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Palladium-Catalyzed Regio- and Stereoselective Synthesis of Aryl and 3-Indolyl Substituted-4-Methylene- isoquinolin-1(*2H*)-ones.

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Abstract

Cascade cyclocarbopalladation of the readily available aryl/alkyl-substituted propargylic amides containing an aryl iodide moiety, followed by Suzuki-Miyaura coupling with arylboronic acids, allowed an efficient regio- and stereoselective synthesis of tetrasubstituted-4-methylene-isoquinolin-1(2H)-ones. Moreover cascade cyclocarbopalladation, followed by reaction with 2- alkynyltrifluoroacetanilides, accomplished a double cyclization, to afford challenging 4-methylene-isoquinolin-1(2H)-ones bearing a 3-indolyl substituent, through aminopalladation/reductive elimination

Keywords

Isoquinolinones; Indoles; Palladium; Arylboronic Acids; Alkynylanilines.

Introduction

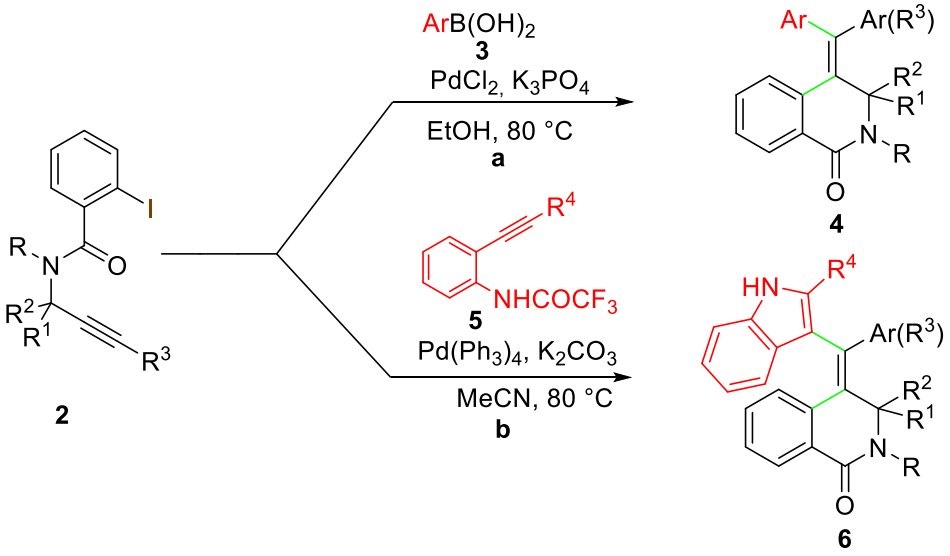
The isoquinolinone nucleus is a key constituent of many natural products [1] and pharmaceuticals. [2] Substituted isoquinolinones have been found in biologically active small molecules which exhibit antihypertensive activity. [3] Moreover, these heterocycles can be used as 5-HT3 antagonists, [4] rhokinase inhibitors, [5] thymidylate synthetase inhibitors, [6] PARP-1-inhibitors, [7] melatonin MT_1 and MT_2 receptor agonist, [8] and fascin-targeted anti metastatic agents. [9] Fittingly, the development of efficient strategies for their construction and peripheral functionalization represents still an active research area aimed to achieve structural diversity. [10]

Carbometalations of alkynes constitute a powerful tool for the regio- and stereoselective formation of carbon-carbon bonds. [11] Intramolecular palladium-catalyzed versions are particularly attractive, since they afford polycarbo- and heterocyclic systems via sequential reactions of the intermediate vinylpalladium. [12] In this field, a variety of regio- and stereoselective Pd-catalyzed cascade reactions, consisting of addition of in situ generated arylpalladium complexes over a proximate carbon-carbon triple bond followed by cross coupling reactions, have been reported. [13]

Our continuing interest on the palladium-catalyzed reaction of functionalized alkynes with boronic acids [14] prompted us to explore the palladium-catalyzed reaction of the readily available alkynyliodobenzamides **2** with boronic acids **3** as a viable route to the regio- and stereoselective synthesis of 4-alkylidene-3,4-dihydroisoquinolin-1(2H)-ones

3 (Scheme 1a). We are pleased to report here that this cascade reaction takes place efficiently, resulting in the regio- and stereoselective formation of the poly-substituted isoquinolinones **4** in good to high yield. Applications of this reaction can be relevant for improvements of structure diversity and fine tuning of the chemical and physical properties of the products.

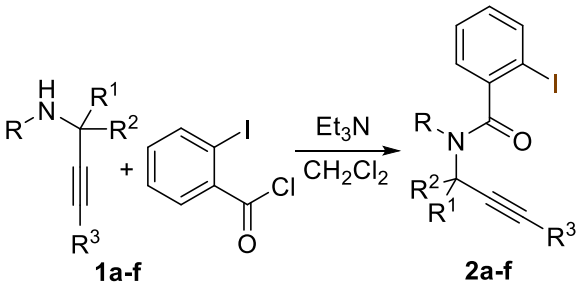
Furthermore, over the years we have reported a general methodology for the Pd-catalyzed synthesis of 3-substituted indoles, now referred as “Cacchi reaction”, [15] through aminopalladation/reductive elimination sequence starting from 2-alkynyltrifluoroacetanilides. In all these procedures, the activation of the triple bond was obtained by mean of a σ-organyl palladium complex, in turn generated *in situ* by oxidative addition of a Pd(0) species to suitable organic electrophiles (aryl and vinyl halides or triflates, [16] alkyl halides, [17] alkynyl halides [18], α-iodoenones [19]) or by transmetalation of a Pd(II) with boronic acids. [14b] In this context, we decided to explore the use of substrates **2** in the reaction with 2-alkynyltrifluoroacetanilides **5** through a sequential cyclocarbopalladation/aminopalladation/reductive elimination process, widening in such a way the scope of the methodology and allowing challenging synthesis of 4-methylene-isoquinolin-1(2H)-ones **6** bearing an indole substituent (Scheme 1b).



Scheme 1. Planned approach to tetrasubstituted-4-methylene-isoquinolin-1*(2H)*-ones **4** and **6**.

Results and Discussion

The starting propargylic 2-iodobenzamides **1** were easily obtained by the reaction of the readily available [20] propargylic amines **1** with 2-iodobenzoyl chloride in CH_2Cl_2 at room temperature (Scheme 2).



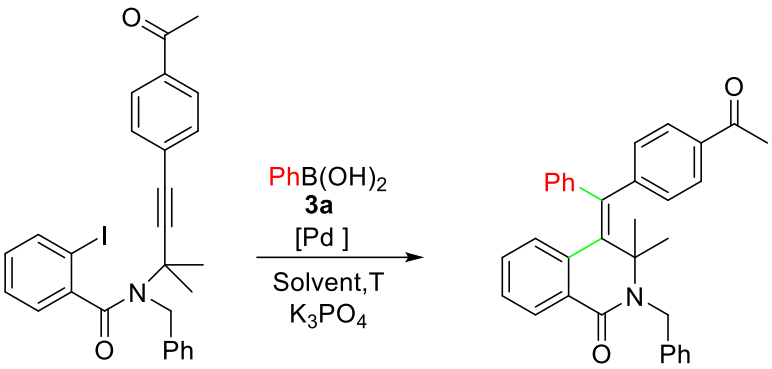
2a (91%): R = -CH_2Ph; R^1 = R^2 = -CH_3; R^3 = *p*-CH_3CO-C_6H_4-
2b (80%): R = -CH_2Ph; R^1 = R^2 = -CH_3; R^3 = *p*-CH_3O-C_6H_4-
2c (80%): R = -CH_2Ph; R^1 = R^2 = -CH_3; R^3 = *p*-CF_3-C_6H_4-
2d (94): R = -CH_2Ph; R^1 = R^2 = -$(CH_2)_5$; R^3 = -$(CH_2)_4$-CH_3
2e (86%): R = -CH_2Ph; R^1 = Ph-; R^2 = -H; R^3 = Ph-
2f (82%): R = -CH_2Ph; R^1 = R^2 = -H; R^3 = *p*-CH_3CO-C_6H_4-

Scheme 2. Preparation of the starting propargylic 2-iodobenzamides **2**.

Initially, we explored the reaction of the *N*-(4-(4-acetylphenyl)-2-methylbut-3-yn-2-yl)-*N*-benzyl-2-iodobenzamide **2a** with a variable excess of the phenylboronic acid **3a** in the presence of K_3PO_4 as the base (K_3PO_4: **2a** = 3) by using 5 mol % of different palladium catalysts/solvent/temperature combinations. The results are reported in Table 1.

