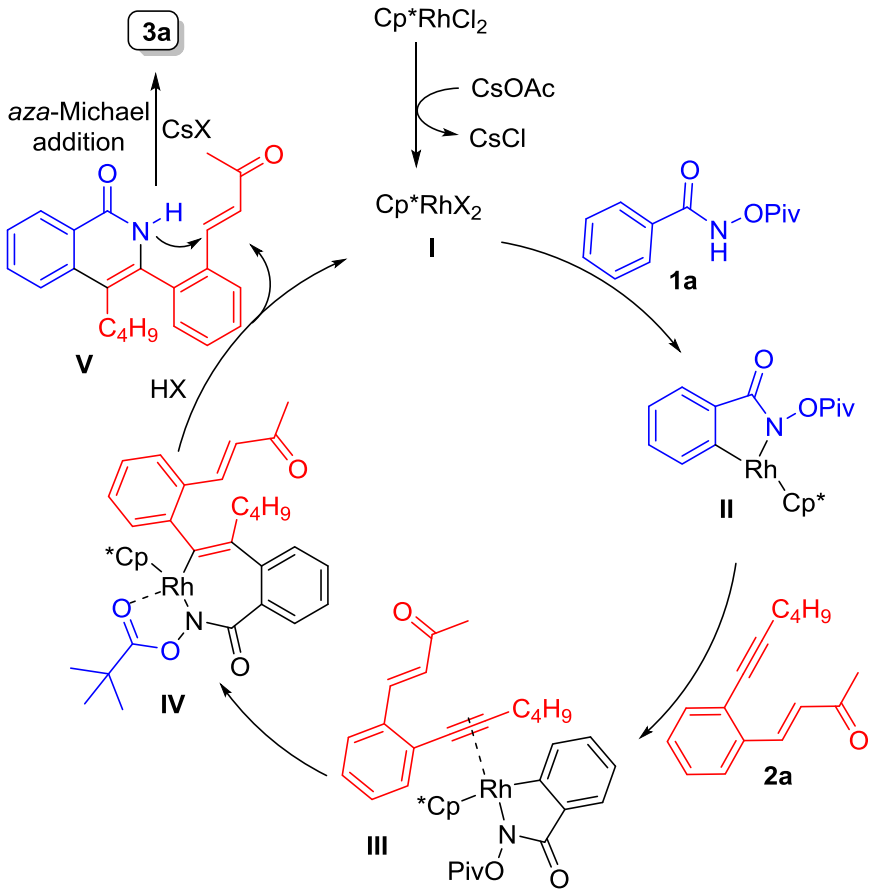


Figure 2: Possible Reaction Mechanism

elimination and oxidative addition of N-O bond followed by the protonation generates the isoquinolinone **V**. In the presence of base, intramolecular conjugate 1,4-addition of N-H to the double bond of **V** produces the product **3a**.

CONCLUSION

In conclusion, a domino [4+2] annulation/aza-Michael addition of *N*-(pivaloyloxy)benzamides with 1,5-enynes catalyzed by Rh(III)-complex was developed. This efficient method provides an easy access to distinctly substituted aromathecins in good to excellent yields from readily

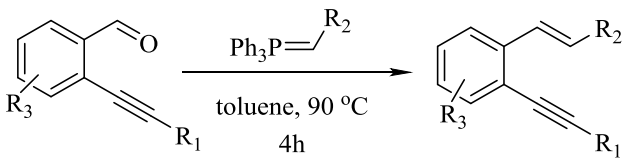
accessible starting materials. Oxidant-free mild reaction conditions and broad substrate scope with good functional group tolerance makes the present method valuable.

EXPERIMENTAL SECTION

General Methods: All the reactions were performed in oven-dried glass apparatus, the air and moisture sensitive reactions were carried out under inert atmosphere (nitrogen) using freshly distilled anhydrous solvents. Commercially available reagents were used as such without any further purification. All reactions were monitored by thin-layer chromatography carried out on silica plates using UV-light and anisaldehyde for visualization. Column chromatography was performed on silica gel (100-200 mesh) using hexanes and ethyl acetate as eluent. ^{1}H NMR was recorded in $CDCl_3$ on 500 MHz, 400 MHz and 300 MHz instruments, ^{13}C NMR was recorded on 125 MHz, 100 MHz and 75 MHz, using TMS as an internal standard. Chemical shifts are given in ppm and *J* values are given in Hz (hertz). δ 7.26 and δ 77 are the residual peaks of $CDCl_3$ in ^{1}H NMR and ^{13}C NMR respectively. FTIR spectra were recorded on Alpha (Bruker) infrared Spectrophotometer. High resolution mass spectra (HRMS) [ESI+] were obtain using either a TOF or a double focusing spectrometer.

N-(pivaloyloxy)arylamides (**1a-1j)**,[9] 2-alkynyl arylaldehydes[10] and *2*- alkynyl enynones (**2b**, **2c** and **2m**)[11] were prepared using the literature procedures, NMR data of all these compounds was compared with the corresponding reported data.

General procedure for the Synthesis of *2- a*lkynyl enynones (2):



A solution of the aldehyde (1 equiv.) and (acetylmethylene)triphenylphosphorane (1.2 equiv.) in toluene (0.5 M) was stirred at 90 °C for 4 h. After completion of the reaction (confirmed by the TLC), the reaction mixture was allowed to attain room temperature and concentrated under reduced pressure. The obtained crude product was purified by column chromatography over silica gel using hexane/$EtOA_C$ as an eluent.

***(E)-4-(2-(hept-1-yn-1-yl)phenyl)but-3-en-2-one (2a)*:** Following the general procedure, 2-(hept-1-yn-1-yl)benzaldehyde[10d] (0.5g, 2.5 mmol) in toluene was allowed to react with (acetylmethy lene)triphenylphosphorane (0.95 g, 3.0 mmol) at 90 ^oC for 4 h. After that the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (3% EtOAc in petroleum ether) and got the compound **2a** (0.42 g, 70% yield) as a yellow liquid ; R_f = 0.4 (hexanes: EtOAc = 19: 1); ^1H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, J = 16.5 Hz, 1H), 7.64 – 7.60 (m, 1H), 7.49 – 7.43 (m, 1H), 7.32 – 7.28 (m, 2H), 6.72 (d, J = 16.5 Hz, 1H), 2.50 (t, J = 7.1 Hz, 2H), 2.41 (s, 3H), 1.58 –1.72 (m, 2H), 1.34 – 1.51 (m, 4H), 0.95 (t, J = 7.0 Hz, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ 198.9, 142.1, 135.6, 132.9, 130.0, 128.4, 127.9, 125.9, 125.3, 97.3, 78.9, 31.2, 28.5, 26.9, 22.3, 19.7, 14.0; IR(Neat): 3011, 2937, 1660, 1605, 1482, 1259, 1035, 758 cm^{-1}; HRMS (ESI) m/z: $(M + H)^+$ Calcd for $C_{17}H_{21}O$ 241.1592; Found 241.1577.

(E)-4-(2-(cyclohexylethynyl)phenyl)but-3-en-2-one (2d): Following the general procedure, 2-(cyclohexylethynyl)benzaldehyde[10e] (0.5 g, 2.35 mmol) in toluene was allowed to react with (acetylmethylene)triphenylphosphorane (0.89 g, 2.82 mmol) at 90 ^oC for 4 h. After that the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (4% EtOAc in petroleum ether) and got the compound **2d** (0.38 g, 64% yield) as a white solid; R_f = 0.4 (Hexanes: EtOAc

= 19: 1); mp: 52-54 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, J = 16.5 Hz, 1H), 7.65 – 7.58 (m, 1H), 7.49 – 7.43 (m, 1H), 7.33 – 7.28 (m, 2H), 6.72 (d, J = 16.5 Hz, 1H), 2.78 – 2.65 (m, 1H), 2.41 (s, 3H), 1.87 – 1.96 (m, 2H), 1.83 – 1.75 (m, 2H), 1.64 – 1.53 (m, 3H), 1.46 – 1.36 (m, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ 198.8, 142.1, 135.6, 132.8, 129.9, 128.4, 127.9, 125.9, 125.3, 101.2, 78.3, 32.7, 29.9, 26.8, 25.9, 24.8; IR(KBr): 3366, 2959, 1607, 1481, 1220, 1604, 769 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{21}O$ 253.1592; Found 253.1576.

