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Synthesis and Reactivity of Oxazinoindolones *via* Regioselective 6-*exo-dig* Iodolactonization Reaction

Sokaina Hammoud,^[a] Elsa Anselmi,^[a, b] Khalil Cherry,^[c] Jean-Claude Kizirian,^[a] and Jérôme Thibonnet*^[a]

Abstract: An efficient protocol for facile construction of 3,4-dihydro-10-iodo-3-iodomethylene-[1,4]-oxazino[4,3-*a*]indol-1-ones has been developed by using a regio- and stereoselective iodolactonization reaction. Subsequent palladium cross-coupling reactions of 3,4-dihydro-10-iodo-3-iodomethylene-[1,4]-oxazino[4,3-*a*]indol-1-ones readily afforded functionalized oxazinoindolones.

Introduction

Substituted N-fused indole moieties are important heterocyclic molecules that are present in a large number of natural products, pharmaceuticals, alkaloids, and agrochemicals and exhibit potent and wide-ranging biological activity.^[1] In particular, indole-fused oxazinones gained considerable attention in recent years because of their great importance in biological sciences and they are also of interest in the field of optoelectronic materials.^[2] There are various tricyclic oxazinoindolones among which are the structures **A**, **B** or **C** (Figure 1). Substituted 3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indol-1-ones **C** have attracted much attention due to the broad scope of their biological activities. They are mainly 1,2-fused system types with six-membered rings fused to indoles with substituents on C3, C8 and C10. For example, a recent patent reported the effectiveness of the corresponding oxazinoindolone **1** as an anticancer agent.^[3] Oxazinoindolones **2** and **3** showed anti-inflammatory^[4] and herbicidal activities,^[5] respectively (Figure 1). Moreover, oxazinoindolones can be used as intermediates in the chemistry of bioactive compounds.^[6] Also, 1,2-fused oxazinoindolones have rarely been described in the literature and much less than the 2,3-fused system. So, we envisioned that the incorporation of the indole moiety into the oxazinone scaffold may lead to potentially bioactive molecules. The exploration of new methodologies that allow rapid access to these N-fused polycyclic indole scaffolds remains an important challenge facing organic chemists.

Synthetic methods for access to this kind of structure include lactonization from the ester or acid indoles,^[7] transesterification,^[3,8] Friedel-Crafts alkylation,^[9] cyclodehydration from the free-NH indole,^[10] aza-Michael addition,^[11] copper catalyzed cyclization,^[12] hydroamination^[13] of the acid system and more recently by gold catalyzed cyclization of the carboxylic acid.^[14] In contrast to these, the construction of oxazinoindolones by iodolactonization is rare. To the best of our knowledge, there is only one report by B. Joseph et al. which described a system with NIS and 2,6-lutidine at -20 °C allowing the formation of iodo-oxazinoindolone.^[15] Herein, we report a new protocol for the synthesis of a variety of substituted 1,2-fused indoles under mild reaction conditions using an iodolactonization methodology.

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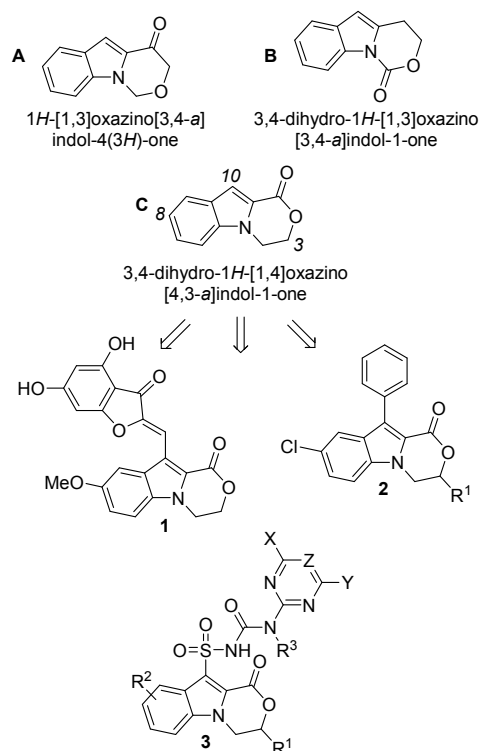
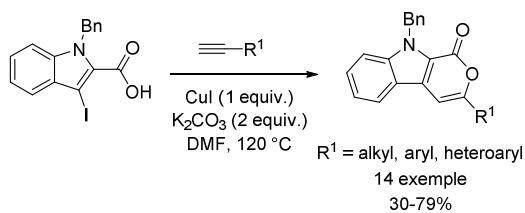


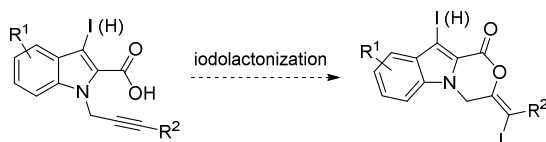
Figure 1. Fused tricyclic oxazinoindolone derivatives and examples of *N*-fused polycyclic indole scaffolds.

Driven by our interest in the preparation of 1,2-fused polycyclic indoles, and in conjunction with our successful previous research on the tandem coupling/cyclization reaction of iodo-carboxylic indoles,^[16] we explored the reactivity of carboxylic *N*-propargylic indoles in the iodolactonization reaction, followed by palladium cross-coupling functionalization of the residual iodine. This approach allows the preparation of original substituted oxazinoindolones in positions 3 and 10 (Scheme 1).