When 1,4-dioxane was used as the solvent in the presence of the commercially available $PdCl_2(PPh_3)_2$ as the catalyst at 100 °C, the reaction of **2a** with 1.5 equiv. of the phenylboronic acid **3a** delivered the target (*Z*)- dihydroisoquinolin-1(*2H*)-one **4aa** in 51 % yields. Better yields were observed by increasing the excess of the phenylboronic acid (Table 1, entries 1-3) or by halving the amount of the solvent in the presence 1,5 equiv. of **3a** (Table 1, entry 4). Under these latter conditions a beneficial effect was obtained by using a mixture 9:1 of 1,4-dioxane/H_2O as the reaction medium (Table 1, entry 5). While MeCN, DMF, THF and DMSO as solvents gave worse results (Table 1, entries 6-9), the environmentally friendly EtOH proved to be the most efficient reaction medium (Table 1, entry 10). Further attempts to increase the yield of **4aa** by tuning the catalytic system showed that the ligand-free $PdCl_2$ was the most effective catalyst (Table 1, entry 14). Other catalysts such as $Pd(PPh_3)_4$, Pd/C or $Pd(OAc)_2$ provided inferior results (Table 1, entries 11-13).

Table 1: Optimization of the reaction of propargyl 2-iodobenzamide **2a** with phenylboronic acid **3a**.[a]

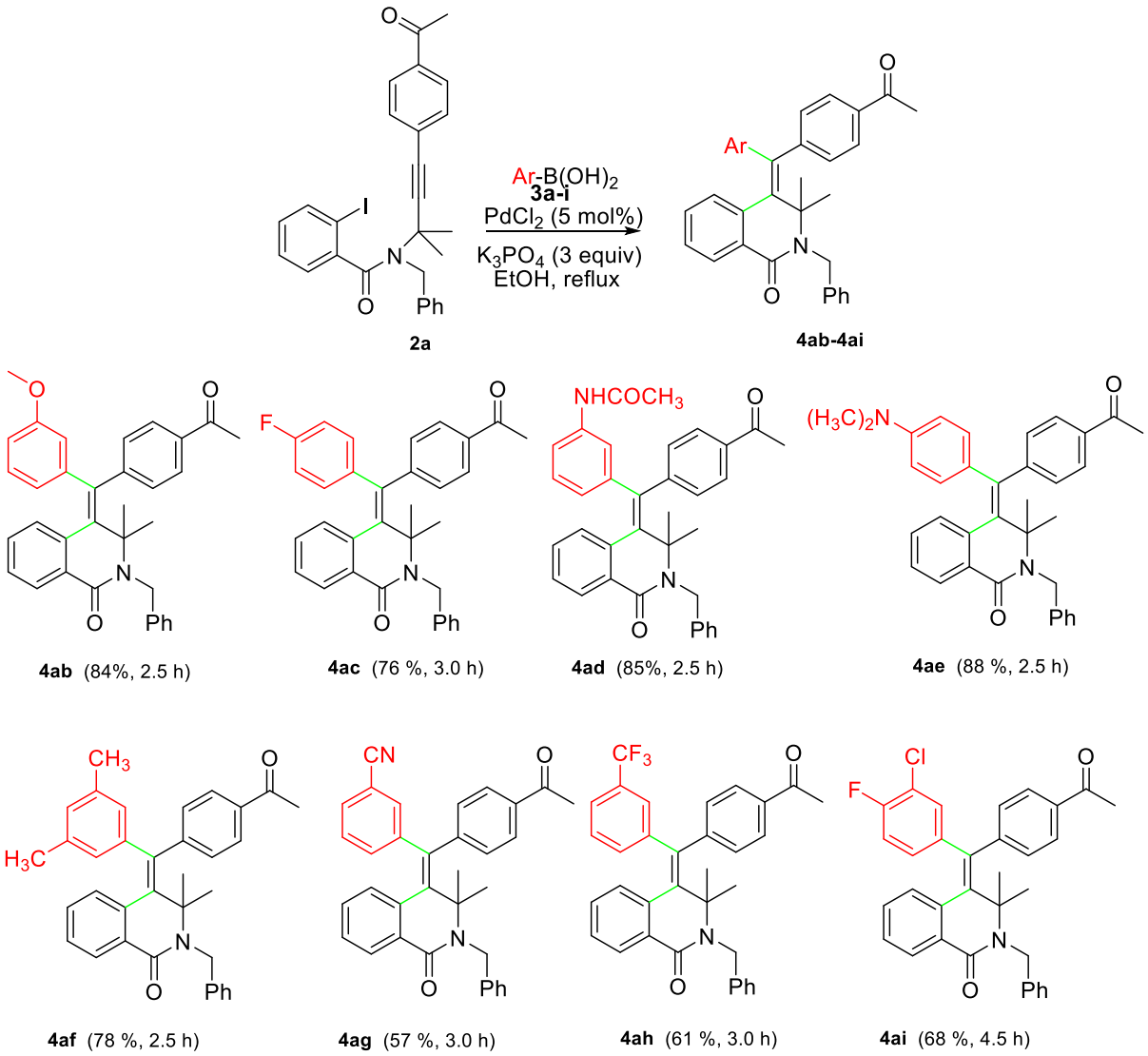


2a **4aa**

Entry	Solvent/Temp. (°C)	**3a**:**2a** ratio	Catalyst	Time (h)	**4aa** (yield %[b])
1	Dioxane/100	1.5	$PdCl_2(PPh_3)_2$	7	51
2	Dioxane/100	2.0	$PdCl_2(PPh_3)_2$	2	94
3	Dioxane/100	3.0	$PdCl_2(PPh_3)_2$	2	97
4	Dioxane/100	1.5	$PdCl_2(PPh_3)_2$	4	67[c]
5	Dioxane-water (9:1)/100	1.5	$PdCl_2(PPh_3)_2$	2	80[c]
6	MeCN/80	1.5	$PdCl_2(PPh_3)_2$	7	41[c]
7	THF/60	1.5	$PdCl_2(PPh_3)_2$	7	27[c]
8	DMF/110	1.5	$PdCl_2(PPh_3)_2$	2.5	58[c]
9	DMSO/110	1.5	$PdCl_2(PPh_3)_2$	2.5	41[c]
10	EtOH/80	1.5	$PdCl_2(PPh_3)_2$	3	85[c]
11	EtOH/80	1.5	$Pd(PPh_3)_4$	3	74[c]
12	EtOH/80	1.5	Pd/C	3	66[c]
13	EtOH/80	1.5	$Pd(OAc)_2$	2.5	77[c]
14	**EtOH/80**	**1.5**	**$PdCl_2$**	**2.5**	**91[c]**

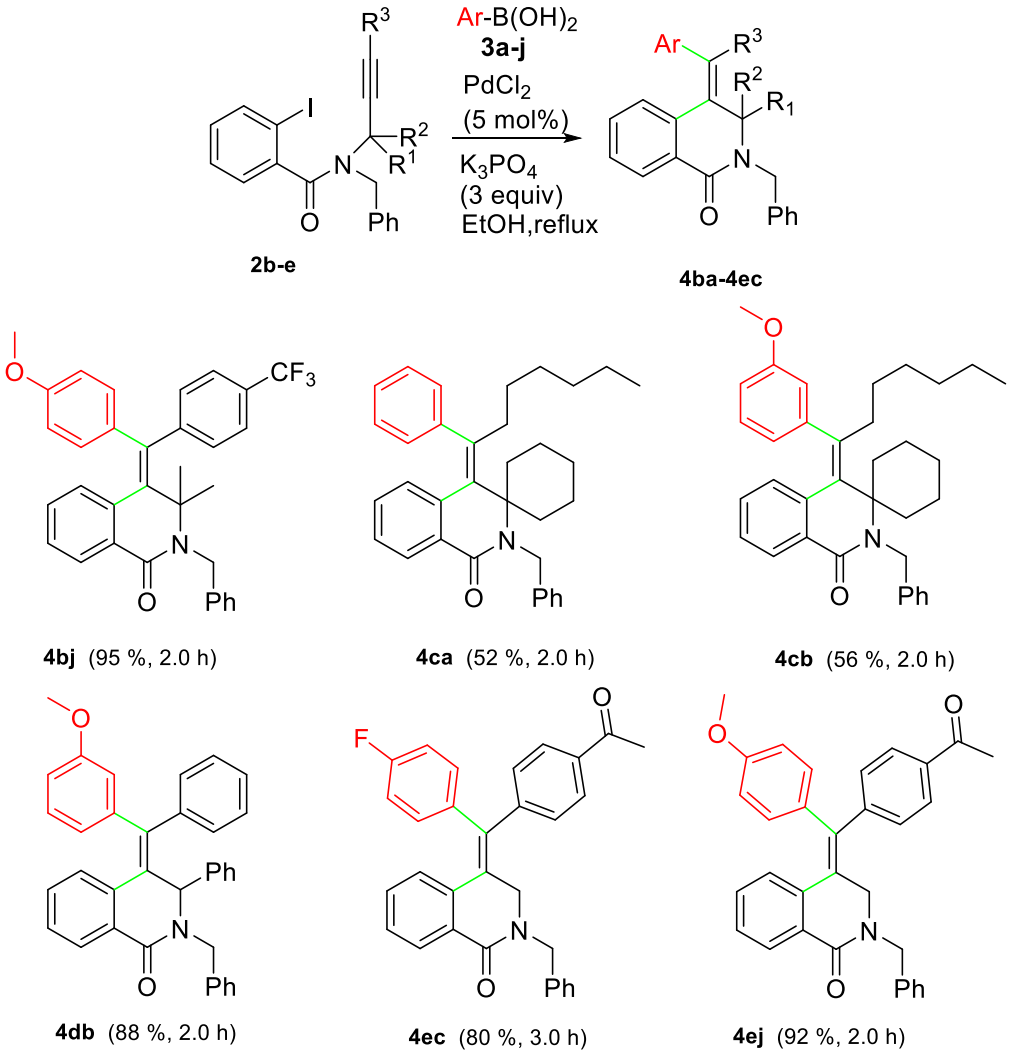
[a]Reactions were carried out on a 0.19 mmol scale, using 3 equiv. of base, 0.10 equiv. of ligand and 0.05 equiv. of the palladium catalyst in 1.0 mL of solvent under nitrogen atmosphere. [b] Yields are given for isolated products. [c] 1.0 mL of solvent.