(E)-4-(2-(3-hydroxyprop-1-yn-1-yl)phenyl)but-3-en-2-one(2e): Following the general procedure, 2-(3-hydroxyprop-1-yn-1-yl) benzaldehyde[10e] (0.5 g, 3.12 mmol) in toluene was allowed to react with (acetylmethylene)triphenylphosphorane (1.19 g, 3.74 mmol) at 90 ^{o}C for 4 h. After that the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (15 % EtOAc in petroleum ether) and got the compound **2e** (0.45 g, 72% yield) as a liquid; R_f = 0.4 (Hexanes: EtOAc = 3: 2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 16.4 Hz, 1H), 7.65 – 7.58 (m, 1H), 7.49 – 7.44 (m, 1H), 7.35 – 7.28 (m, 2H), 6.75 (d, J = 16.4 Hz, 1H), 4.57 (s, 2H), 2.40 (s, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ 199.1, 141.4, 135.7, 133.1, 130.0, 128.8, 128.3, 126.1, 123.9, 94.0, 82.9, 51.5, 27.7; IR (KBr): 3015, 2958, 2865, 2228, 1672, 1220, 744 cm^{-1}; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{12}NaO_2$ 223.0735; Found 223.0721.

(E)-4-(2-(hex-1-yn-1-yl)-5-methoxyphenyl)but-3-en-2-one (2f): Following the general procedure, 2-(hex-1-yn-1-yl)-5-methoxybenzaldehyde[10c] (0.5 g, 2.31 mmol) in toluene was allowed to react with (acetylmethylene)triphenylphosphorane (0.88 g, 2.77 mmol) at 90 ^{o}C for 4 h. After that the reaction the mixture was cooled to room temperature and concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (5% EtOAc in petroleum ether) and got the compound **2f** (0.415 g, 70% yield) as a liquid; R_f =

0.4 (Hexanes: EtOAc = 4: 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 16.4 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.10 (d, J = 2.5 Hz, 1H), 6.88 (dd, J = 8.4, 2.6 Hz, 1H), 6.68 (d, J = 16.5 Hz, 1H), 3.83 (s, 3H), 2.51 (t, J = 6.9 Hz, 2H), 2.41 (s, 3H), 1.58 – 1.67 (m, 2H), 1.47 – 1.57 (m, 2H), 0.98 (t, J = 7.2, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ 198.7, 159.0, 142.0, 136.8, 134.0, 133.9, 128.5, 117.8, 116.7, 110.1, 95.3, 55.3, 30.8, 26.7, 22.0, 19.3, 13.6; IR(KBr): 3222. 2936, 2437, 1766, 1718, 1644, 1367, 768 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{21}O_2$ 257.1542; Found 257.1542.

***(E)-4-(6-(hex-1-yn-1-yl)benzo[d][1,3]dioxol-5-yl)but-3-en-2-one (2g)*:** Following the general procedure, 6-(hex-1-yn-1-yl)benzo[d][1,3]dioxole-5-carbaldehyde[10a] (0.5 g, 2.17 mmol) in toluene was allowed to react with (acetylmethylene)triphenylphosphorane (0.82 g, 2.60 mmol) at 90 ^{o}C for 4 h. After that the reaction mixture was cooled to room temperature, and concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (5% EtOAc in petroleum ether) and got the compound **2g** (0.45 g, 76 % yield) as a white solid; R_f = 0.4 (hexanes: EtOAc = 9: 1); mp: 61-63 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, J = 16.4 Hz, 1H), 7.05 (s, 1H), 6.87 (s, 1H), 6.53 (d, J = 16.4 Hz, 1H), 6.00 (s, 2H), 2.48 (t, 2H), 2.38 (s, 3H), 1.66 – 1.60 (m, 2H), 1.56 – 1.49 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 198.7, 149.4, 148.0, 141.9, 130.6, 126.6, 120.5, 112.0, 104.9, 101.9, 96.0, 78.1, 30.8, 26.8, 22.1, 19.3, 13.7; IR(KBr): 2950, 2873, 1728, 1515, 1255, 1093 763 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{19}O_3$ 271.1334; Found 271.1336.

***(E)-4-(2-(hex-1-yn-1-yl)-4,5-dimethoxyphenyl)but-3-en-2-one (2h)*:** Following the general procedure, 2-(hex-1-yn-1-yl)-4,5-dimethoxybenzaldehyde[10g] (0.5 g, 2.03 mmol) in toluene was allowed to react with (acetylmethylene)triphenylphosphorane (0.77 g, 2.43 mmol) at 90 ^{o}C for 4

h. After that the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (4% EtOAc in petroleum ether) and got the compound **2h** (0.45 g, 77% yield) as a white solid; R_f = 0.4 (Hexanes: EtOAc = 4: 1); mp: 57-59 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (d, J = 16.4 Hz, 1H), 7.06 (s, 1H), 6.90 (s, 1H), 8.60 (d, J = 16.4 Hz, 1H) 3.91 (s, 2H), 3.90 (s, 3H), 2.51 (t, J = 7.0 Hz, 2H), 2.40 (s, 3H) 1.62 – 1.68 (m, 2H), 1.48 – 1.57 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ 198.7, 150.7, 149.0, 142.0, 128.7, 126.4, 118.9, 114.4, 107.5, 95.3, 78.0, 55.95, 55.86, 30.8, 26.5, 22.05, 19.25, 13.6; IR(KBr): 3366, 2959, 1607, 1481, 1220, 1604, 769 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{23}O_3$ 287.1647; Found: 287.1636.

***(E)-4-(2-(hex-1-yn-1-yl)-5-nitrophenyl)but-3-en-2-one (2i)*:** Following the general procedure, 2-(hex-1-yn-1-yl)-5-nitrobenzaldehyde[10b] (0.5 g, 2.16 mmol) in toluene was allowed to react with (acetylmethylene)triphenylphosphorane (0.82 g, 2.59 mmol) at 90 ^{o}C for 4 h. After that the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (4% EtOAc in petroleum ether) and got the compound **2i** (0.39 g, 66% yield) as a yellow liquid; R_f = 0.5 (Hexanes: EtOAc = 19: 1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.47 (d, J = 2.3 Hz, 1H), 8.14 (dd, J = 8.6, 2.3 Hz, 1H), 7.99 (d, J = 16.4 Hz, 1H), 7.59 (d, J = 8.6 Hz, 1H), 6.86 (d, J = 16.4 Hz, 1H), 2.56 (t, J = 7.0 Hz, 2H), 2.43 (s, 3H), 1.71 – 1.65 (m, 2H), 1.57 – 1.51 (m, 2H), 0.99 (t, J = 7.3 Hz, 3H); ^{13}C{1H} NMR (125 MHz, $CDCl_3$): δ 197.6, 146.8, 139.0, 137.0, 133.8, 131.3, 130.1, 123.9, 120.9, 103.1, 77.4, 30.4, 27.8, 22.1, 19.5, 13.5; IR(KBr): 3366, 2959, 1607, 1481, 1220, 1604, 769 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{18}NO_3$ 272.1287; Found 272.1275.

***(E)-4-(2-(hex-1-yn-1-yl)quinolin-3-yl)but-3-en-2-one (2j)*:** Following the general procedure, 2-(hex-1-yn-1-yl)quinoline-3-carbaldehyde[10f] (0.5 g, 2.10 mmol) in toluene was allowed to react with (acetylmethylene)triphenylphosphorane (0.8 g, 2.52 mmol) at 90 ^{o}C for 4 h. After that the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (5% EtOAc in petroleum ether) and got the compound **2j** (0.43 g, 74% yield) as a pale yellow solid; R_f = 0.4 (hexanes: EtOAc = 4: 1); mp: 142-144 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.36 (s, 1H), 8.13 (d, J = 16.4 Hz, 1H), 8.06 (d, J = 8.5 Hz, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.71 – 7.75 (m, 1H), 7.53 – 7.56 (m, 1H), 6.87 (d, J = 16.4 Hz, 1H), 2.65 – 2.56 (t, 2H), 2.46 (s, 3H), 1.77 – 1.68 (m, 2H), 1.62 – 1.52 (m, 2H), 0.99 (t, J = 7.3 Hz, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ 198.0, 148.4, 143.9, 139.8, 133.3, 131.1, 129.9, 129.0, 128.9, 128.0, 127.5, 126.7, 97.1, 78.9, 30.3, 27.1, 22.2, 19.3, 13.6; IR(KBr): 3366, 2959, 1607, 1481, 1220, 1604, 769 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{20}NO$ 278.1545; Found: 278.1545.