Previous work^[16]



This work

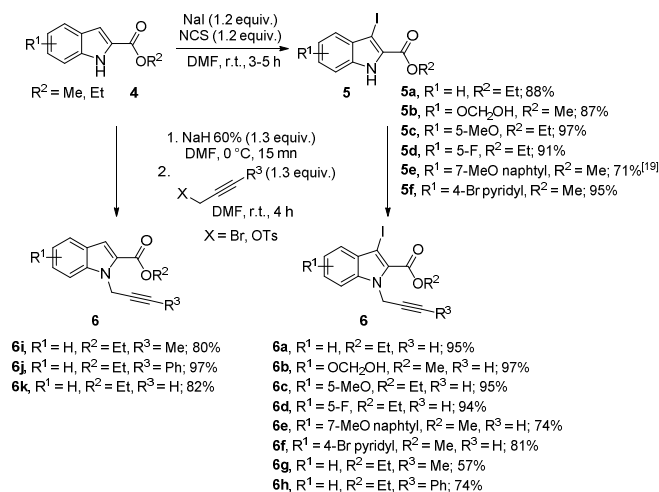


Scheme 1. Synthesis of indoles fused at 2,3 and 1,2.

Results and Discussion

The appropriate cyclization precursors were obtained by successive electrophilic iodination, *N*-alkylation of the ester indole, followed by saponification of the ester. Two different approaches were explored, from the starting iodine propargyl indole acids, or from a non-iodinated precursor (Scheme 2).

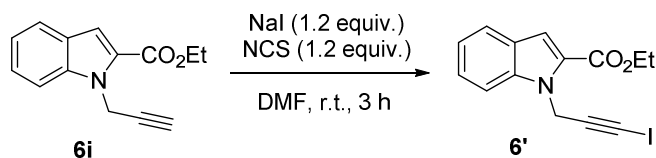
We started by the iodination reaction of the ester indole **4** (commercially available or synthesized by the Hemetsberger-Knittel method)^[17] with the NaI/NCS system.^[18] This method allowed the preparation of various alkyl 3-iodo-1*H*-indole-2-carboxylates **5**, obtained cleanly and in excellent yields after simple recrystallization.



Scheme 2. Precursor preparation.

We next turned our attention to the *N*-propargylation of the resulting iodo-indole compounds. The *N*-alkylation reaction was carried out with NaH.^[20] Initially, the reaction was performed with 1.1 equiv. of NaH followed by 1.2 equiv. of propargylic bromide in THF at room temperature. Only 30% conversion was observed. The choice of solvent was then optimized and we found that using DMF, we effectively improved the conversion to reach 94% for the product **6a** in only 3 hours. It should be noted that the use of an excess of NaH and propargyl bromide leads to both *N*-propargylation and also to transesterification of the ethyl ester to the propargyl ester, in accordance with Vandavasi' work.^[21] The scope was investigated with the iodine indoles **5** to afford the *N*-propargylated indoles **6a-6f** and **6k** with good yields. In the same experimental conditions, products **6g-6h** were obtained from the corresponding tosylate substrates. The preparation of the non-iodinated substrates **6i-6k** was also carried out for the study of the following iodolactonization reaction.

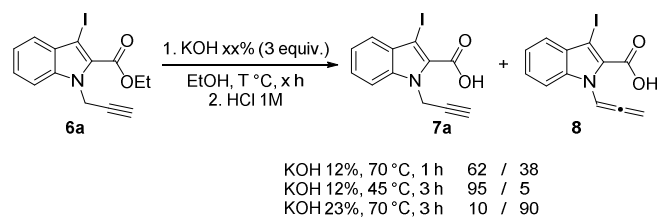
We also attempted the iodination of compound **6i** but only introduction of iodine on the propargyl function to give **6'** was observed (38% yield) (Scheme 3).



Scheme 3. Iodination of **6i**.

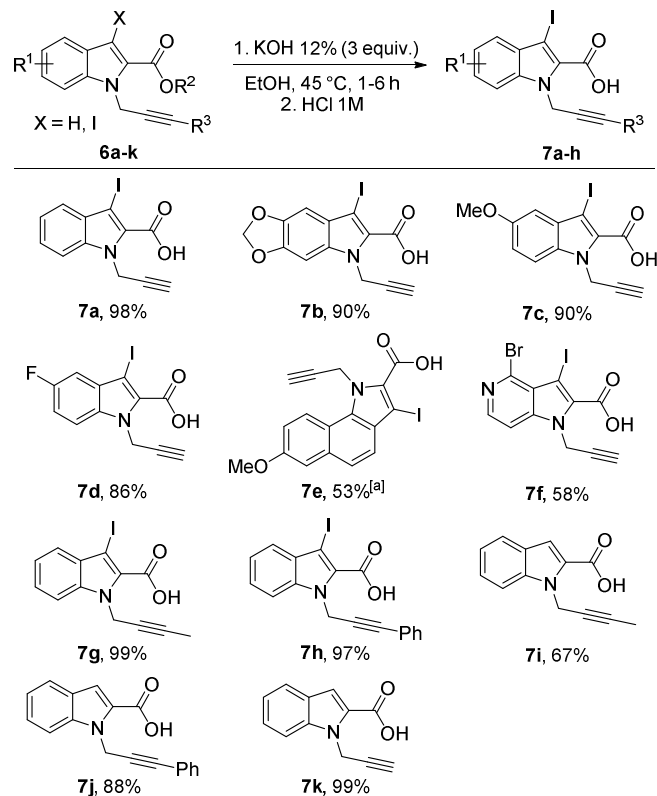
Concerning the saponification step, we applied the previously reported conditions to the compound **6a**,^[22] which involved 12% aq. KOH in EtOH at 70 °C for 1 h, to produce a mixture of compound **7a** and its allene isomer **8** (62/38). Screening was pursued with various amounts of KOH and different reaction times (Scheme 4). We observed the formation of the allene **8** as the major product (90/10) when the