We then examined the reaction of **2a** with 1.5 equiv. of a variety of arylboronic acids. Using the optimized reaction condition of entry 14, **2a** reacted smoothly with diversely substituted arylboronic acids **3a-i** to afford regio- and stereoselectively the corresponding tetrasubstituted-4-methylene-isoquinolin-1(*2H*)-ones **4ab-4ai** in moderate to good yields (Scheme 3). Gratifying, various functional groups such as amino, acetamido, -F, -Cl, -OMe, -CF_3, and -CN were found to be compatible with our reaction conditions, and only the homocoupling of the arylboronic acids was observed as side reaction to some extent. [21] The best results were obtained with arylboronic acids containing electron-donating substituents; electron-poor arylboronic acids proved to be slightly less effective, probably because of their lower nucleophilicity that could affect the trans-metalation step.



Scheme 3. Substrate scope of the reaction of propargyl-2-iodobenzamide **2a** with arylboronic acids **3a-i**.

Moreover, we screened the reaction of a number of aromatic boronic acids **3a-j** with a set of propargyl-2-iodobenzamides **2b-e** (Scheme 4).



Scheme 4. Substrate scope of the reaction of propargyl-2-iodobenzamides **2b-f** with arylboronic acids **3a-j**.

All reaction successfully delivered the desired products **4** in moderate to good yields. Remarkably, an alkyl substituent was tolerated at terminal C_{sp} of the starting propargyl-2-iodobenzamides **2**. Furthermore, 2-iodobenzamides **2d** and **2e** (mono-substituted and unsubstituted at the propargylic position) were successfully used as starting materials, affording the corresponding products **4db**, **4ec** and **4ej** in good yields. According to the literature, the highly stereoselective formation of products 4cj-4fc resulted from the intramolecular syn-addition of the in situ generated arylpalladium iodide complex to the triple bond to give an (*E*)-vinylpalladium intermediate which

underwent cross-coupling with an arylboronic acid leading to the final product by reductive elimination, with the regeneration of the Pd(0) catalyst.

Finally, we envisaged that the above mentioned (*E*)-vinyl palladium intermediate **A** (generated *in situ* from the insertion of carbon-carbon triple bond in the initially formed arylpalladium complex) could also be involved the aminopalladation with the alkynyltrifluoroacetanilides **5** through the formation of the π-complex **B**, followed by base-assisted cyclization and reductive elimination from the resulting σ-indolylpalladium complex **C** (Scheme 6).

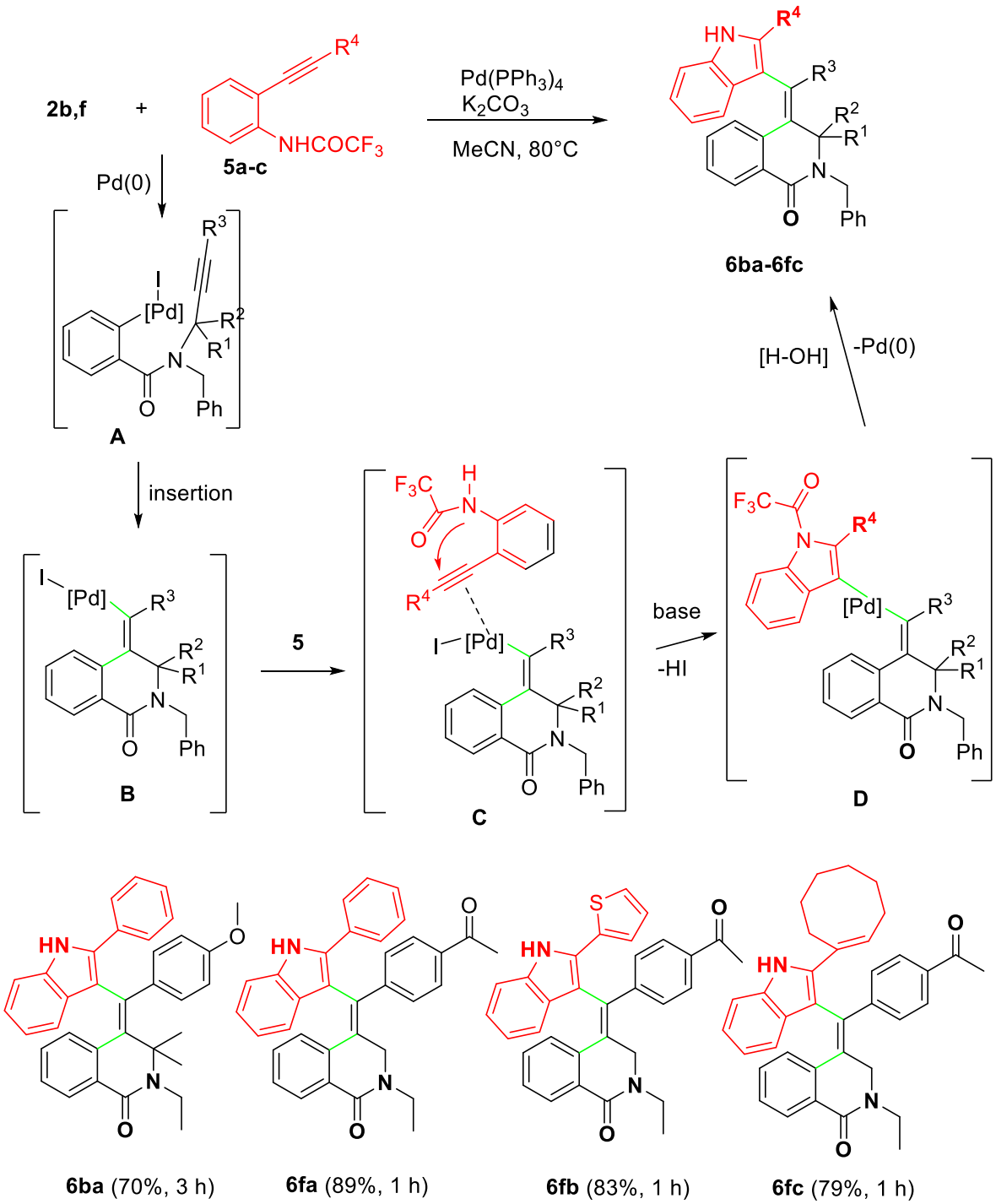
The reaction led to the stereoselective formation of indole derivatives **6ba-6fc;** aryl, heteroaryl and vinyl group were allowed in the substrates **5** in good to high yield.

The stereochemistry of compounds **4** and **6** was unambiguously confirmed by NMR spectroscopy.[22]

Conclusions

In conclusion, we have demonstrated that cascade cyclocarbopalladation of the readily available aryl/alkyl-substituted propargylic 2-iodobenzamides **2** followed by Suzuki-Miyaura coupling reactions with arylboronic acids in the presence of a catalytic amount of the ligand-free $PdCl_2$ in environmentally friendly ethanol achieve an efficient regio- and stereoselective synthesis of 4-methylene-isoquinolin-1(2H)-ones **4**. It is worth noting that, during the preparation of this manuscript, a related article focused on the palladium-catalyzed regioselective cascade cyclization of propargylamides/coupling with $ArB(OH)_2$ in dioxane-water, to give trisubstituted arylidene-isoquinolinones. [23] However, the Ugi four-component reaction used to construct the starting building blocks was limited to the preparation of propargylic 2-halobenzamides unsubstituted

at the propargyl carbon, allowing the synthesis of isoquinolinones without substituents at C-3; the present methodology overcome this limitations.