***(E)-3-(2-(hept-1-yn-1-yl)phenyl)acrylonitrile (2k)*:** Following the general procedure, 2-(hept-1-yn-1-yl)benzaldehyde[10d] (0.5 g, 2.5 mmol) in toluene was allowed to react with (triphenylphosphoranylidene)acetonitrile (0.9 g, 3.0 mmol) at 90 ^{o}C for 4 h. After that the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (5% EtOAc in petroleum ether) and got the compound **2k** (0.38 g, 68% yield) as a colorless liquid; R_f = 0.4 (Hexanes: EtOAc = 9: 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (d, J = 16.8 Hz, 1H), 7.55 – 7.41 (m, 2H), 7.39 – 7.24 (m, 2H), 5.99 (d, J = 16.8 Hz, 1H), 2.48 (t, J = 7.1 Hz, 2H), 1.73 – 1.60 (m, 2H), 1.52 – 1.35 (m, 4H), 0.95 (t, J = 7.0 Hz, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ 149.1, 134.5, 133.2, 130.6, 127.9, 125.4, 124.7, 118.4, 97.9, 97.3, 77.8, 31.2, 28.3, 22.2, 19.6, 14.0; IR(KBr):

3092, 2946, 2869, 2225, 1678, 1519, 1344, 1258, 750cm^{-1}; HRMS (ESI) m/z: $(M + H)^+$ Calcd for $C_{16}H_{18}N$ 224.1439; Found: 224.1445.

***Ethyl (E)-3-(2-(hept-1-yn-1-yl)phenyl)acrylate (2l)*:** Following the general procedure, 2-(hept-1-yn-1-yl)benzaldehyde[10d] (0.5 g, 2.5 mmol) in toluene was allowed to react with ethyl (triphenylphosphoranylidene)acetate (1.04 g, 3.0 mmol) at 90 ^oC for 4 h. After that the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (5% EtOAc in petroleum ether) and got the compound **2l** (0.45 g, 66% yield) as a colorless liquid; R_f = 0.4 (Hexanes : EtOAc = 4: 1); ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, J = 16.1 Hz, 1H), 7.57 – 7.61 (m, 1H), 7.42 – 7.46 (m, 1H), 7.25 – 7.30 (m, 2H), 6.50 (d, J = 16.1 Hz, 1H)), 4.32 – 4.20 (q, J = 7.1 Hz 2H), 2.49 (t, J = 7.1 Hz, 2H), 1.61 – 1.71 (m, 2H), 1.41 – 1.51 (m, 2H), 1.37 – 1.41 (m, 2H), 1.36 – 1.32 (t, J = 7.1 Hz, 3H), 0.93 (t, J = 7.1 Hz, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.0, 142.9, 135.7, 132.9, 129.6, 127.8, 126.1, 125.0, 119.4, 97.1, 78.3, 60.5, 31.2, 28.4, 22.3, 19.7, 14.4, 14.0; IR(KBr): 3366, 2959, 1607, 1481, 1220, 1604, 769 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{23}O_2$ 271.1698; Found: 271.1685.

triethyl (E)-hex-1-en-5-yne-1,3,3-tricarboxylate (5): To a stirred solution of diethyl 2-(prop-2-yn-1-yl)malonate (990 mg, 5 mmol) in 10 mL of acetonitrile at room temperature, 10 mol % of triphenyl phosphine was added, after stirring for few minutes ethyl propiolate (5 mmol) was added drop wise to the reaction mixture and continued the stirring for 30 min at same temperature. After that the reaction mixture was concentrated under reduced pressure without doing any work up and the obtained crude product was purified by column chromatography on silica gel (10 % EtOAc in petroleum ether) and obtained the compound triethyl-hex-1-en-5-yne-1,3,3-tricarboxylate **2n** (1.2 g, 81 % yield, E/Z 9:1) as a colorless liquid; R_f = 0.5 (Hexanes :

EtOAc = 8:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 16.3 Hz, 1H), 6.01 (d, J = 16.3 Hz, 1H), 4.34 – 4.18 (m, 6H), 2.98 (d, J = 2.6 Hz, 2H), 2.04 (t, J = 2.6 Hz, 1H), 1.33 – 1.22 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9(2C), 165.6, 141.9, 123.8, 78.0, 72.0, 62.5(2C), 60.8, 59.0, 24.7, 14.2, 13.9(2C); IR(neat): 3297, 2984, 1728, 1653, 1190, 1034, 747 cm^{-1} HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{21}O_6$ 297.1338; Found: 297.1345.

General procedure for the Rh(III)-catalyzed annulation:

To a solution of *N*-(pivaloyloxy) arylamide **1** (1.5 equiv) and 2-alkynyl enone **2** (1 equiv) in dry acetone (2.0 mL), $[RhCp^*Cl_2]_2$ (0.05 equiv.) and CsOAc (2 equiv.) were added under nitrogen atmosphere at room temperature. The reaction mixture was stirred vigorously at room temperature till the completion of the reaction (monitored by TLC), the reaction mixture was filtered through celite pad and washed with CH_2Cl_2 (10 mL × 3).The filtrate was concentrated under reduced pressure and the obtained crude mixture was purified by column chromatography.

Gram scale reaction procedure for compound

7-(2-Oxopropyl)-12-pentylisoindolo[2,1-b]isoquinolin-5(7H)-one(3a): Following the general procedure, *N*-(Pivaloyloxy)benzamide[9c] **1a** (66 mg, 0.30 mmol) was allowed to react with (*E*)-4-(2-(hept-1-yn-1-yl)phenyl)but-3-en-2-one **2a** (50 mg, 0.20 mmol) in the presence of $[RhCp^*Cl_2]_2$ (6.2 mg 0.01 mmol) and CsOAc (76.4 mg, 0.4 mmol) for 12 h. After filtration the filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (14 % EtOAc in petroleum ether) and got the compound **3a** (57.4 mg, 80% yield) as a white solid; R_f = 0.4 (hexanes: EtOAc = 7:3); mp: 126 -128 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.51 (dd, J = 8.0, 1.0 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.85 (d, J = 8.2 Hz, 1H), 7.77 – 7.71 (m, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.40-7.46 (m, J = 7.2 Hz, 1H), 6.03 (dd, J = 8.1, 3.0 Hz, 1H), 3.94 (dd, J = 17.6, 3.1 Hz, 1H), 3.22 – 3.08 (m,

2H), 2.83 (dd, *J* = 17.6, 8.2 Hz, 1H), 2.19 (s, 3H), 1.80 – 1.68 (m, 2H), 1.53-1.63 (m, 2H), 1.47 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H); $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$): δ 205.8, 160.4, 142.7, 137.9, 137.4, 133.5, 132.2, 129.2, 128.7, 127.6, 126.2, 125.1, 123.8, 123.6, 122.9, 113.7, 59.1, 45.9, 32.1, 30.4, 28.9, 26.1, 22.6, 14.1; IR (KBr): 3210, 2958, 1718, 1650, 1608, 1479, 1365, 768, cm^1; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{24}H_{26}NO_2$ 360.1964; Found: 360.1974.

Gram scale reaction procedure for compound 3a:

To a solution of *N*-(Pivaloyloxy)benzamide[9c] **1a** (1.5 equiv) and (*E*)-4-(2-(hept-1-yn-1-yl)phenyl) but-3-en-2-one **2a** (1g, 4.16 mmol, 1equiv) in dry acetone (25 mL), $[RhCp^*Cl_2]_2$ (0.05 equiv.) and CsOAc (2 equiv.) were added under nitrogen atmosphere at room temperature. The reaction mixture was stirred vigorously at room temperature till the completion of the reaction (24 h monitored by TLC), the reaction mixture was filtered through celite pad and washed with CH_2Cl_2 (15 mL × 3).The filtrate was concentrated under reduced pressure and the obtained crude mixture was purified by column chromatography on silica gel to obtained the compound as white solid (1.13g)76% yield.

2-Bromo-7-(2-oxopropyl)-12-pentylisoindolo[2,1-b]isoquinolin-5(7H)-one **(3b):** Following the general procedure, 4-bromo-(pivaloyloxy)benzamide[9b] **1b** (90 mg, 0.3 mmol) was allowed to react with (*E*)-4-(2-(hept-1-yn-1-yl)phenyl)but-3-en-2-one **2a** (50 mg, 0.2 mmol) in the presence of $[RhCp^*Cl_2]_2$ (6.2 mg, 0.01 mmol) and CsOAc (76.4 mg, 0.4 mmol) for 12 h. After filtration the filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (12 % EtOAc in petroleum ether) and got the compound **3b (**66.5 mg, 76% yield) as a white solid; R_f = 0.5 (Hexanes: EtOAc = 7:3); mp: 162-164 ^oC; ^1H NMR (500 MHz, $CDCl_3$): δ 8.34 (d, *J* = 8.5 Hz, 1H), 7.95 (d, *J* = 1.7 Hz, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.59 (dd, *J* = 8.5, 1.6 Hz, 2H), 7.51 (t, *J* = 7.3 Hz, 1H), 7.46 (dt, *J* = 7.4, 3.8

Hz, 1H), 5.99 (dd, *J* = 8.1, 3.0 Hz, 1H), 3.90 (dd, *J* = 17.7, 3.1 Hz, 1H), 3.14 – 3.06 (m, 2H), 2.83 (dd, *J* = 17.7, 8.2 Hz, 1H), 2.19 (s, 3H), 1.67 – 1.77 (m, 2H), 1.62 – 1.56 (m, 2H), 1.42 – 1.51 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H); $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$): δ 205.6, 160.0, 143.0, 139.6, 138.9, 133.3, 129.7, 129.5, 129.4, 128.9, 127.7, 125.7, 124.0, 123.8, 123.7, 112.6, 59.3, 45.8, 32.1, 30.4, 28.9, 26.1, 22.6, 14.1; IR (KBr): 3016, 2953, 1708, 1622, 1362, 1218, 762 cm^{-1}; HRMS (ESI) m/z: Calcd for $C_{24}H_{25}NO_2Br$ $[M + H]^+$ 438.1069; Found: 438.1073.