temperature was increased to 70 °C with 23% aq. KOH. The reaction conducted at 45 °C with aq. KOH 12% led to the *N*-propargyl acid indole **7a** with only 5% of the allene **8**.



Scheme 4. Optimization of the saponification reaction conditions.

The reaction of the different esters **6** with 3 equivalents of 12% aq. KOH in ethanol at 45 °C afforded the corresponding acids **7** with good to excellent yields (Scheme 5). The moderate yield of **7f** could be explained by its low solubility, leading to difficulties during the purification process. However for **7e** only the transesterification product was observed. After optimization of the conditions (changing the solvent to MeOH, 2 days at 100 °C), 53% yield of **7e** was obtained. The saponification was also performed on non-iodinated substrates **7i-7k** with excellent results.



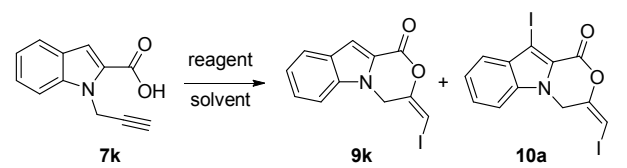
Yields refer to isolated product. [a] MeOH, 100 °C, 2 days.

Scheme 5. Scope of the saponification step.

For the iodolactonization reaction, we initially tested the non-iodinated substrate 1-(prop-2-yn-1-yl)-1*H*-indole-2-carboxylic acid **7k**. Different iodine sources, bases, solvents and temperatures were investigated and the results are summarized in Table 1. Interestingly, the reaction provides exclusively the six-membered ring product but always with a mixture of mono- **9k** and di-iodinated **10a** products (Table 1, entries 1-6). The use of I₂ and NaHCO₃^[23] gave a better result than NIS and lutidine^[24] but we

still obtained a mixture of mono and di-iodinated products (entries 1-3). Temperature had no significant effect on the observed results (entry 3). In the presence of iodine, silver nitrate and sodium carbonate in THF at room temperature overnight, we obtained the same result, with the di-iodinated **10a** as the major product but mixed with 9% of mono-iodinated **9k** (entry 6). Indeed, this system, described by Xu Zhang *et al.*^[25] in 2011, is an effective protocol for the synthesis of fused benzimidazoles using iodine and silver nitrate through *exo*- or *endo*-dig cyclization pathways. Silver nitrate is an important additive that significantly improves the reaction yield because it prevents the formation of the bis-iodine by-product.^[26] We then tried to optimize these conditions by varying the quantity of reagents, but unfortunately we always had a small amount (9%) of mono-iodinated product and it was impossible to remove it from the mixture.

Table 1. Optimization of the iodolactonization step

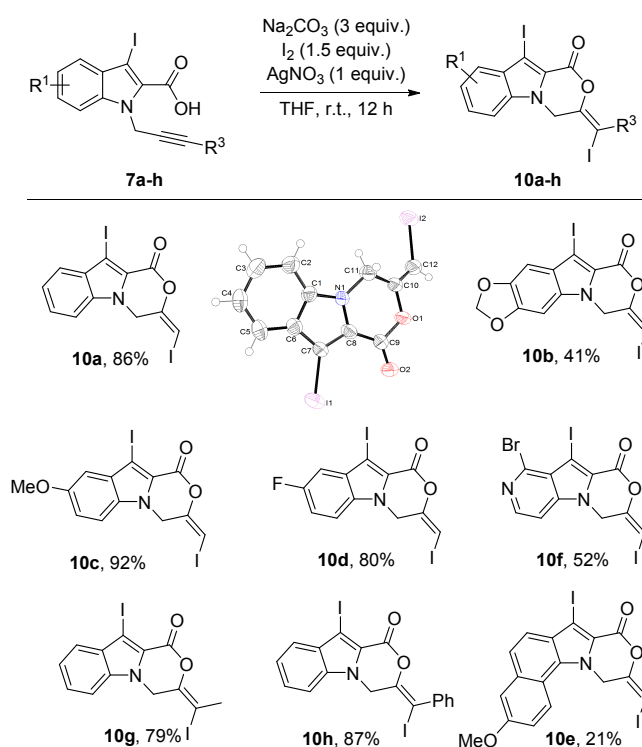


Entry	Reagent (equiv.)	Solvent	T (°C)	Time (h)	Ratio 9k / 10a [%] ^[a]
1	NIS (2), 2,6-lutidine (1,5)	CH ₂ Cl ₂	-20	3.5	17/83
2	I ₂ (2), NaHCO ₃ (2)	CHCl ₃ /H ₂ O	0	2.5	12/88
3	I ₂ (2), NaHCO ₃ (2)	CHCl ₃ /H ₂ O	70	4	8/92
4	I ₂ (1), Na ₂ CO ₃ (3), AgNO ₃ (1) ^[b]	THF	20	12	71/14
5	I ₂ (3), Na ₂ CO ₃ (3), AgNO ₃ (1)	THF	20	12	58/42
6	I ₂ (8), Na ₂ CO ₃ (3), AgNO ₃ (1)	THF	20	12	9/91