Scheme 6. Reaction of propargyl-2-iodobenzamides **2b-f** with the 2-alkynyltrifluoroacetanilides **5a-c**

Moreover, the previously developed strategy of indole synthesis through aminopalladation/reductive elimination process has been significantly extended to include σ-vinyl Pd(II) intermediates **B** obtained through oxidative addition/insertion of substrates **2** with Pd(0). This reaction efficiently led to challenging indoloquinolinones **6** through a sequential double cyclization.

It is worth noting that, in both cases, the intramolecular alkyne insertion in the initially formed arylpalladium iodide **A** (leading to **B**) resulted faster than the direct reaction of **A** with arylboronic acids or with 2-alkynyltrifluoroacetanilides.

Experimental

General Methods.

Melting points are uncorrected. IR spectra were recorded with a Perkin Elmer Spectrum Two FT/IR spectrometer. ^{1}H-NMR spectra were recorded at 400 MHz on Bruker Avance 400 instrument. Chemical shifts (in ppm) were referenced to tetramethylsilane (δ = 0 ppm) in $CDCl_3$ as an internal standard. ^{13}C-NMR spectra were recorded at 100.6 MHz and were calibrated with $CDCl_3$ (δ = 77.00 ppm) or tetramethylsilane (δ = 0 ppm). Mass measurement was performed using a MALDI-TOF spectrometer AB SCIEX TOF/TOF 5800 System using 3-hydroxycoumarin or α-cyano-4-hydroxycinnamic acid as matrix in combination with KI for the ionization. Unless otherwise stated, all starting materials, catalysts, and solvents were commercially available and were used as purchased. Reaction products were purified by flash chromatography on silica gel by elution with *n*-hexane/EtOAc mixtures. Compounds **1a**,[23] **1b-c**,[20] **1d**,[24] **1e**[25] and **5a-c**,[26] are known products and were identified by comparison of their physical and spectral data reported in the cited references.

Procedures

Procedure for the preparation of 1-(4-(3-(benzylamino)prop-1-yn-1-yl)phenyl)ethanone (1f).

To a solution of *N*-benzylprop-2-yn-1-amine (0.25 g, 1,72 mmol) in 3 mL of anhydrous THF were added diisopropyl amine (1.2 mL, 8.6 mmol), 4-iodoacetophenone (0.505 g, 2.06 mmol), $PdCl_2(PPh_3)_2$ (18,1 mg, 0.026 mmol) and CuI (9.8 mg, 0.051 mmol). The mixture was stirred at room temperature under N_2 atmosphere for 2 hours. Then the reaction mixture was diluted with ethyl acetate, washed with solution of NH_4Cl 0.5 M, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, *n*-hexane-EtOAc, 65:35 v/v) to afford the 1-(4-(3-(benzylamino)prop-1-yn-1-yl)phenyl)ethanone **1f** (385.0 mg, 85%) as brown oil; AT-IR: 3329, 3028, 2240, 1678, 1601, 1358, 1260, 833, 737, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.94-7.91 (m, 2H), 7.55-7.52 (m, 2H), 7.41-7.29 (m, 5H), 3.98 (s, 2H), 3.70 (s, 2H), 2.62 (s, 3H) 1.82 (bs, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.3, 139.3, 136.2, 131.78, 131.77, 131.8, 128.49, 128.48, 128.4, 128.2, 128.1, 127.2, 91.2, 83.1, 52.6, 38.3, 26.6 ppm; HRMS: *m*/*z* (MALDI-TOF) positive ion, calculated for $C_{18}H_{17}KNO$: $[M+K]^+$ 302.0947, Found: 302.0954.

Typical procedure for the preparation of *N*-benzyl-2-iodobenzamides (2a-f).

To a solution 0.25 mM of the propargylic amine[27] **1** (1 equiv.) in anhydrous dichloromethane (5 mL) were added at room temperature under N_2 atmosphere the 2-iodobenzoyl chloride (1.5 equiv.) and anhydrous triethylamine (2 equiv.). The reaction mixture was stirred under N_2 until complete consumption of the starting propargylic amine (monitored by TLC). Then the reaction mixture was diluted with ethyl acetate, washed with solution of NH_4Cl 0.5 M, dried over Na_2SO_4 and concentrated under

reduced pressure. The residue was purified by flash chromatography (silica gel, *n*-hexane-EtOAc) to afford the *N*-benzyl-2-iodobenzamides **2.**

***N*-(4-(4-acetylphenyl)-2-methylbut-3-yn-2-yl)-*N*-benzyl-2-iodobenzamide (2a)** **(**520.0 mg, 83%) as sticky solid; AT-IR: 2233, 1751, 1680, 1641, 1600, 1392, 1357, 1261, 842, 744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ **=** 7.84-7.82 (m, 2H), 7.78 (d, *J*=7.9, 1H), 7.34 – 7.27 (m, 2H), 7.26-7.18 (m, 7H), 6.95 (ddd, *J* = 7.9, 6.0, 3.1 Hz, 1H), 4.95 (d, *J* = 17.4 Hz, 1H), 4.53 (d, *J* = 17.4 Hz, 1H), 2.57 (s, 3H), 2.13 (s, 3H), 2.05 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ **=** 197.3, 171.4, 143.1, 139.0, 138.7, 136.1, 131.6, 130.0, 128.5, 128.2, 128.1, 127.6, 127.05, 127.02, 126.3, 96.1, 92.7, 84.0, 57.1, 52.8, 28.8, 27.6, 26.7 ppm; HRMS: *m*/*z* (MALDI-TOF) positive ion, calculated for $C_{27}H_{24}IKNO_2$: $[M+K]^+$ 560.0489, Found: 560.0486.

***N*-benzyl-2-iodo-N-(4-(4-methoxyphenyl)-2-methylbut-3-yn-2-yl)benzamide (2b)** (489.0 mg, 80%) as sticky solid; AT-IR: 2250, 1622, 1605, 1509, 1408, 1154, 972, 834, 764 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66 (ddd, *J* = 8.0, 1.0, 0.6 Hz, 1H), 7.20-7.16 (m, 2H), 7.13-7.08 (m, 3H), 7.06-7.03 (m, 2H), 6.98-6.94 (m, 2H), 6.84 (ddd, *J* = 8.0, 6.6, 2.7 Hz, 1H), 6.67-6.63 (m, 2H), 4.91 (d, *J* = 17.3 Hz, 1H), 4.38 (d, *J* = 17.3 Hz, 1H), 3.66 (s, 3H), 2.00 (s, 3H), 1.95 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.3, 159.6, 143.6, 139.1, 133.0, 129.8, 128.3, 128.1, 127.1, 126.9, 126.6, 114.8, 113.9, 92.8, 91.4, 85.0, 57.6, 55.3, 53.0, 29.1, 27.7 ppm; HRMS: *m*/*z* (MALDI-TOF) positive ion, calculated for $C_{26}H_{24}IKNO_2$: $[M+K]^+$ 548.0489, Found: 548.0489.

***N*-benzyl-2-iodo-N-(2-methyl-4-(4-(trifluoromethyl)phenyl)but-3-yn-2-yl)benzamide (2c)** (492.0 mg, 75%) as sticky solid; AT-IR: 2103, 1652, 1602, 1395, 1319, 1165, 1123, 841, 750, 727 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.71-7.69 (m, 1H), 7.41-7.38 (m, 2H), 7.24-7.08 (m, 9H), 6.88 (ddd, *J* = 8.0, 6.2, 2.9 Hz, 1H), 4.84 (d, *J* = 17.3 Hz, 1H), 4.43 (d, *J* = 17.3 Hz, 1H), 2.02 (s, 3H) 1.94 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.3, 143.2, 139.0, 138.8, 131.6, 129.80, 129.75 (q, $^{2}J_{CF}$ =32.6

Hz), 128.3, 128.0, 126.94, 126.90, 126.5 (q, $^{5}J_{CF}$ =1.4 Hz), 126.2, 124.9 (q, $^{3}J_{CF}$ =3.8Hz), 123.8 (q, $^{1}J_{CF}$ =272.1 Hz), 95.2, 92.5, 83.3, 57.0, 52.7, 28.7, 27.4 ppm; HRMS: *m*/*z* (MALDI-TOF) positive ion, calculated for $C_{26}H_{21}F_3INNaO_2$: $[M+Na]^+$ 586.0467, Found: 586.0459.

***N*-benzyl-2-iodo-*N*-(1-(oct-1-yn-1-yl)cyclohexyl)benzamide (2d)** (520.0 mg, 76%) as pale yellow oil; AT-IR: 2927, 2860, 1647, 1392, 1247, 1616, 724, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67 (d, *J* = 7.9 Hz, 1H), 7.18-7.14 (m, 2H), 7.11-7.01 (m, 4H), 6.96 (m, 1H), 6.83 (td, *J* = 7.7, 1.6 Hz, 1H), 4.94 (d, *J* = 17.3 Hz, 1H), 4.31 (d, *J* = 17.3 Hz, 1H), 2.95 – 2.70 (m, 2H), 2.01-1.66 (m, 4H), 1.63 – 1.51 (m, 5H), 1.26-1.11 (m, 9H), 0.79 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.4, 144.0, 139.6, 138.9, 129.4, 128.0, 127.9, 126.9, 126.6, 126.4, 92.5, 89.4, 80.6, 63.3, 52.7, 34.7, 33.7, 31.3, 28.5, 28.4, 24.9, 24.1, 23.9, 22.5, 18.8, 14.0 ppm; HRMS: *m*/*z* (MALDI-TOF) positive ion, calculated for $C_{28}H_{34}IKNO$: $[M+K]^+$ 566.1322, Found: 566.1320.