2-Chloro-7-(2-oxopropyl)-12-pentylisoindolo[2,1-b]isoquinolin-5(7H)-one (3c): Following the general procedure, 4-chloro-*N*-(pivaloyloxy)benzamide[9b] **1c** (77 mg, 0.3 mmol) was allowed to react with (*E*)-4-(2-(hept-1-yn-1-yl)phenyl)but-3-en-2-one **2a** (50 mg 0.2 mmol) in the presence of $[RhCp^*Cl_2]_2$ (6.2 mg, 0.01 mmol) and CsOAc (76 mg, 3.22 mmol) for 12 h. After filtration the filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (13 % EtOAc in petroleum ether) and got the compound **3c** (56.6 mg, 72% yield) as a white solid; R_f = 0.5 (Hexanes: EtOAc = 7:3); mp: 168-170 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.43 (d, *J* = 8.6 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 1.8 Hz, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.1 Hz, 1H), 7.48 – 7.42 (m, 2H), 6.00 (dd, *J* = 8.1, 3.0 Hz, 1H), 3.91 (dd, *J* = 17.6, 3.1 Hz, 1H), 3.06 – 3.14(m, 2H), 2.84 (dd, *J* = 17.6, 8.1 Hz, 1H), 1.78 – 1.67 (m, 2H), 1.62 – 1.58 (m, 2H), 1.42 – 1.51 (m, 2H), 0.98 (t, *J* = 7.2 Hz, 3H). $^{13}C\{1H\}$ NMR (100 MHz) δ 205.6, 159.9, 143.0, 139.4, 139.0, 138.9, 133.3, 129.7, 129.5, 128.9, 126.7, 124.0, 123.7, 123.5, 122.5, 112.7, 59.3, 45.8, 32.1, 30.4, 28.9, 26.2, 22.6, 14.1; IR (KBr): 3213, 2975, 1776, 1660, 1477, 1078, 699 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{24}H_{25}NO_2Cl$ 394.1574; Found: 394.1573.

2-Nitro-7-(2-oxopropyl)-12-pentylisoindolo[2,1-b]isoquinolin-5(7H)-one (3d): Following the general procedure, 4-nitro-N-(pivaloyloxy)benzamide[9c] **1d** (80 mg, 0.30 mmol) was allowed to

react with (*E*)-4-(2-(hept-1-yn-1-yl)phenyl)but-3-en-2-one **2a** (50 mg, 0.20 mmol) in presence of $[RhCp^*Cl_2]_2$ (6.2 mg, 0.01 mmol) and CsOAc (76 mg, 0.4 mmol) for 14 h. After filtration the filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (14 % EtOAc in petroleum ether) and got the compound **3d** (61 mg, 75% yield) as a yellow solid; R_f = 0.5 (Hexanes: EtOAc = 7:3); mp: 135-137 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.71 (d, *J* = 2.0 Hz, 1H), 8.65 (d, *J* = 8.8 Hz, 1H), 8.24 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 7.4 Hz, 1H), 7.57 – 7.47 (m, 2H), 6.03 (dd, *J* = 8.0, 3.0 Hz, 1H), 3.89 (dd, *J* = 17.7, 3.1 Hz, 1H), 3.17 – 3.25 (m, 2H), 2.89 (dd, *J* = 17.7, 8.0 Hz, 1H), 2.20 (s, 3H), 1.71 – 1.81 (m, 2H), 1.65 – 1.59 (m, 2H), 1.44 – 1.53 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ 205.4, 159.3, 150.4, 143.0, 140.0, 138.8, 132.9, 130.2, 129.8, 129.1, 128.5, 124.3, 123.7, 119.6, 118.8, 113.3, 59.6, 45.4, 32.0, 30.4, 29.0, 26.2, 22.5, 14.0; IR (KBr): 2950, 2734, 1710, 1649, 1603, 1469, 766 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{24}H_{25}N_2O_4$ 405.1814; Found: 405.1816.

***2-Methyl-7-(2-oxopropyl)-12-pentylisoindolo[2,1-b]isoquinolin-5(7H)-one (3e)*:** Following the general procedure, 4-methyl-N-(pivaloyloxy)benzamide[9b] **1e** (70 mg, 0.3 mmol) was allowed to react with (*E*)-4-(2-(hept-1-yn-1-yl)phenyl)but-3-en-2-one **2a** (50 mg, 0.20 mmol) in presence of $[RhCp^*Cl_2]_2$ (6.2 mg, 0.01 mmol) and CsOAc (76.4 mg, 0.4 mmol) for 12 h. After filtration the filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (12% EtOAc in petroleum ether) and got the compound **3e** (54 mg, 72% yield) as a white solid; R_f = 0.5 (Hexanes: EtOAc = 7:3); mp 145-147 ^oC; ^1H NMR (500 MHz, $CDCl_3$): δ 8.39 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.59 (d, *J* = 10.5 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 6.00 (dd, *J* = 8.1, 2.7 Hz, 1H), 3.93 (dd, *J* = 17.6, 3.1 Hz, 1H), 3.09 – 3.18 (m, 2H), 2.81 (dd, *J* = 17.6, 8.2 Hz,

1H), 2.56 (s, 3H), 2.19 (s, 3H), 1.69 – 1.78 (m, 2H), 1.53 – 1.63 (m, 2H), 1.43 – 1.51 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ 205.9, 160.5, 142.9, 142.6, 138.1, 137.6, 133.8, 129.2, 128.7, 127.9, 127.7, 123.9, 123.7, 123.1, 122.8, 113.6, 59.1, 46.1, 32.2, 30.4, 29.0, 26.2, 22.6, 22.3, 14.2; IR (KBr): 2953, 1717, 1648, 1473, 1359, 1172, 769, cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{25}H_{28}NO_2$ 374.2120; Found 374.2121.

***2-Methoxy-7-(2-oxopropyl)-12-pentylisoindolo[2,1-b]isoquinolin-5(7H)-one(3f)*:** Following the general procedure, 4-methoxy-*N*-(pivaloyloxy)benzamide[9b] **1f** (70 mg, 0.3 mmol) was allowed to react with (*E*)-4-(2-(hept-1-yn-1-yl)phenyl)but-3-en-2-one **2a** (50 mg, 0.20 mmol) in presence of $[RhCp^*Cl_2]_2$ (6.2 mg, 0.01 mmol) and CsOAc (76.4 mg, 0.4 mmol) for 15 h. After filtration the filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (12 % EtOAc in petroleum ether) and got the compound **3f** (53 mg, 68% yield) as a white solid; R_f = 0.4 (hexanes: EtOAc = 3:2); mp 127-129 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (d, J = 8.8 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.59 (d, J = 7.5 Hz, 1H), 7.49 (t, J = 7.3 Hz, 1H), 7.43 (t, J = 7.1 Hz, 1H), 7.19 (d, J = 2.3 Hz, 1H), 7.10 (dd, J = 8.9, 2.3 Hz, 1H), 5.99 (dd, J = 8.1, 3.0 Hz, 1H), 3.96 (s, 3H), 3.95 -3.90 (dd, J = 17.6, 3.1 Hz 1H), 3.19 – 3.07 (m, 2H), 2.82 (dd, J = 17.5, 8.2 Hz, 1H), 2.18 (s, 3H), 1.79 – 1.70 (m, 2H), 1.61 – 1.55 (m, 2H), 1.42 – 1.52 (m, 2H), 0.97 (t, J = 7.2 Hz, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ 206.0, 162.9, 143.1, 140.1, 138.2, 133.7, 129.8, 129.3, 128.7, 123.9, 123.7, 119.3, 114.6, 114.6, 113.3, 105.4, 59.1, 55.5, 46.2, 32.2, 30.5, 28.8, 26.3, 22.6, 14.2; IR (KBr): 3019, 2958, 1715, 1648, 1471 ,1218 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{25}H_{28}NO_3$ 390.2069; Found 390.2061.