[a] ¹H NMR analysis. [b] 15% of starting material.

Finally, we preferred to carry out the reaction on the acid **7a** to obtain only the di-iodinated product **10a** in the presence of Na₂CO₃ (3 equiv.), I₂ (1.5 equiv.) and AgNO₃ (1 equiv.) in THF at r.t. (Scheme 6).

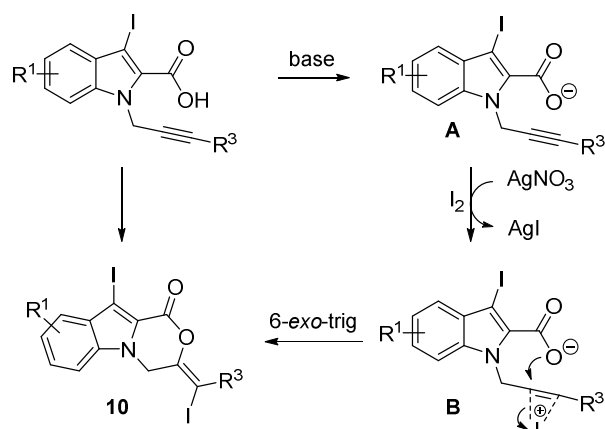
Under these conditions, a good yield (86%) of isolated pure (*E*)-oxazinoindol-1-one **10a** was obtained and the structure of this compound was unambiguously determined by a single-crystal X-ray diffraction study (Scheme 6, for details see Supporting Information SI-1).^[27] The scope of the reaction was then investigated directly with the iodinated precursors **7b-7h** (Scheme 6). The products **10a-10e** were cleanly obtained by a simple recrystallization in moderate to good yields (41-92%). Furthermore, the scope of this iodolactonization reaction was examined by using electron-rich or electron-deficient substrates which successfully underwent this transformation with high stereoselectivity. Significantly, the protocol is also tolerant to R³ substituents (Me or Ph) to furnish the products **10g** and **10h** in 79% and 87% yield respectively. The lower yields for **10b**, **10f** and **10e** could be due to poor solubility of the corresponding starting material and of the final desired product, but also formation of the by-product from iodine decarboxylation, already described in the literature.^[23] After successfully examining the substrate scope, we performed a gram-scale synthesis of **10a** (3.24 g) starting from **7a**.



Scheme 6. Scope of the iodolactonization and X-Ray structure of compound **10a** with displacement ellipsoids drawn at the 50% probability level.

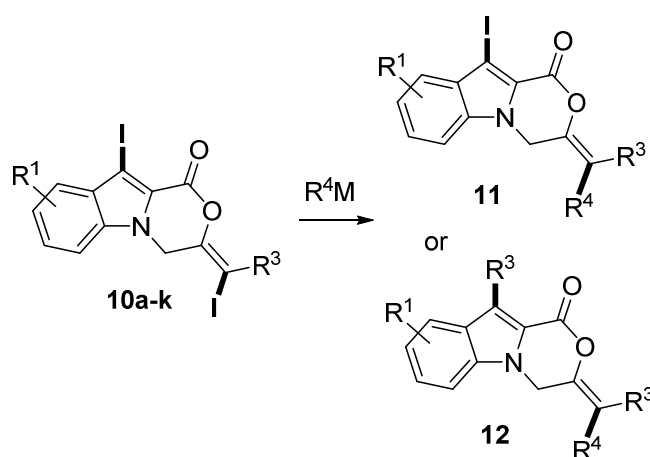
Considering stereoselectivity aspects, (*Z*)-isomers were never observed in the crude reaction mixtures. Addition of iodine to **10a** (3 equiv. for 7 days) did not allow us to observe the formation of the (*Z*)-isomer. The thermodynamic stabilities of these two diastereoisomers were also evaluated by AM1 calculations (B3LYP theory) with the B3LYP-def2-TZVP basis set. The results reveal a higher stability of the *E* vs. *Z* stereoisomer, with a difference of stability close to 1.1 kJ mol^{-1} ($0.26 \text{ kcal mol}^{-1}$).^[28, 29] A proposed plausible mechanism for the iodolactonization is depicted in Scheme 7 on the basis of the literature^[26, 30] and our own observations. First, the alkyne function in the carboxylate **A** is activated by coordination to the electrophilic iodine source I^+ to furnish the corresponding cyclic iodonium **B**. Subsequently, regioselective intramolecular nucleophilic attack of the oxygen then proceeds *via* a 6-*exo*-*tri*g ring-closing pathway to form the oxazinoindolones **10**. Addition of silver nitrate probably allow

an ionic reaction.^[31] The formation of AgI in the reaction medium will prevent the iodide ions from attacking the intermediate **B**, avoiding the formation of bis-iodinated by-products.