***N*-benzyl-*N*-(1,3-diphenylprop-2-yn-1-yl)-2-iodobenzamide (2e)** complex mixture of four slowly interconverting amide geometric 1S,1E/1S,1Z and 1R,1E/1R,1Z isomers; see supplementary; (442.0 mg , 70%) as viscous oil; AT-IR:1639, 1600, 1401, 750, 686 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.94, 7.92, 7.81, 7.79, 7.64, 7.60, 7.58, 7.54, 7.53, 7.48, 7.47, 7.31, 7.30, 7.25, 7.18, 7.06, 7.04, 6.97, 6.95, 6.91, 6.87, 6.85, 6.80, 6.78, 6.76, 5.79, 5.72, 5.11, 4.91, 4.87, 4.79, 4.76, 4.45, 4.41, 4.35, 4.31, 4.26 ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.1, 170.6, 141.7, 141.4, 140.2, 139.92, 139.88, 138.9, 138.0, 137.7, 137.2, 136.3, 135.1, 133.0, 131.7, 131.6, 131.0, 130.6, 130.3, 129.9, 129.8, 129.1, 128.9, 128.7, 128.4, 128.3, 128.2, 127.8, 127.7, 127.54, 127.48, 126.8, 126.7, 122.5, 93.1, 92.3, 88.1, 87.4, 85.3, 56.2, 55.3, 50.2, 49.8, 47.1, 46.4 ppm; HRMS: *m*/*z* (MALDI-TOF) positive ion, calculated for $C_{29}H_{22}IKNO$: $[M+K]^+$ 566.0383, Found: 566.0385.

***N*-(3-(4-acetylphenyl)prop-2-yn-1-yl)-*N*-benzyl-2-iodobenzamide (2f)** Mixture of two slowly interconverting geometric *E*/*Z* isomers; (414.0 mg, 70%) as viscous oil; AT-IR 3064, 3029, 1681, 1643, 1600, 1414, 1359, 1260, 747, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83-7.82 (m, 2H + 2H), 7.77 (ddd, *J*=8.0, 2.4, 0.8 Hz, 1H+1H), 7.46-7.40 (m, 2H + 2H), 7.38-7.21 (m, 6H + 6H), 7.16-7.13 (m, 1H + 1H), 7.04-6.97 (m, 1H + 1H), 5.19 (d, *J*=14.4 Hz, 1H), 4.86 (d, *J*=16.5 Hz, 1H), 4.59 (d, *J*=14.4 Hz, 1H), 4.45 (d, *J*=17.9 Hz, 2H), 4.09 (d, *J*=16.5 Hz, 1H), 3.91 (s, 2H), 2.51 (s, 3H), 2.50 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.2, 197.1, 170.6, 170.4, 141.6, 141.3, 139.45, 139.36, 136.6, 136.4, 136.0, 135.4, 131.9, 131.8, 130.6, 130.5, 129.0, 128.9, 128.7, 128.44, 128.38, 128.25, 128.23, 128.1, 127.9, 127.7, 127.6, 127.5, 127.3, 127.0, 92.8, 92.5, 87.0, 86.6, 84.3, 83.5, 51.7, 47.5, 38.5, 34.0, 26.6 ppm; HRMS: *m*/*z* (MALDI-TOF) positive ion, calculated for $C_{25}H_{20}IKNO_2$: $[M+K]^+$ 532.0176, Found: 532.0175.

Typical Procedure for the preparation of-2-benzyl-3,4-dihydroisoquinolin-1(2H)-ones (4): preparation of (*Z*)-4-((4-acetylphenyl)(phenyl)methylene)-2-benzyl-3,3-dimethyl-3,4-dihydroisoquinolin-1(2H)-one (4aa)

To a stirred solution 0.2 M of *N*-(4-(4-acetylphenyl)-2-methylbut-3-yn-2-yl)-*N*-benzyl-2-iodobenzamide **2a** (100 mg, 0.19 mmol) in EtOH (1 mL), were added phenylboronic acid **3a** (34.7 mg, 0.285 mmol) and K_3PO_4 (120.9 mg, 0.57 mmol); after 5 min stirring at room temperature $PdCl_2$ (2 mg, 0.0095 mmol) was added. The mixture was stirred at 79 °C under N_2 atmosphere and stirring was continued at that temperature until complete consumption of the starting propargylamide **2a** (monitored by TLC). Then the reaction mixture was cooled to room temperature, diluted with ethyl acetate (EtOAc), washed with solution of NH_4Cl 0.5 M, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, *n*-hexane-EtOAc, 70:30 v/v) to afford the dihydroisoquinolin-1(2H)-one **4aa** (82.0 mg, 91%) as colourless powder; mp 147-149 °C; AT-IR: 1690, 1640,1594, 1356, 700 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.77-7.75 (m, 2H), 7.22-7.11 (m, 8H), 7.01-6.95 (m, 4H), 6.85-6.83 (m, 2H), 6.71 (dd, *J* = 7.8, 0.9 Hz, 1H), 4.88 (bs, 2H), 2.50 (s, 3H), 1.10 (s, 6H) ppm; ^{13}C NMR (101 MHz, CDCl3) δ = 197.5, 165.8, 148.9, 143.7, 139.8, 139.7, 138.4, 137.8, 135.7, 131.1, 131.0, 130.6, 129.5, 128.5, 128.2, 128.1, 127.6, 127.4, 127.1, 126.85, 126.76, 62.9, 45.1, 29.0, 26.6 ppm; HRMS: *m*/*z* (MALDI-TOF) positive ion, calculated for $C_{33}H_{29}KNO_2$: $[M+K]^+$ 510.1835, Found: 510.1835.

(*E*)-4-((4-acetylphenyl)(3-methoxyphenyl)methylene)-2-benzyl-3,3-dimethyl-3,4-dihydroisoquinolin-1(2H)-one (4ab) (79.0 mg, 84%) as colourless powder; mp 151-153 °C; AT-IR:1685, 1639, 1594, 1271, 710 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.76-7.74 (m, 2H), 7.22-7.19 (m, 8H), 7.00 (td, *J* = 7.6, 1.3 Hz, 1H), 6.91 (t, *J* = 7.9 Hz, 1H), 6.78 (ddd, *J* = 7.8, 1.1, 0.5 Hz, 1H), 6.56 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 6.44 (ddd, *J* = 7.7, 1.6, 1.0 Hz, 1H), 6.37 (dd, *J* = 2.6, 1.6 Hz, 1H), 4.88 (bs, 2H), 3.50 (s, 3H), 2.50 (s, 3H), 1.09 (s, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.5, 165.9, 159.2, 148.8, 144.9, 139.7, 139.6, 138.5, 137.8, 135.8, 130.9, 130.7, 129.5, 129.1, 128.5, 128.2, 127.7, 127.4, 126.9, 126.8, 123.6, 116.7, 112.6, 62.9, 55.2, 45.1, 29.0, 26.6 ppm; HRMS: *m*/*z* (MALDI-TOF) positive ion, calculated for $C_{34}H_{31}NNaO_3$: $[M+Na]^+$ 524.2202, Found: 524.2210.

(*E*)-4-((4-acetylphenyl)(4-fluorophenyl)methylene)-2-benzyl-3,3-dimethyl-3,4-dihydroisoquinolin-1(2H)-one (4ac) (71.0 mg, 76%) as colourless powder; mp 145-147 °C; AT-IR: 1685, 1640, 1599, 1503, 1397, 1362, 1261, 837 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00 (ddd, *J* = 7.8, 1.4, 0.5 Hz, 1H), 7.78-7.76 (m, 2H), 7.23-7.19 (m, 5H), 7.16-7.09 (m, 3H), 7.02 (td, *J* = 7.6, 1.4 Hz, 1H), 6.80 (dd, *J* = 9.0, 5.4 Hz, 2H), 6.72-6.67 (m, 3H), 4.87 (bs, 2H), 2.50 (s, 3H), 1.09 (s, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.4, 165.7, 161.7 (d, $^{1}J_{CF}$ =248.3 Hz), 148.6, 139.7, 139.6, 138.6, 138.23, 138.15 (d, $^{4}J_{CF}$ =0.7 Hz), 135.9, 132.6 (d, $^{3}J_{CF}$ =8.1 Hz), 131.0, 130.7, 130.1, 129.5,

128.4, 128.2, 127.7, 127.5, 126.82, 126.75, 115.2 (d, $^2J_{CF}$ =21.5 Hz), 62.9, 45.1, 28.9, 26.6 ppm; HRMS: *m*/*z* (MALDI-TOF) positive ion, calculated for $C_{33}H_{28}FKNO_2$: $[M+K]^+$ 528.1741, Found: 528.1738.