7-(2-Oxopropyl)-12-pentyl-[1,3]dioxolo[4,5-g]isoindolo[2,1-b]isoquinolin-5(7H)-one (3g): Following the general procedure, *N*- (pivaloyloxy)benzo[d][1,3]dioxole-5-carboxamide[9a] **1g** (79 mg, 0.30 mmol) was allowed to react with (*E*)-4-(2-(hept-1-yn-1-yl)phenyl)but-3-en-2-one **2a**

(50 mg, 0.20 mmol) in presence of $[RhCp^*Cl_2]_2$ (6.4 mg, 0.01 mmol) and CsOAc (79 mg, 0.41 mmol) for 15 h. After filtration the filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (13 % EtOAc in petroleum ether) and got the compound **3g** (59 mg, 73% yield) as a white solid; R_f = 0.5 (Hexanes: EtOAc = 7:3); mp: 155-157 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, J = 8.5 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 7.4 Hz, 1H), 7.50 – 7.39 (m, 2H), 7.06 (d, J = 8.5 Hz, 1H), 6.15 (dd, J = 2.9, 1.5 Hz, 2H), 5.97 (dd, J = 8.0, 2.8 Hz, 1H), 3.87 (dd, J = 17.5, 2.8 Hz, 1H), 2.97 – 3.54 (m, 2H), 2.82 (dd, J = 17.5, 8.1 Hz, 1H), 2.18 (s, 3H), 1.66 – 1.78 (m, 2H), 1.57 – 1.49 (m, 2H), 1.40 – 1.47 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ 205.8, 159.8, 150.2, 142.8, 142.3, 137.6, 133.6, 129.3, 128.7, 124.1, 123.9, 123.6, 123.3, 120.8, 112.1, 108.7, 101.4, 59.1, 46.2, 32.1, 30.4, 29.6, 27.7, 22.5, 14.1; IR (KBr): 2953, 2866, 1708, 1622, 1218, 762 cm^{-1}; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{25}NO_4Na$ 426.1681; Found: 426.1675.

5-(2-Oxopropyl)-14-pentylbenzo[g]isoindolo[2,1-b]isoquinolin-7(5H)-one (3h): Following the general procedure *N*-(pivaloyloxy)-2-naphthamide[9c] **1h** (81 mg, 0.30 mmol) was allowed to react with (*E*)-4-(2-(hept-1-yn-1-yl)phenyl)but-3-en-2-one **2a** (50 mg, 0.20 mmol) in presence of $[RhCp^*Cl_2]_2$ (6 mg, 0.01 mmol) and CsOAc (76 mg, 0.4 mmol) for 13 h. After filtration the filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (14 % EtOAc in petroleum ether) and got the compound **3h** (57 mg, 70% yield) as a white solid; R_f = 0.4 (hexanes:EtOAc = 7:3); mp: 173-175 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 9.07 (s, 1H), 8.23 (s, 1H), 8.04 (d, J = 8.2 Hz, 1H), 8.00 (d, J = 8.3 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.58 (d, J = 7.7 Hz, 2H), 7.49 (t, J = 7.7 Hz, 2H), 7.42 (t, J = 7.4 Hz, 1H), 6.02 (dd, J = 7.9, 2.7 Hz, 1H), 3.90 (dd, J = 17.5, 3.2 Hz, 1H), 3.26 –3.20 (m, 2H), 2.85

(dd, *J* = 17.5, 8.1 Hz, 1H), 2.20 (s, 3H), 1.83 – 1.76 (m, 2H), 1.59 – 1.69 (m, 2H), 1.44 – 1.55 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ 205.9, 161.0, 142.7, 136.4, 135.2, 134.0, 133.6, 131.2, 129.2 (2C), 128.71, 128.68, 128.0 (2C), 125.9, 123.9, 123.8, 123.6, 121.6, 113.6, 58.8, 46.5, 32.2, 30.4, 28.8, 26.3, 22.6, 14.1; IR(KBr): 3221, 2951, 2592, 1646, 1609, 1474, 1230, 766 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$: Calcd for $C_{28}H_{28}NO_2$ 410.2120 Found 410.2118.

***9-(2-Oxopropyl)-4-pentylthieno[3',2':4,5]pyrido[2,1-a]isoindol-11(9H)-one (3i)*:** Following the general procedure, *N*-(pivaloyloxy)thiophene-2-carboxamide[9a] **1i** (68 mg, 0.3 mmol) was allowed to react with (*E*)-4-(2-(hept-1-yn-1-yl)phenyl)but-3-en-2-one **2a** (50 mg, 0.20 mmol) in presence of $[RhCp^*Cl_2]_2$ (6.2 mg, 0.01 mmol) and CsOAc (76.4 mg, 0.4 mmol) for 15 h. After filtration the filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (12 % EtOAc in petroleum ether) and got the compound **3i** (50 mg, 69% yield) as a white solid; R_f = 0.5 (Hexanes: EtOAc = 3:2); mp: 154-157 ^oC; ^1H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, *J* = 7.9 Hz, 1H), 7.73 (d, *J* = 5.2 Hz 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 5.3 Hz, 1H), 5.98 (dd, *J* = 8.1, 3.0 Hz, 1H), 4.00 (dd, *J* = 17.7, 3.1 Hz, 1H), 3.16 – 3.06 (m, 2H), 2.84 (dd, *J* = 17.7, 8.2 Hz, 1H), 2.19 (s, 3H), 1.76 – 1.70 (m, 2H), 1.69 –1.78 (m, 2H), 1.48 – 1.55 (m, 2H), 1.38 – 1.46 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ 205.8, 156.9, 147.8, 142.7, 139.3, 133.5, 133.0, 129.1, 128.8, 128.6, 123.7, 123.3, 123.0, 113.4, 59.3, 45.6, 32.0, 30.4, 29.4, 28.3, 22.6, 14.1; IR (KBr): 2966, 2824, 1616, 1453, 1361, 770 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{24}NO_2S$ 366.1528; Found 366.1529.

5-Methyl-8-(2-oxopropyl)-13-pentyl-5,8-dihydro-6H-benzo[1,2]indolizino[6,7-b]indol-6-one (3j): Following the general procedure, 1-methyl-*N*-(pivaloyloxy)-1*H*-indole-2-carboxamide[9a] **1j**

(82 mg, 0.30 mmol) was allowed to react with (*E*)-4-(2-(hept-1-yn-1-yl)phenyl)but-3-en-2-one **2a** (50 mg, 0.20 mmol) in presence of $[RhCp^*Cl_2]_2$ (6.2 mg, 0.01 mmol) and CsOAc (76.4 mg, 0.40 mmol) for 14 h. After filtration the filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (14% EtOAc in petroleum ether) and got the compound **3j** (61 mg, 74% yield) as an off-white solid; R_f = 0.5 (Hexane: EtOAc = 3:2); mp: 182-184 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, J = 8.2 Hz, 1H), 7.85 (d, J = 7.9 Hz, 1H), 7.56 – 7.48 (m, 3H), 7.49 – 7.43 (m, 1H), 7.36 (d, J = 7.5 Hz, 1H), 7.30 – 7.28 (m, 1H), 6.04 (dd, J = 8.2, 2.9 Hz, 1H), 4.37 (s, 3H), 4.00 (dd, J = 17.5, 3.1 Hz, 1H), 3.44 – 3.39 (m, 2H), 2.80 (dd, J = 17.5, 8.3 Hz, 1H), 2.20 (s, 3H), 1.82 – 1.95 (m, 2H), 1.71 – 1.62 (m, 2H), 1.54 – 1.44 (m, 2H), 0.99 (t, J = 7.3 Hz, 3H); $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$): δ 205.9, 154.4, 142.2, 141.4, 134.1, 134.0, 128.6, 127.9, 126.5, 126.3, 125.7, 123.5, 122.9, 122.3, 121.8, 120.3, 114.6, 110.2, 59.2, 46.1, 32.2, 31.3, 30.4, 28.7, 28.0, 22.7, 14.12; IR (KBr): 3224, 2929, 2856, 1719, 1645, 1478, 1367, 766 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ Calcd for C_{27} H_{29} N_2O_2: 413.2229; Found 413.2237.