Scheme 7. Proposed mechanism for iodolactonization.

We also performed the iodolactonization in these conditions on the allene **8**. It resulted in the formation of an unseparable mixture of compounds including **10a** and other undetermined products. Having established a set of conditions for the formation of di-iodide compounds, we turned our attention to the functionalization of such derivatives, by exploiting the reactivity of both carbon-iodine bonds by employing them in various cross-coupling reactions (Scheme 8). Iododerivatives **10a-k** were first functionalized through a Stille cross coupling reaction.^[32] This reaction has many advantages, because the organotin reagents are easily prepared, have a high stability against oxidation and heating, and tolerate a wide variety of sensitive functional groups.^[33] This popular method has often been used in the synthesis of synthetic natural products.^[34]

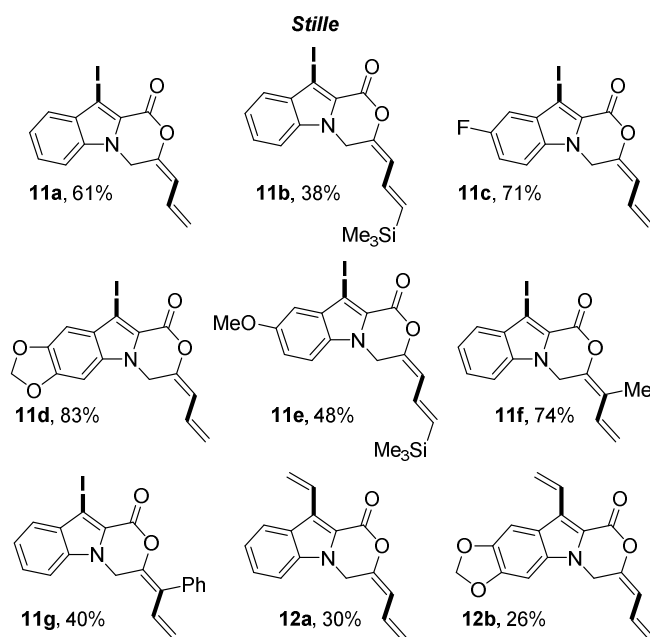


Scheme 8. C-C coupling reactions: Stille, Sonogashira or Suzuki.

The reaction was carried out in classical conditions, and the results are summarized in Scheme 9. Stille coupling was first performed in the presence of tri-*n*-butyl(vinyl)stannane (1.1 equiv.), and a catalytic amount of PdCl₂(MeCN)₂ in DMF at room temperature. Under these stoichiometric conditions, mono-coupling was successfully achieved and regioselectively on the exocyclic vinyl iodine, providing the desired tricyclic derivatives **11a**, **11c** and **11d** in 61-83% yield. Significantly, the protocol is also tolerant

to R³ substituents (Me or Ph) to afford the products **11f** and **11g** in 74% and 40% yield respectively. The Stille mono-coupling with (*E*)-trimethyl(2-(tri-*n*-butylstannyl)vinyl)silane gave products **11b** and **11e** in lower yields (38% and 48% respectively). Coupling carried out in the presence of an excess of tri-*n*-butyl(vinyl)stannane (3 equiv.) under the same operating conditions made it possible to react the second carbon-iodine bond, but gave the corresponding products with low yields, respectively 30% and 26% (**12a**, **12b**). A simple method for the removal of organotin residues was by column chromatography using 10% w/w anhydrous K₂CO₃-SiO₂ as the stationary phase.^[35]

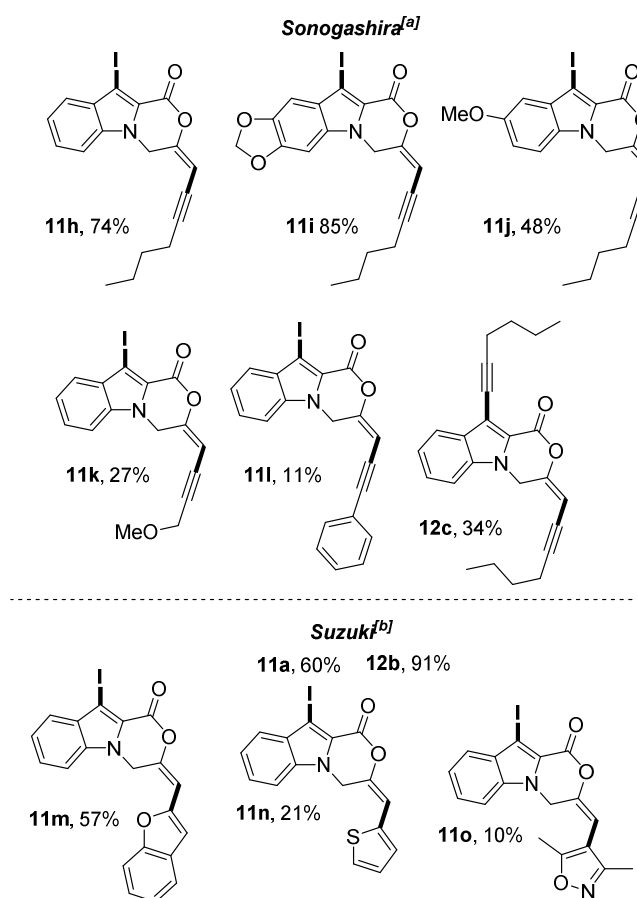
To explain this difference in reactivity of the two C-I bonds, we performed various calculations and analyzed the X-ray structure of **10a**.^[28] The X-ray analysis shows that the C-I bond [2.059 (6) Å] of the endocyclic-iodine (C7I1) moiety is slightly shorter than the C-I bond [2.076 (6) Å] of the exocyclic-iodine (C12-I2) (Scheme 6). By calculation, we can see that C-I distances are smaller in the case of the iodine atom localised in the endocyclic position as the C15-I17 distances: 2.095 Å vs that obtained by looking at C5-I6 (2.106 Å). Furthermore, the I17C15C16C2 dihedral angle is close to 1.6°, while the dihedral angle is close to 183.7° for O3C4C5I6. This shows in fact that the iodine atom in position 17 is in the same 3D Euclidean space than atoms in composing the aromatic cycles, which is not the case of iodine in the position exocyclic (see Supporting Information SI-2). These differences in bond distances and dihedral angles could explain the better reactivity of this exocyclic-iodine when the Pd catalyst is used.