(*E*)-*N*-(3-((4-acetylphenyl)(2-benzyl-3,3-dimethyl-1-oxo-2,3-dihydroisoquinolin-4(1H)ylidene)methyl)phenyl)acetamide (4ad) (85.0 mg, 85%) as pale yellow powder; mp 163-165 °C; AT-IR: 3266, 1693, 1676, 1623, 1598, 1266, 705 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.93 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.73-7.71 (m, 2H), 7.56 (s, 1H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.20-7.08 (m, 7H), 6.99 (td, *J* = 7.6 1.4 Hz, 1H), 6.93 (t, *J* = 7.9 Hz, 1H), 6.88 (s, 1H), 6.78 (d, *J* = 7.7 Hz, 1H), 6.57 (d, *J* = 7.8 Hz, 1H), 4.86 (bs, 2H), 2.47 (s, 3H), 1.96 (s, 3H), 1.08 (s, 6H) ppm;^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.6, 168.5, 166.0, 148.5, 144.3, 139.5, 139.4, 138.3, 138.2, 137.9, 135.8, 131.01, 130.9, 129.8, 129.5, 128.9, 128.5, 128.2, 127.8, 127.3, 126.8, 126.6, 121.8, 118.7, 63.0, 45.1, 28.9, 26.6, 24.5 ppm; HRMS: *m*/*z* (MALDI-TOF) positive ion, calculated for $C_{35}H_{32}KN_2O_3$: $[M+K]^+$ 567.2050, Found: 567.2052.

(*E*)-4-((4-acetylphenyl)(4-(dimethylamino)phenyl)methylene)-2-benzyl-3,3-dimethyl-3,4-dihydroisoquinolin-1(2H)-one (4ae) (86.0 mg, 88%)as yellow powder; mp 179-181; AT-IR: 1739, 1636, 1603, 1519, 1360, 816, 713 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.98 (ddd, *J* = 7.7, 1.5, 0.5 Hz, 1H), 7.76-7-74 (m, 2H), 7.20-7.09 (m, 8H), 7.03 (td, *J* = 7.6, 1.5 Hz, 1H), 6.82 (ddd, *J* = 7.8, 1.2, 0.6 Hz, 1H), 6.64-6.62 (m, 2H), 6.32-6.29 (m, 2H), 4.88 (bs, 2H), 2.79 (s, 6H), 2.50 (s, 3H), 1.08 (s, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.6, 166.1, 149.9, 149.3, 140.1, 139.8, 139.5, 135.6, 135.3, 132.4, 131.3, 130.7, 129.89, 129.86, 129.3, 128.4, 128.0, 127.2, 127.0, 126.8, 126.6, 111.5, 63.1, 45.1, 40.2, 28.9, 26.6 ppm; HRMS: *m*/*z* (MALDI-TOF) positive ion, calculated for $C_{35}H_{34}KN_2O_2$: $[M+K]^+$ 553.2257, Found: 553.2254.

(*E*)-4-((4-acetylphenyl)(3,5-dimethylphenyl)methylene)-2-benzyl-3,3-dimethyl-3,4-dihydroisoquinolin-1(2H)-one (4af) (74.0 mg, 78%) as colourless powder; mp

146-149 °C; AT-IR: 1681, 1640, 1599, 1261, 799 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.99 (ddd, *J* = 7.8, 1.4, 0.5 Hz, 1H), 7.76-7.74 (m, 2H), 7.22-7.11 (m, 8H), 6.98 (td, *J* = 7.6, 1.4 Hz, 1H), 6.74 (ddd, *J* = 7.8, 1.2, 0.6 Hz, 1H), 6.64 (bs, 1H), 6.43 (bs, 2H), 4.87 (bs, 2H), 2.50 (s, 3H), 2.00 (s, 6H), 1.08 (s, 6H) ppm;^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.6, 166.0, 149.1, 143.4, 140.0, 139.7, 138.6, 137.5, 137.2, 135.7, 131.0, 130.5, 129.8, 129.4, 128.9, 128.6, 128.4, 128.1, 127.4, 127.3, 126.9, 126.7, 62.9, 45.2, 29.0, 26.6, 21.2 ppm; HRMS: *m*/*z* (MALDI-TOF) positive ion, calculated for $C_{35}H_{33}KNO_2$: $[M+K]^+$ 538.2148, Found: 538.2140.

(*E*)-3-((4-acetylphenyl)(2-benzyl-3,3-dimethyl-1-oxo-2,3-dihydroisoquinolin-4(1H)-ylidene)methyl)benzonitrile (4ag) (54.0 mg, 57%) as colourless powder; mp 159-161°C; AT-IR: 2228, 1685, 1643, 1597, 1385, 1267, 776, 695 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.04 (ddd, *J* = 7.8, 1.4, 0.4 Hz, 1H), 7.80-7.78 (m, 2H), 7.31 (ddd, 6.6, 2.2, 1.6 Hz, 1H), 7.27 – 7.08 (m, 11H), 7.02 (td, *J* = 7.6, 1.4 Hz, 1H), 6.62 (ddd, *J* = 7.8, 1.1, 0.6 Hz, 1H), 4.87 (bs, 2H), 2.52 (s, 3H), 1.10 (s, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.3, 165.5, 147.5, 145.0, 140.0, 139.5, 137.33, 137.28, 136.3, 135.3, 134.2, 131.05, 130.96, 130.7,130.2, 129.6, 129.0, 128.54, 128.51, 128.4, 127.9, 126.9, 118.3, 112.5, 63.0, 45.2, 29.7, 28.9, 26.6 ppm; HRMS: *m*/*z* (MALDI-TOF) positive ion, calculated for $C_{34}H_{28}KN_2O_2$: $[M+K]^+$ 535.1788, Found: 535.1787.

(*E*)-4-((4-acetylphenyl)(3-(trifluoromethyl)phenyl)methylene)-2-benzyl-3,3-dimethyl-3,4-dihydroisoquinolin-1(2H)-one (4ah) (62.0 mg, 61%) as colourless powder; mp 161-163 °C; AT-IR 1683, 1630, 1597, 1257, 779, 672 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02 (ddd, *J* = 7.8, 1.4, 0.5 Hz, 1H), 7.79-7.77 (m, 2H), 7.28-7.01 (m, 12H), 6.98 (td, *J* = 7.6, 1.4 Hz, 1H), 6.61 (ddd, *J* = 7.8, 1.2, 0.5 Hz, 1H), 4.88 (bs, 2H), 2.51 (s, 3H), 1.10 (s, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 196.4, 164.6, 146.8, 143.4, 138.5, 138.4, 137.0, 136.6, 135.1, 133.2 (q, $^{4}J_{CF}$ =1.2 Hz), 129.9, 129.8, 129.6 (q, $^{2}J_{CF}$ =32.4 Hz), 129.0, 128.6, 127.6, 127.5, 127.3, 127.1, 126.7, 126.4 (q, $^{3}J_{CF}$ =3.8

Hz), 125.9, 125.8, 122.8 (q, $^{3}J_{CF}$ =3.7 Hz), 122.6 (q, $^{1}J_{CF}$ =272.5 Hz), 61.9, 44.2, 27.9, 25.6 ppm; HRMS: *m*/*z* (MALDI-TOF) positive ion, calculated for $C_{34}H_{28}F_3KNO_2$: $[M+K]^+$ 578.1709, Found: 578.1715.

(*E*)-4-((4-acetylphenyl)(3-chloro-4-fluorophenyl)methylene)-2-benzyl-3,3-dimethyl-3,4-dihydroisoquinolin-1(2H)-one (4ai) (68.0 mg, 68%) as colourless powder; mp 148-150 °C; AT-IR: 1685, 1644, 1599, 1260, 801 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.03 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.79-7.77 (m, 2H), 7.25 (td, *J* = 7.6, 1.0 Hz, 1H), 7.24 – 7.09 (m, 7H), 7.06 (td, *J* = 7.6, 1.3 Hz, 1H), 6.84 (dd, *J* = 7.0, 2.2 Hz, 1H), 6.76 (t, *J* = 8.5 Hz, 1H), 6.71- 6.67 (m, 2H), 4.87 (bs, 2H), 2.51 (s, 3H), 1.08 (s, 6H) ppm;^{13}C NMR (101 MHz, $CDCl_3$) δ = 196.3, 164.6, 156.0 (d, $^{1}J_{CF}$ =251.0 Hz), 146.9, 139.7 (d, $^{4}J_{CF}$ =4.2 Hz), 138.5, 138.1, 136.7, 136.3, 135.1, 131.7, 130.0, 129.9, 129.8 (d, $^{3}J_{CF}$ =7.1 Hz), 129.0, 128.5, 127.5, 127.4, 127.1, 126.7, 125.9, 125.8, 119.9 (d, $^{2}J_{CF}$ =18.0 Hz), 115.3 (d, $^{2}J_{CF}$ =21.2 Hz), 61.9, 44.2, 27.9, 25.6 ppm; HRMS: m/z (MALDI-TOF) positive ion, calculated for $C_{33}H_{27}ClFKNO_2$: $[M+K]^+$ 562.1351, Found: 562.1354.