***7-(2-Oxopropyl)-12-propylisoindolo[2,1-b]isoquinolin-5(7H)-one (4a)*:** Following the general procedure, *N*-(Pivaloyloxy)benzamide **1a** (66 mg, 0.3 mmol) was allowed to react with (*E*)-4-(2-(pent-1-yn-1-yl)phenyl)but-3-en-2-one[11a] **2b** (42. mg, 0.2 mmol) in presence of $[RhCp^*Cl_2]_2$ (6.2 mg, 0.01 mmol) and CsOAc (76.4 mg, 0.4 mmol) for 12 h. After filtration the filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (12 % EtOAc in petroleum ether) and got the compound **4a** (52 mg, 79% yield) as a white solid; R_f = 0.5 (Hexanes: EtOAc = 7:3); mp: 166-168 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.50 (dd, J = 8.0, 0.9 Hz, 1H), 7.86 (dd, J = 12.9, 8.1 Hz, 2H), 7.76 – 7.69 (m, 1H), 7.58 (d, J = 7.5 Hz, 1H), 7.54 – 7.46 (m, 2H), 7.39 – 7.45 (m, 1H), 6.01 (dd, J = 8.0, 2.8

Hz, 1H), 3.93 (dd, *J* = 17.6, 3.0 Hz, 1H), 3.16 – 3.12 (m, 2H), 2.82 (dd, *J* = 17.6, 8.1 Hz, 1H), 2.19 (s, 3H), 1.70 – 1.81 (m, 2H), 1.18 (t, *J* = 7.3 Hz, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ 205.8, 160.5, 142.8, 138.0, 137.6, 133.6, 132.2, 129.3, 128.7, 127.6, 126.2, 125.1, 123.9, 123.6, 123.0, 113.5, 59.2, 45.9, 30.4, 28.1, 22.5, 14.3; IR (KBr): 3064, 2960, 1716, 1648, 1606, 1477, 1363, 766 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{22}NO_2$ 332.1651; Found 332.1644.

***12-Butyl-7-(2-oxopropyl)isoindolo[2,1-b]isoquinolin-5(7H)-one (4b)*:** Following the general procedure, *N*-(Pivaloyloxy)benzamide **1a** (66 mg, 0.3 mmol) was allowed to react with (*E*)-4-(2-(hex-1-yn-1-yl)phenyl)but-3-en-2-one[11b] **2c** (45 mg, 0.2 mmol), in presence of $[RhCp^*Cl_2]_2$ (6.2 mg, 0.01 mmol) and CsOAc (76.4 mg, 0.4 mmol) for 12 h. After filtration the filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (12 % EtOAc in petroleum ether) and got the compound **4b** (56 mg, 81% yield) as an off-white solid; *Rf* = 0.4 (Hexanes: EtOAc = 7:3); mp: 142-145 ^oC; ^1H NMR (300 MHz, $CDCl_3$): δ 8.51 (d, *J* = 7.8 Hz, 1H), 7.87 (dd, *J* = 14.2, 8.0 Hz, 2H), 7.74 (t, *J* = 7.4 Hz, 1H), 7.59 (d, *J* = 7.3 Hz, 1H), 7.39 – 7.55 (m, 3H), 6.02 (d, *J* = 6.1 Hz, 1H), 3.94 (d, *J* = 17.5 Hz, 1H), 3.21 – 3.12 (m, 2H), 2.82 (dd, *J* = 17.6, 8.1 Hz, 1H), 2.19 (s, 3H), 1.79 – 1.67 (m, 2H), 1.67 – 1.56 (m, 2H), 1.06 (t, *J* = 6.8 Hz, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ 205.8, 160.5, 142.8, 137.9, 137.4, 133.6, 132.2, 129.2, 128.7, 127.6, 126.2, 125.1, 123.8, 123.6, 122.9, 113.6, 59.1, 45.9, 31.4, 30.4, 25.9, 23.1, 14.0; IR (KBr): 3407, 3011, 1715, 1643, 1481, 764 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{24}NO_2$ 346.1807; Found 346.1801.

***12-Cyclohexyl-7-(2-oxopropyl)isoindolo[2,1-b]isoquinolin-5(7H)-one (4c)*:** Following the general procedure, *N*-(pivaloyloxy)benzamide **1a** (66 mg, 0.3 mmol) was allowed to react with (*E*)-4-(2-(cyclohexylethynyl)phenyl)but-3-en-2-one **2d** (50.4 mg, 0.2 mmol) in presence of $[RhCp^*Cl_2]_2$ (6.2 mg 0.01 mmol) and CsOAc (76.4 mg, 0.4 mmol) for 12 h. After filtration the

filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (12 % EtOAc in petroleum ether) and got the compound **4c** (58 mg, 78% yield) as a white solid; R_f = 0.5 (Hexanes: EtOAc = 3:2); mp: 171-173 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.51 (dd, J = 8.0, 1.3 Hz, 1H), 8.22 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 7.9 Hz, 1H), 7.65 – 7.69 (m, 1H), 7.60 (d, J = 7.5 Hz, 1H), 7.46 – 7.50(m, 2H), 7.43 (td, J = 7.5, 0.9 Hz, 1H), 6.01 (dd, J = 8.1, 3.1 Hz, 1H), 3.91 (dd, J = 17.6, 3.1 Hz, 1H), 3.79 (tt, J = 12.7, 3.5 Hz, 1H), 2.80 (dd, J = 17.6, 8.1 Hz, 1H), 2.42 – 2.28 (m, 2H), 2.20 (s, 3H), 1.83 – 2.05 (m, 5H), 1.45 – 1.4 (m, 3H); ^{13}C{1H} NMR (125 MHz, $CDCl_3$): δ 205.9, 160.4, 143.1, 137.7, 137.6, 134.0, 131.0, 129.3, 128.6, 127.8, 126.0, 125.9, 125.7, 124.3, 123.8, 118.8, 59.0, 46.2, 39.0, 31.4, 30.9, 30.4, 27.6, 27.5, 26.1; IR (KBr): 3018, 2930, 2856, 1716, 1639, 1216, 751 cm^{-1}; HRMS (ESI) m/z: Calcd for $C_{25}H_{26}NO_2$ $[M + H]^+$ 372.1964; Found 372.1972.

***12-(Hydroxymethyl)-7-(2-oxopropyl)isoindolo[2,1-b]isoquinolin-5(7H)-one (4d)*:** Following the general procedure, *N*-(Pivaloyloxy)benzamide **1a** (66 mg, 0.3 mmol) was allowed to react with (*E*)-4-(2-(3-hydroxyprop-1-yn-1-yl)phenyl)but-3-en-2-one **2e** (40 mg, 0.2 mmol), in presence of $[RhCp^*Cl_2]_2$ (6.2 mg, 0.01 mmol) and CsOAc (76.4 mg, 0.50 mmol) for 14 h. After filtration the filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (20 % EtOAc in petroleum ether) and obtained the compound **4d** (48 mg, 75% yield) as a white solid; *Rf* = 0.5 (Hexanes: EtOAc = 1:1); mp: 160-162 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (d, J = 7.9 Hz, 1H), 8.06 (dd, J = 7.9 1.1 Hz, 1H), 7.98 (d, J = 8.3 Hz, 1H), 7.63 – 7.59 (m, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.42 (td, J = 7.4 Hz, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.08 (m, 1H), 5.41 (dd, J = 8.3, 2.8 Hz, 1H), 5.21 (q, J = 12.9 Hz, 2H), 3.66 (dd, J = 17.7, 3.0 Hz, 1H), 3.33 (s, 1H), 2.65 (dd, J = 17.7, 8.4 Hz, 1H), 2.10 (s, 3H); ^{13}C{1H} NMR (125 MHz, $CDCl_3$): δ 205.4, 160.6, 142.7, 140.5, 137.1, 132.5, 130.0, 129.0,

127.4, 126.2, 124.9, 124.1, 123.4, 122.7, 111.2, 59.2, 56.0, 45.3, 30.3; IR (KBr): 3010, 2937, 2859, 1662, 1506, 1260, 752 cm^{-1}; cm^{-1}; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{15}NO_3Na$ 342.1106; Found 342.1112.

***12-Butyl-9-methoxy-7-(2-oxopropyl)isoindolo[2,1-b]isoquinolin-5(7H)-one (4e)*:** Following the general procedure, *N*- (Pivaloyloxy)benzamide **1a** (66 mg, 0.3 mmol) was allowed to react with (*E*)-4-(2-(hex-1-yn-1-yl)-5-methoxyphenyl)but-3-en-2-one **2f** (51 mg, 0.2 mmol) in presence of $[RhCp^*Cl_2]_2$ (6.2 mg, 0.01 mmol) and CsOAc (76.4 mg, 0.4 mmol) for 12 h. After filtration the filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (12 % EtOAc in petroleum ether) and got the compound **4e** (62 mg, 82% yield) as a white solid; R_f = 0.5 (Hexanes: EtOAc = 7:3); mp: 165 -167 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.48 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.79 (dd, *J* = 8.4, 5.4 Hz, 2H), 7.75 – 7.68 (m, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 2.2 Hz, 1H), 7.02 (dd, *J* = 8.7, 2.4 Hz, 1H), 5.95 (dd, *J* = 8.2, 2.8 Hz, 1H), 3.95 (dd, *J* = 17.7, 3.0 Hz, 1H), 3.87 (s, 3H), 3.07 – 3.15 (m, *J* = 19.0, 12.1 Hz, 2H), 2.78 (dd, *J* = 17.7, 8.3 Hz, 1H), 2.20 (s, 3H), 1.74 – 1.66 (m, 2H), 1.55 – 1.63 (m, 2H), 1.05 (t, *J* = 7.2 Hz, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ 206.1, 160.8, 160.6, 145.0, 138.2, 137.6, 132.2, 127.7, 126.2, 125.8, 125.0, 124.7, 122.7, 115.6, 111.8, 108.4, 59.1, 55.7, 46.1, 31.4, 30.4, 25.9, 23.1, 14.1; IR (KBr): 2931, 2862, 1735, 1652, 1608, 1184, 768 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{24}H_{26}NO_3$ 376.1913; Found 376.1909.