Scheme 9. Structures and yields of the Stille coupling. Reagents and conditions: vinyltin (1.1 equiv.), PdCl₂MeCN₂ (5 mol%), DMF, r.t., 18 h.

For Sonogashira^[36] coupling we first investigated the reactivity of the exocyclic carbon-iodine bond (Scheme 10). The first tests were attempted on compounds **10a-10c** and 1-hexyne using palladium acetate, copper iodide as catalyst, triethylamine and DMF as solvent at room temperature. The corresponding **11h-11j** were obtained with a moderate to good yields (48-85%). However, the use of the alkynes phenylacetylene or methoxypropyne with **10a** allowed us to obtain the products **11i** and **11j** only with low yields (27% and 11% respectively), resulting probably from the duplication of terminal

alkynes. A double Sonogashira coupling reaction with hexyne and di-iodide **10a** furnished **12c** but only in 34% yield.



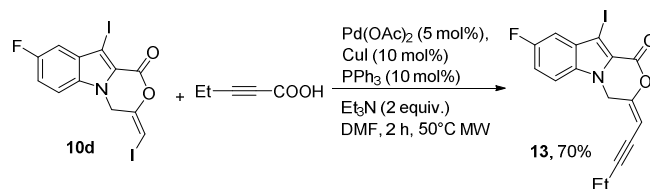
Scheme 10. Structures and yields of the Sonogashira and Suzuki couplings.

^[a] Reagents and conditions for Sonogashira: Alkyne (1.5 equiv.), CuI (10 mol%), PPh₃ (10 mol%), Pd(OAc)₂ (5 mol%), Et₃N, DMF, 15 h. ^[b] Reagents and conditions for Suzuki coupling: R³BF₃K (1.2 equiv.), PdCl₂dppf (5 mol%), Cs₂CO₃ (1.5 equiv.), toluene/H₂O (5/1), 70 °C, 24 h.

Starting from compound **10a** we finally tested the reactivity of the exocyclic iodine toward a Suzuki–Miyaura^[37] coupling reaction with 4-methylphenylboronic acid. However a complex and inseparable mixture of products was obtained. Finally, we considered the Suzuki–Miyaura cross coupling conditions with potassium vinyltrifluoroborate, which is commercially available and air-stable. This compound has been widely employed as a versatile vinylating agent in Suzuki–Miyaura cross-coupling reactions in recent years, and has proven to be a powerful C2 building block to access a variety of styrenic derivatives.^[38]

Thus, the use of potassium vinyltrifluoroborate (1.2 equiv.) with compound **10a** in the presence of cesium carbonate (1.5 equiv.), PdCl₂dppf (5 mol%) in a 5:1 mixture of toluene/H₂O at 70 °C for 24 h furnished **11a** in 60 % yield. In addition, potassium vinyltrifluoroborate (3 equiv.) was also an efficient coupling partner with **10b** for a double transformation to give the desired product **12b** in 91% yield. Finally, the introduction of a heterocyclic unit as a coupling partner (benzofuran, thiophene, isoxazole) allows access to products **11m**, **11n** and **11o** with average to low yields (Scheme 10).

We recently developed an efficient method for the Sonogashira decarboxylative cross coupling reaction^[39] between aryl halides and alkynyl carboxylic acids, and we explored this reaction with compound **10d** and pent-2-ynoic acid (Scheme 11). The corresponding decarboxylative coupling product **13** on the vinyl iodine atom only was isolated in 70% yield.