(*E*)-2-benzyl-4-((4-methoxyphenyl)(4-(trifluoromethyl)phenyl)methylene)-3,3-dimethyl-3,4-dihydroisoquinolin-1(2H)-one (4cj) (85.0 mg, 95%) as colourless powder; mp 165-167 °C; AT-IR: 1637, 1594, 1320, 1126, 773, 713, 696 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00 (ddd, *J* = 7.8, 1.5, 0.6 Hz, 1H), 7.42-7.40 (m, 2H), 7.22-7.12 (m, 8H), 7.00 (td, *J* = 7.6, 1.3 Hz, 1H), 6.91 (t, *J* = 8.0 Hz, 1H), 6.78 (ddd, *J* = 7.8, 1.2, 0.6 Hz, 1H), 6.56 (ddd, *J* = 8.3, 2.6, 0.8 Hz, 1H), 6.43 (ddd, *J* = 7.6, 1.6, 0.9 Hz, 1H), 6.36 (dd, *J* = 2.4, 1.7 Hz, 1H), 4.88 (bs, 2H), 3.50 (s, 3H), 1.08 (s, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.7, 158.2, 146.3 (q, $^{5}J_{CF}$ = 1.4 Hz), 143.9, 138.7, 138.1, 137.4, 137.1, 129.8, 129.7, 128.8, 128.5, 128.3 (q, $^{2}J_{CF}$ = 32.4 Hz), 128.1, 127.4, 126.7, 126.4, 125.9, 125.8, 124.0 (q, $^{3}J_{CF}$ = 3.5 Hz), 123.0 (q, $^{1}J_{CF}$ = 272.3 Hz), 122.5, 115.7, 111.5, 61.9, 54.1, 44.1, 28.0 ppm; HRMS: *m*/*z* (MALDI-TOF) positive ion, calculated for $C_{33}H_{28}F_3KNO_2$: $[M+K]^+$ 566.1709, Found: 566.1711.

(*E*)-2'-benzyl-4'-(1-phenylheptylidene)-2',4'-dihydro-1'H-spiro[cyclohexane-1,3'-isoquinolin]-1' (*4'H*)-one (4da) (47.0 mg, 52%) as yellow oil; AT-IR 3062, 3031, 1638, 1597, 1454, 1389, 1258, 768, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.85 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.32-7.30 (m, 3H), 7.25-7.18 (m, 4H), 7.16-7.09 (m, 1H), 7.03 (td, *J* = 7.6, 1.1 Hz, 1H), 6.98 (t, *J* = 8.7 Hz, 1H), 6.81 (td, *J* = 7.6, 1.3 Hz, 1H), 6.31-6.29 (m, 2H), 4.99 (d, *J* = 15.0 Hz, 1H, CH_2 AB system), 4.94 (d, *J* = 15.0 Hz, 1H, CH_2 AB system), 2.81-2.54 (m, 2H), 2.20-1.59 (m, 7H), 1.27-1.17 (m, 4H), 1.11-0.83 (m, 9H), 0.74 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.5, 144.9, 142.8, 140.9, 140.1, 131.9, 131.2, 131.1, 130.7, 129.9, 128.9, 128.5, 128.4, 127.5, 126.8, 126.7, 126.0, 125.8, 65.8, 44.7, 39.4, 35.7, 33.0, 31.5, 29.5, 28.1, 25.8, 24.9, 23.8, 22.6, 14.0 ppm; HRMS: *m*/*z* (MALDI-TOF) positive ion, calculated for $C_{34}H_{39}KNO$: $[M+K]^+$ 516.2669, Found: 516.2667.

(*E*)-2'-benzyl-4'-(1-(3-methoxyphenyl)heptylidene)-2',4'-dihydro-1'H-spiro[cyclohexane-1,3'-isoquinolin]-1'(*4'H*)-one (4db) (54.0 mg, 56%) as yellow oil; AT-IR 3067, 3036, 1641, 1599, 1455, 1392, 1283, 1261, 769, 725, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.86 (bs, 1H), 7.32 – 7.30 (m, 2H), 7.23 (t, *J* = 7.5 Hz, 2H), 7.19 (s, 1H), 7.15 (t, *J* = 7.2 Hz, 1H), 7.05 (t, *J* = 8.2 Hz, 2H), 6.85 (td, *J* = 7.5, 1.0 Hz, 1H), 6.55 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.43-6.40 (m, 1H), 6.37-6.35 (m, 1H), 4.96 (bs, 2H), 3.70 (s, 3H), 2.79-2.55 (m, 2H), 2.18-2.16 (m, 1H), 1.95-1.44 (m, 7H), 1.26-1.00 (m, 10H), 0.75 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.5, 161.00, 156.87, 146.26, 140.95, 140.04, 130.56, 130.10, 128.63, 128.47, 127.48, 126.83, 126.72, 126.04, 107.75, 106.37, 101.50, 65.8, 55.2, 44.7, 39.5, 35.7, 33.0, 31.5, 29.5, 28.2, 25.8, 24.9, 23.8, 22.6, 14.0 ppm; HRMS: *m*/*z* (MALDI-TOF) positive ion, calculated for $C_{35}H_{41}KNO_2$: $[M+K]^+$ 546.2774, Found: 546.2771.

(*Z*)-2-benzyl-4-((3-methoxyphenyl)(phenyl)methylene)-3-phenyl-3,4-dihydroisoquinolin-1(2H)-one (4eb) (84.0 mg, 88%) a colourless solid; mp 151-153;

AT-IR: 3069, 3034, 1649, 1599, 1262, 762, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.07 (d, *J* = 7.8 Hz, 1H), 7.40 -7.06 (m, 11H), 7.00-6.96 (m, 2H), 6.91-6.88 (m, 2H), 6.80-6.70 (m, 3H), 6.64-6.47 (m, 4H), 5.65 (d, *J* = 14.8 Hz, 1H), 5.02 (s, 1H), 3.51 (s, 3H), 3.48 (d, *J* = 14.8 Hz, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.0, 159.4, 142.5, 142.2, 140.7, 139.4, 137.4, 135.8, 130.8, 130.5, 129.7, 129.5, 129.3, 128.8, 128.7, 128.63, 128.60, 128.5, 128.30, 128.27, 128.2, 128.2, 127.9, 127.8, 127.38, 127.36, 127.1, 126.8, 122.7, 115.7, 113.0, 62.0, 55.1, 48.5 ppm; HRMS: *m*/*z* (MALDI-TOF) positive ion, calculated for $C_{36}H_{29}KNO_2$: $[M+K]^+$ 546.1835, Found: 546.1835.

(*E*)-4-((4-acetylphenyl)(4-methoxyphenyl)methylene)-2-benzyl-3,4-dihydroisoquinolin-1(2H)-one (4fj) (75.0 mg, 92%); Colourless solid; mp 143-144; AT-IR: 3066, 3036, 1689, 1653, 1603, 1511, 1246, 768, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.05 (d, *J*= 7.8 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.22 (td, *J* = 7.7, 0.9 Hz, 1H), 7.09-7.03 (m, 6H), 6.96 (d, *J* = 8.2 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.77 (d, J = 7.8 Hz, 1H), 6.68-6.60 (m, 2H), 4.57 (s, 2H), 3.96 (s, 2H), 3.70 (s, 3H), 2.53 (s, 3H) ppm;^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.4, 164.0, 159.4, 146.4, 140.8, 137.1, 136.9, 136.2, 132.8, 132.1, 130.6, 129.8, 128.5, 128.4, 128.2, 127.9, 127.3, 127.0, 113.9, 55.2, 50.3, 50.1, 26.6 ppm; HRMS: *m*/*z* (MALDI-TOF) positive ion, calculated for $C_{32}H_{27}KNO_3$: $[M+K]^+$ 512.1628, Found: 512.1628.