12-Butyl-5-(2-oxopropyl)-[1,3]dioxolo[4',5':5,6]isoindolo[2,1-b]isoquinolin-7(5H)-one (4f): Following the general procedure, *N*-(Pivaloyloxy)benzamide **1a** (66 mg, 0.3 mmol) was allowed to react with (*E*)-4-(6-(hex-1-yn-1-yl)benzo[d][1,3]dioxol-5-yl)but-3-en-2-one **2g** (54 mg, 0.2 mmol) in presence of $[RhCp^*Cl_2]_2$ (6.2 mg, 0.01 mmol) and CsOAc (76.4 mg, 0.4 mmol) for 12 h. After filtration, the filtrate was concentrated under reduced pressure. The obtained residue was

purified by column chromatography on silica gel (12% EtOAc in petroleum ether) and got the compound **4f** (64 mg, 83% yield) as a white solid; R_f = 0.4 (Hexanes: EtOAc = 7:3); mp: 138-140 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.46 (d, J = 7.9 Hz, 1H), 7.79 (d, J = 8.3 Hz, 1H), 7.71 (t, J = 7.6 Hz, 1H), 7.47 (t, J = 7.5 Hz, 1H), 7.29 (s, 1H), 7.03 (s, 1H), 6.06 (d, J = 1.2 Hz, 2H), 5.86 (d, J = 8.0 Hz, 1H), 3.94 (dd, J = 17.7, 2.8 Hz, 1H), 3.10 – 3.01 (m, 2H), 2.73 (dd, J = 17.7, 8.3 Hz, 1H), 2.18 (s, 3H), 1.73 – 1.64 (m, 2H), 1.54 – 1.64 (m, 2H), 1.05 (t, J = 7.2 Hz, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$): δ 206.1, 160.3, 149.0, 148.6, 138.0, 137.7, 137.6, 132.2, 127.6, 126.8, 125.8, 124.6, 122.7, 111.8, 104.2, 103.8, 101.9, 58.8, 45.9, 31.4, 30.4, 25.7, 23.0, 14.0; IR (KBr): 2957, 1647, 1481, 1281, 1041, 769 cm^{-1}; HRMS (ESI): *m/z* Calcd for $C_{24}H_{24}NO_4$ $(M+H)^+$: 390.1705, Found:. 390.1712.

***12-Butyl-9,10-dimethoxy-7-(2-oxopropyl)isoindolo[2,1-b]isoquinolin-5(7H)-one(4g)*:**

Following the general procedure, *N*-(pivaloyloxy)benzamide **1a** (66 mg, 0.2 mmol) was allowed to react with (*E*)-4-(2-(hex-1-yn-1-yl)-4,5-dimethoxyphenyl)but-3-en-2-one **2h** (57 mg, 0.2 mmol) in presence of $[RhCp^*Cl_2]_2$ (6.2 mg, 0.01 mmol) and CsOAc (76.4 mg, 0.4 mmol) for 12 h. After filtration the filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (12% EtOAc in petroleum ether) and got the compound **4g** (61 mg, 76% yield) as a white solid; R_f = 0.5 (Hexanes: EtOAc = 7:3); mp: 124-127 ^oC; ^1H NMR (500 MHz, $CDCl_3$): δ 8.47 (dd, J = 8.0, 1.2 Hz, 1H), 7.80 (d, J = 8.2 Hz, 1H), 7.68 – 7.73 (m, 1H), 7.44 – 7.49 (m, 1H), 7.36 (s, 1H), 7.12 (s, 1H), 5.90 (dd, J = 8.5, 2.7 Hz, 1H), 4.01 (dd, J = 17.8, 3.1 Hz, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.08 – 3.02 (m, 2H), 2.62 (dd, J = 17.7, 8.5 Hz, 1H), 2.14 (s, 3H), 1.70 – 1.77 (m, 2H), 1.58 – 1.65 (m, 2H), 0.99 (t, J = 7.3 Hz, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ 206.4, 160.4, 150.6, 149.6, 138.0, 137.9, 136.3, 132.1, 127.6, 125.7, 125.6, 124.6, 122.5, 111.4, 106.3, 106.2, 59.0, 56.12, 56.08, 46.1, 31.5, 30.4, 25.9,

23.3, 14.1; IR (KBr): 2940, 2866, 1667, 1609, 1220, 759 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$: Calcd for $C_{25}H_{28}NO_4$ 406.2018: Found 406.2020.

12-Butyl-9-nitro-7-(2-oxopropyl)isoindolo[2,1-b]isoquinolin-5(7H)-one (4h): Following the general procedure, *N*-(Pivaloyloxy)benzamide **1a** (66 mg, 0.3 mmol) was allowed to react with (*E*)-4-(2-(hex-1-yn-1-yl)-5-nitrophenyl)but-3-en-2-one **2i** (54 mg, 0.2 mmol) in presence of $[RhCp^*Cl_2]_2$ (6.2 mg, 0.01 mmol) and CsOAc (76.4 mg, 0.4 mmol) for 14 h. After filtration the filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (13 % EtOAc in petroleum ether) and got the compound **4h** (64 mg, 82% yield) as a yellow solid; R_f = 0.5 (Hexanes: EtOAc = 7:3); mp: 172 - 174 ^oC; ^1H NMR (500 MHz, $CDCl_3$): δ 8.50 (dd, *J* = 8.0, 0.9 Hz, 1H), 8.41 (d, *J* = 1.3 Hz, 1H), 8.37 (dd, *J* = 8.7, 2.0 Hz, 1H), 8.01 (d, *J* = 8.7 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.82 – 7.75 (m, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 6.03 (dd, *J* = 7.9, 2.6 Hz, 1H), 3.94 (dd, *J* = 18.2, 2.9 Hz, 1H), 3.18 – 3.22 (m, 2H), 3.04 (dd, *J* = 18.2, 8.0 Hz, 1H), 2.20 (s, 3H), 1.70 – 1.77 (m, 2H), 1.60 – 1.69 (m, 2H), 1.08 (t, *J* = 7.2 Hz, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ 205.3, 160.2, 147.7, 143.9, 139.6, 137.3, 135.6, 132.6, 127.8, 127.5, 125.7, 124.4, 124.1, 123.5, 119.1, 117.1, 59.0, 45.1, 31.5, 30.2, 26.1, 23.1, 14.0; IR (KBr): 3173, 2938, 2857, 1654, 1607, 1507, 1286, 770 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{23}N_2O_4$ 391.1658; Found 391.1666.

6-Butyl-13-(2-oxopropyl)benzo[6,7]indolizino[1,2-b]quinolin-11(13H)-one **(4i):** Following the general procedure, *N*-(pivaloyloxy)benzamide **1a** (66 mg, 0.2 mmol) was allowed to react with (*E*)-4-(2-(hex-1-yn-1-yl)quinolin-3-yl)but-3-en-2-one **2j** (55.4 mg, 0.2 mmol) in presence of $[RhCp^*Cl_2]_2$ (6.2 mg, 0.01 mmol) and CsOAc (76.4 mg, 0.4 mmol) for 15 h. After filtration the filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (12 % EtOAc in petroleum ether) and got the compound **4i** (60 mg,

76% yield) as a yellow solid; R_f = 0.5 (Hexanes: EtOAc = 7:3); mp: 195-197 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, J = 7.9 Hz, 1H), 8.31 (s, 1H), 8.16 (d, J = 8.5 Hz, 1H), 7.99 (d, J = 8.2 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.82 – 7.71 (m, 2H), 7.58 (dd, J = 14.1, 6.9 Hz, 2H), 6.15 (d, J = 7.4 Hz, 1H), 4.21 (dd, J = 18.1, 2.7 Hz, 1H), 3.81 – 3.89 (m, 2H), 2.81 (dd, J = 18.1, 9.2 Hz, 1H), 2.23 (s, 3H), 1.80 – 1.71 (m, 2H), 1.63 – 1.70 (m, 2H), 1.09 (t, J = 7.2 Hz, 3H); $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$): δ 206.1, 160.5, 154.4, 148.9, 137.8, 134.5, 133.7, 132.3, 130.7, 129.8, 129.8, 128.1, 127.7, 127.2 (2C), 127.0, 126.3, 124.2, 118.6, 56.8, 46.2, 32.4, 30.3, 24.2, 23.1, 14.1; IR (KBr): 3018, 2940, 1666, 1469, 1217, 1034 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{26}H_{25}N_2O_2$ 397.1916; Found 397.1921.