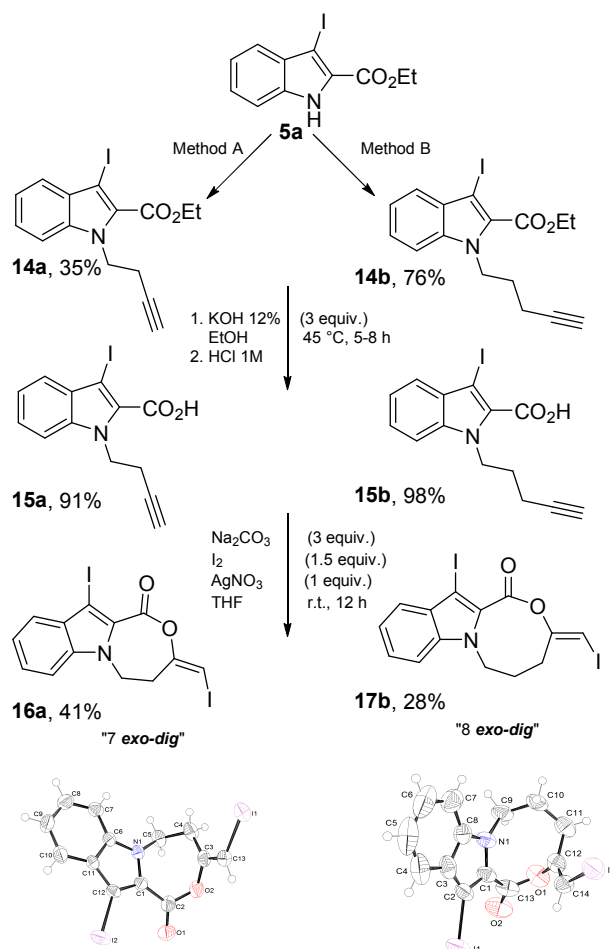


Scheme 11. Sonogashira decarboxylative cross-coupling reaction with **10d**.

Finally, we tried to extend this methodology to indoles with longer alkynyl chains in order to obtain extended 7-membered or 8-membered cycles (Scheme 12). Compound **14b** was synthesized according to the previously described procedure with a good yield. However, the same strategy employed for the preparation of **14a** failed whatever the starting material employed (4-bromobut-1-yne, but-3-yn-1-yl-methylbenzenesulfonate or 4-(trimethylsilyl)but-3-yn-1-yl methylbenzenesulfonate in basic conditions). Fortunately, Mitsunobu conditions^[40] allowed the formation of the homopropargyl indole **14a** though the yield is low (35%), enabling the next step, saponification, with a good yield (91%).

Finally, iodocyclization of these two compounds was performed in the conditions described previously, and led to the formation of exclusively the *exo*-dig products in both cases. The low yield could be explained by the formation of the corresponding iodinated-decarboxylated by-products (observed in the propargyl series). The structures of **16a** and **17b**, were confirmed by X-ray crystallography (see Supporting Information SI-1). Effect of substituent on the alkynyl chain led to the formation of a mixture of undetermined products while it is not the case with propargyl chain.^[41]

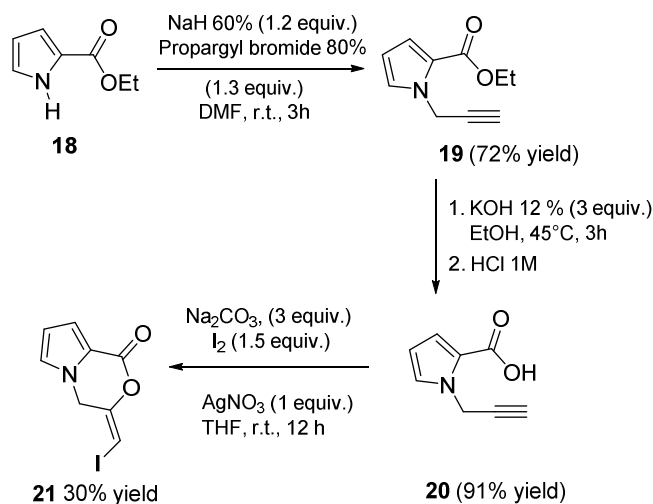
Despite their ubiquitous existence within various biologically active natural products and pharmaceuticals, the formation of 1,2-fused indoles with medium sized rings is generally difficult to achieve.^[42] The methods for obtaining these products remains a major challenge in organic synthesis and they are mainly based on the use of metal complexes.^[43] This new methodology therefore makes it possible to access new 1,2-fused substituted indoles with medium-sized (seven- to eight-membered) carbocycle.



Method A : But-3-yn-1-ol (1 equiv.), DEAD (1.2 equiv.), PPh₃ (1.2 equiv.), THF, r.t., 12 h
 Method B : NaH (60%) (1.1 equiv.), 5-chloropent-1-yne (1.1 equiv.), DMF, 70°C, 12 h

Scheme 12. Extended alkynyl chain indoles and X-Ray structures of compounds **16a** and **17b** with displacement ellipsoids.

Finally, we tested iodocyclization in the pyrrole series. By the same methodology previously described for commercial pyrrole **18** (*N*-propargylation with propargyl bromide; saponification with KOH), we obtained the pyrrole acid **20** in good yield (Scheme 13).^[14, 44] Under the previously used iodocyclization conditions [Na₂CO₃ (3 equiv.), I₂ (1.5 equiv.) and AgNO₃ (1 equiv.) in THF at r.t.], a moderate yield (30%) of isolated pure (*E*)-pyrrolo-oxazin-1-one **21** was obtained (Scheme 13). The (*E*)-pyrrolo-oxazin-1-one scaffold exhibits wide-ranging biological activity against a multitude targets, making it an important intermediate.