(*E*)-4-((4-acetylphenyl)(4-fluorophenyl)methylene)-2-benzyl-3,4-dihydroisoquinolin-1(2H)-one (4fc) (70.0 mg, 80%) as colourless solid; mp 139-140; AT-IR: 1679, 1645, 1599, 1505, 1261, 763, 628 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.06 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.77-7.75 (m, 2H), 7.24 (ddd, *J* = 7.8, 1.0, 0.5 Hz, 1H), 7.10-7.06 (m, 3H), 7.05-7.01 (m, 3H), 6.95-6.93 (m, 2H), 6.92-6.88 (m, 2H), 6.83-6.79 (m, 2H), 6.70 (dd, *J* = 7.9, 0.6 Hz, 1H), 4.57 (s, 2H), 3.97 (s, 2H), 2.53 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 196.4, 162.9, 161.4 (d, $^{1}J_{CF}$ = 248.7 Hz), 144.8, 139.0, 135.7, 135.6, 135.5 (d, $^{4}J_{CF}$ = 3.5 Hz), 135.3, 131.5 (d, $^{3}J_{CF}$ = 8.1 Hz), 129.7, 128.8,

128.7, 127.5, 127.32, 127.30, 127.23, 127.21 (d, $^5J_{CF}$ = 0.7 Hz), 126.9, 126.3, 114.6 (d, $^2J_{CF}$ = 21.5 Hz), 49.2, 49.1, 25.6 6 ppm; HRMS: *m*/*z* (MALDI-TOF) positive ion, calculated for $C_{31}H_{24}FKNO_2$: $[M+K]^+$ 500.1428, Found: 500.1435.

General procedure for the preparation of indole substituted dihydroisoquinolin-1(2H)-ones 6

To a stirred solution of propargylic amide **2** (0.1 mmol) in MeCN (2 mL) were added 2-alkynyltrifluoroacetylanilide **5** (0.12 mmol) and K_2CO_3 (0.3 mmol); after 5 min stirring at room temperature, $Pd(PPh_3)_4$ (0.005 mmol) was added. The mixture was stirred at 80 °C under N_2 atmosphere until complete consumption of the starting propargylic amide (monitored by TLC). Then the reaction mixture was cooled to room temperature, diluted with ethyl acetate, washed with 0.5 M solution of NH_4Cl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, *n*-hexane-EtOAc, 80:20-50:50 v/v) to afford the desired dihydroisoquinolin-1(2H)-one **6**.

(*E*)-2-benzyl-4-((4-methoxyphenyl)(2-phenyl-1H-indol-3-yl)methylene)-3,3-dimethyl-3,4-dihydroisoquinolin-1(2H)-one (6ba) (40.0 mg, 70%) as pale yellow powder; mp 186-188 °C; AT-IR: 3279, 1630, 1599, 1507, 1248, 1029, 769, 744, 693 cm^{-1}; ^{1}H NMR (400 MHz, CDCl3) δ = 7.88 (s, 1H), 7.58 (dd, *J* = 7.7, 0.8 Hz, 1H), 7.37 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.22 (dd, *J* = 6.7, 5.4 Hz, 2H), 7.20-7.10 (m, 8H), 7.06-6.99 (m, 4H), 6.97-6.91 (m, 1H), 6.88 (t, *J* = 7.5 Hz, 1H), 6.80 (td, *J* = 8.3, 2.0 Hz, 2H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.66 (dd, *J* = 8.5, 2.7 Hz, 1H), 4.86 (d, *J* = 16.2 Hz, 1H), 4.47 (d, *J* = 16.2 Hz, 1H), 3.73 (s, 3H), 1.20 (s, 3H), 1.12 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.1, 159.0, 140.3, 140.1, 137.0, 136.8, 136.3, 135.9, 133.4, 132.1, 131.8, 130.6,

129.9, 129.8, 129.3, 128.7, 128.4, 128.3, 128.1, 127.6, 127.3, 126.8, 126.5, 126.22, 126.18, 122.1, 120.4, 113.9, 112.7, 110.8, 63.4, 55.2, 45.8, 29.7, 28.3 ppm; HRMS: *m*/*z* (MALDI-TOF) positive ion, calculated for $C_{40}H_{34}N_2O_2$: $[M]^+$ 574.2620, Found: 574.2614.

(*E*)-4-((4-acetylphenyl)(2-phenyl-1H-indol-3-yl)methylene)-2-benzyl-3,4-dihydroisoquinolin-1(2H)-one (6fa) (49.0 mg, 89%) as yellow powder; mp 210-211 °C; AT-IR: 3243, 3070, 1680, 1630, 1599, 1268, 741,698 cm^{-1}; ^1H NMR (400 MHz, CDCl3) δ = 8.25 (s, 1H), 7.76-7.73 (m, 2H), 7.67 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 7.23-7.16 (m, 2H), 7.11-6.96 (m, 12H), 6.90-6.82 (m, 3H), 6.75 (dd, *J* = 7.9, 0.7 Hz, 1H), 4.76 (d, *J* = 14.7 Hz, 1H, AB system), 4.26 (d, *J* = 14.7 Hz, 1H), 4.16 (d, *J* = 13.1 Hz, 1H, AB system), 4.10 (d, *J* = 13.1 Hz, 1H, AB system), 2.52 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.5, 163.3, 145.8, 138.2, 137.1, 136.9, 136.2, 136.0, 133.8, 131.7, 130.3, 129.7, 129.1, 129.0, 128.8, 128.41, 128.39, 128.17, 128.16, 128.1, 127.7, 127.29, 127.27, 126.8, 126.4, 122.6, 120.5, 119.8, 112.5, 111.0, 49.9, 49.7, 26.6 ppm; HRMS: *m*/*z* (MALDI-TOF) positive ion, calculated for $C_{39}H_{30}N_2NaO_2$: $[M+Na]^+$ 581.2205, Found: 581.2207.

(*E*)-4-((4-acetylphenyl)(2-(thiophen-2-yl)-1H-indol-3-yl)methylene)-2-benzyl-3,4-dihydroisoquinolin-1(2H)-one (6fb) (49.0 mg, 83%) as yellow solid; mp 159-160 °C; AT-IR: 3217, 1682, 1631, 1599, 1265, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.12 (s, 1H), 7.81 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 1H), 7.20-7.15 (m, 3H), 7.11-7.02 (m, 7H), 6.99-6.94 (m, 1H), 6.91-6.83 (m, 2H), 6.78 – 6.72 (m, 2H), 6.69 (dd, *J* = 3.6, 1.2 Hz, 1H), 4.87 (d, J = 14.4 Hz, 1H), 4.23 (d, J = 14.4 Hz, 1H), 4.21 (s, 2H), 2.53 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.6, 163.5, 145.6, 137.7, 137.0, 136.2, 136.0, 133.3, 132.9, 130.5, 130.3, 130.00, 129.6, 129.2, 129.0, 128.5, 128.4, 128.2, 127.75, 127.71, 127.4, 127.3, 126.3, 126.1, 124.9, 123.1,

120.8, 119.6, 113.3, 110.9, 50.0, 49.7, 26.6 ppm; HRMS: *m*/*z* (ESI) positive ion, calculated for $C_{37}H_{29}N_2O_2S$: $[M+H]^+$ 565.1950, Found: 565.1952.

(*E*)-4-((4-acetylphenyl)(2-((E)-cyclooct-1-en-1-yl)-1H-indol-3-yl)methylene)-2-benzyl-3,4-dihydroisoquinolin-1(2H)-one (6fc) (47.0 mg, 79%) as orange solid; mp 155-156 °C; AT-IR: 3523, 3242, 1674, 1633, 1600, 1266, 732, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.98 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.86 (s, 1H) 7.84 (dd, *J* = 8.6, 1.8 Hz,1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.21-7.16 (m, 2H), 7.13-7.06 (m, 3H), 7.05-6.96 (m, 5H), 6.89 (td, *J* = 7.6, 1.4 Hz, 1H), 6.78 (d, *J* = 0.7 Hz, 2H), 6.73 (dd, *J* = 7.6, 0.7 Hz, 1H), 5.55 (t, *J* = 8.2 Hz, 1H), 4.82 (d, *J* = 14.6 Hz, 1H), 4.36 (d, J = 14.6 Hz, 1H), 4.18 (s, 2H), 2.53 (s, 3H), 2.23-2.08 (m, 1H), 2.04-1.93 (m, 1H), 1.89-1.77 (m, 2H), 1.49 (d, *J* = 5.9 Hz, 2H), 1.41-1.14 (m, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.5, 163.9, 145.8, 139.1, 138.7, 137.0, 136.2, 135.0, 134.7, 132.7, 131.4, 130.6, 129.8, 129.3, 128.9, 128.7, 128.4, 128.2, 128.0, 127.8, 127.3, 127.2, 126.7, 122.0, 120.2, 119.3, 111.6, 110.5, 50.0, 49.7, 31.6, 29.4, 27.3, 26.8, 26.6, 26.5, 25.7 ppm; HRMS: *m*/*z* (MALDI-TOF) positive ion, calculated for $C_{41}H_{38}N_2O_2$: $[M]^+$ 590.2933, Found: 590.2935.

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Supporting Information

Supporting Information File 1: copy of ^1H and ^{13}C NMR spectra of all new compounds. 2D NOESY experiments.

File Name: Supporting

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