2-(5-Oxo-12-pentyl-5,7-dihydroisoindolo[2,1-b]isoquinolin-7-yl)acetonitrile (4j): Following the general procedure, *N*-(pivaloyloxy)benzamide **1a** (66 mg, 0.3 mmol) was allowed to react with (*E*)-3-(2-(hept-1-yn-1-yl)phenyl)acrylonitrile **2k** (44.6 mg, 0.2 mmol) in presence of $[RhCp^*Cl_2]_2$ (6.2 mg, 0.01 mmol) and CsOAc (76.4 mg, 0.4 mmol) for 12 h. After filtration the filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (12 % EtOAc in petroleum ether) and got the compound **4j** (46 mg, 68% yield) as a white solid; R_f = 0.5 (hexanes: EtOAc = 7:3); mp: 148-150 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.51 (dd, J = 8.0, 1.1 Hz, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.74 – 7.80 (m, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.59 (dd, J = 11.5, 3.9 Hz, 1H), 7.58 – 7.52 (m, 2H), 5.76 (dd, J = 6.0, 3.9 Hz, 1H), 3.61 – 3.48 (m, 2H), 3.12 – 3.22 (m, 2H), 1.69 – 1.80 (m, 2H), 1.53 – 1.63 (m, 3H), 1.40 – 1.52 (m, 2H), 0.97 (t, J = 7.2 Hz, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.8, 139.1, 138.1, 136.8, 134.2, 132.7, 129.9, 129.6, 127.8, 126.7, 125.1, 124.3, 123.3, 123.1, 116.0, 114.6, 58.7, 32.2, 29.0, 26.2, 22.7, 21.2, 14.1; IR (KBr): 3673, 2952,

2438, 2223, 1669, 1607, 1221, 747 cm^{-1}; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{22}N_2ONa$ 365.1630; Found: 365.1626.

Ethyl 2-(5-oxo-12-pentyl-5,7-dihydroisoindolo[2,1-b]isoquinolin-7-yl)acetate (4k): Following the general procedure, *N*-(Pivaloyloxy)benzamide **1a** (66 mg, 0.3 mmol) was allowed to react with ethyl (*E)*-3-(2-(hept-1-yn-1-yl)phenyl)acrylate (**2l)** (54 mg, 0.2 mmol) in presence of $[RhCp^*Cl_2]_2$ (6.2 mg 0.01 mmol) and CsOAc (76.4 mg, 0.4 mmol) for 12 h. After filtration the filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (12 % EtOAc in petroleum ether) and got the compound **4k** (48 mg, 62% yield) as a white solid; R_f = 0.4 (Hexanes: EtOAc = 4: 1); mp: 166-168 ^oC; ^1H NMR (500 MHz, $CDCl_3$): δ 8.53 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.90 (d, *J* = 7.9 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.72 – 7.76 (m, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.55 – 7.49 (m, 2H), 7.48 – 7.43 (m, 1H), 5.95 (dd, *J* = 7.5, 3.5 Hz, 1H), 4.07 (q, *J* = 7.1 Hz, 2H), 3.64 (dd, *J* = 16.0, 3.6 Hz, 1H), 3.16 (td, *J* = 7.3, 2.2 Hz, 2H), 3.03 (dd, *J* = 16.0, 7.6 Hz, 1H), 1.68 – 1.77 (m, 2H), 1.63 – 1.56 (m, 2H), 1.44 – 1.35 (m, 2H), 1.10 (t, *J* = 7.1 Hz, 3H), 0.94 (t, *J* = 7.1 Hz, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.4, 160.7, 141.9, 138.0, 135.9, 134.0, 132.3, 129.2, 129.0, 127.8, 126.3, 123.9, 123.3, 123.0, 113.7, 60.6, 59.8, 36.8, 32.2, 29.0, 26.2, 22.7, 14.2, 14.0; IR(KBr): 2949, 2866, 1650, 1607, 1477, 765 cm^{-1}; HRMS (ESI) m/z: Calcd for $C_{24}H_{25}NO_2$ $[M + H]^+$ 390.2069; Found 390.2061.

4-butyl-3-(2-vinylphenyl)isoquinolin-1(2H)-one (6): Following the general procedure, *N*-(Pivaloyloxy)benzamide **1a** (66 mg, 0.3 mmol) was allowed to react with 1-(hex-1-yn-1-yl)-2-vinylbenzene [11c](**2m)** (36.8 mg, 0.2 mmol) in presence of $[RhCp^*Cl_2]_2$ (6.2 mg 0.01 mmol) and CsOAc (76.4 mg, 0.4 mmol) for 12 h. After filtration the filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (15 %

EtOAc in petroleum ether) and got the compound **4l** (32.7 mg, 54% yield) as a white solid; R_f = 0.4 (Hexanes: EtOAc = 7: 3); mp: 120-122 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 8.0 Hz, 1H), 8.33 (bs, 1H), 7.75 (d, J = 3.4 Hz, 2H), 7.72 – 7.70 (m, 1H), 7.55 – 7.51 (m, 1H), 7.49 – 7.45 (m, 1H), 7.37 (td, J = 7.5, 1.2 Hz, 1H), 7.31 (dd, J = 7.6, 1.1 Hz, 1H), 6.57 (dd, J = 17.5, 11.0 Hz, 1H), 5.75 (dd, J = 17.5, 0.7 Hz, 1H), 5.23 (dd, J = 11.0, 0.6 Hz, 1H), 2.60 – 2.52 (m, 1H), 2.39 – 2.32 (m, 1H), 1.54 – 1.37 (m, 2H), 1.26 – 1.16 (m, 2H), 0.76 (t, J = 7.3 Hz, 3H); ^{13}C {1H} NMR (100 MHz, CDCl3) δ 161.9, 137.7, 136.5, 135.1, 133.6, 133.4, 132.7, 130.0, 129.6, 128.1, 127.9, 126.4, 126.0, 125.4, 123.7, 116.5, 115.3, 31.9, 27.0, 22.7, 13.6. IR (KBr): 3156, 3021, 2954, 1652, 1477, 769 cm^{-1}; HRMS (ESI) m/z: Calcd for $C_{21}H_{22}NO$ $[M + H]^+$ 304.1701; Found 304.1712.

***diethyl 3-(2-ethoxy-2-oxoethyl)-5-oxo-1,5-dihydropyrrolo[1,2-b]isoquinoline-2,2(3H)-di carboxylate (7)*:** Following the general procedure, *N*-(Pivaloyloxy)benzamide **1a** (66 mg, 0.3 mmol) was allowed to react with triethyl (E)-hex-1-en-5-yne-1,3,3-tricarboxylate (**2n)** (59.2 mg, 0.2 mmol) in presence of $[RhCp^*Cl_2]_2$ (6.2 mg 0.01 mmol) and CsOAc (76.4 mg, 0.4 mmol) for 4 h. After filtration the filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (10 % EtOAc in petroleum ether) and got the compound **4l** (25.7 mg, 31 % yield) as a white solid; R_f = 0.4 (Hexanes: EtOAc = 4: 1); mp: 110-112 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, J = 7.9 Hz, 1H), 7.60 (t, J = 7.5 Hz, 1H), 7.49 – 7.37 (m, 2H), 6.40 (s, 1H), 5.83 (dd, J = 7.6, 3.8 Hz, 1H), 4.37 – 4.24 (m, 2H), 4.23 – 4.19 (m, 2H), 4.12 – 4.07 (m, 2H), 4.03 – 3.93 (m, 1H), 3.56 (d, J = 16.9 Hz, 1H), 3.11 (dd, J = 16.7, 7.6 Hz, 1H), 3.00 (dd, J = 16.7, 3.8 Hz, 1H), 1.26 – 1.17 (m, 9H); ^{13}C{1H} NMR (100 MHz, CDCl3) δ 169.99, 169.10, 167.49, 160.62, 139.72, 137.76, 132.31, 127.43, 126.03, 125.75, 125.10, 100.85, 62.62, 62.58, 60.80, 60.37, 60.10, 37.55, 33.69, 14.00, 13.89, 13.83. IR (KBr):

2981, 2924, 1739, 1634, 1267, 1182, 761 cm^{-1}; HRMS (ESI) m/z: Calcd for $C_{22}H_{26}NO_7$ $[M + H]^+$ 416.1709; Found 416.1718.

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: Copies of ^1H and ^{13}C NMR spectra for all the new compounds.

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