Scheme 13. Pyrrole extension.

Conclusions

In summary, we have developed an iodocyclization of *N*-propargyl indoles, followed by palladium-catalyzed coupling, providing potential biologically and pharmaceutically important oxazinoindolones in moderate to excellent yields. We also carried out analogous transformations to extend this methodology with longer alkynyl chain in order to obtain extended 7-membered or 8-membered cycles. This method provides straightforward access to 1,2-fused tricyclic indoles. After preliminary good results toward resistant bacteria, others tests are in process.

Experimental Section

General Methods: All reactions were carried out under argon atmosphere in dried glassware. THF was distilled under argon from sodium using benzophenone as indicator. Dimethylformamide was dried and freshly distilled from calcium hydride. Chemicals were purchased from commercial sources (Sigma–Aldrich, Alfa Aesar, Fluorochem or ABCR) and used without further purification except **5b**, **5e**, **5f** obtained by Hemetsberger-Knittel [1] method and **2c** by Fischer [2] method.

Reactions were monitored by TLC with Merck® Silica gel 60 F₂₅₄. The developed TLC plates were visualized by using UV light (254 nm) or KMnO₄. Column chromatography was performed on silica gel (40–63 μm) using various mixtures of EtOAc and petroleum ether (35–60 °C fraction) as eluent. ¹H NMR spectra were recorded on a Bruker® Avance 300 (300 MHz) NMR spectrometer, using as internal deuterium lock the solvents CDCl₃ (δ 7.26), (CD₃)₂CO (δ 2.05) or (CD₃)₂SO (δ 2.54). Chemical shifts are quoted in ppm (δ_H, δ_C). Peak multiplicities are defined as: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sxt = sextet, m = multiplet and br = broad. Coupling constants (*J*) are reported in Hz. ¹³C NMR was recorded at 75 MHz on the same instrument, using the solvent peak at as reference CDCl₃ (δ 77.16), (CD₃)₂CO (δ 29.85) or (CD₃)₂SO (δ 39.52). ¹⁹F NMR was recorded at 282 MHz on the same instrument, using the CFCl₃ as internal reference (δ 0.0). Mass spectra were obtained on a Hewlett Packard (engine 5988A) by direct inlet at 70eV. HRMS was obtained with a LCMS-IT-TOF mass spectrometer under conditions of ESI. Infrared spectra were recorded on a Perkin-Elmer Spectrum One spectrophotometer with the sample being prepared as a thin film on a diamond ATR module. Absorption maxima (λ_{max}) are quoted in wavenumbers (cm⁻¹). Melting points were uncorrected. Analytical data for already describes molecules can be find in SI.

General procedure for iodination of indoles

In a two-necked round bottom flask, 4.16 g of NCS (1.2 equiv., 31 mmol) were first dissolved in 40 mL of DMF and then, 4.67 g of NaI (1.2 equiv., 31 mmol) was added in small portions and the mixture was stirred for 30 min at room temperature. 1 equiv. of indole (26 mmol) was dissolved in 10 mL of DMF and added drop by drop to the mixture using a bromine bulb at 0 °C.

According to the solubility, 2 different protocols:

Method A: The mixture was stirred for 4 h at room temperature. The medium was hydrolyzed by 10 mL of Na₂S₂O₃ (20 % aq sol.) and 10 mL of water and then stirred for 30 min. The precipitate formed was dissolved with Et₂O. The organic phase was washed with NH₄Cl (3 × 10 mL), NaCl (2 × 10 mL), dried by MgSO₄ and evaporated under vacuum before recrystallization with CH₂Cl₂.

Method B: The mixture was stirred for 4 h at room temperature. The medium was hydrolyzed by 20 mL of Na₂S₂O₃ (20 % aq. sol.) and 20 mL of water and then stirred for 30 min. The precipitate was filtered on a Büchner funnel and washed by hexane and the precipitate was left to dry for 2 h.

The following products are already described and in accordance with the literature : Ethyl 3-iodo-1*H*-indole-2-carboxylate (method A) **5a**^[16]; Methyl 7-iodo-5*H*-[1,3]dioxolo[4,5-*f*]indole-6-carboxylate (method B) **5b**^[18b]; Ethyl 5-fluoro-3-iodo-1*H*-indole-2-carboxylate **5d**^[18b] (method B).

Ethyl 3-iodo-5-methoxy-1*H*-indole-2-carboxylate 5c: Method (B). Brown solid (8.7 g, 97 %); m.p. 162-164 °C; *R*_f = 0.79 (EtOAc/PE, 20:80). ¹H NMR (300 MHz, CDCl₃): δ = 9.18 (s, 1 H), 7.28 (d, *J* = 9 Hz, 1 H), 7.03 (dd, *J* = 9 Hz, *J* = 2.4 Hz, 1 H), 6.92 (d, *J* = 2.4 Hz, 1 H), 4.45 (q, *J* = 8 Hz, 2 H), 3.90 (s, 3 H), 1.46 (t, *J* = 7.5 Hz, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 160.9, 155.7, 133.0, 131.4, 127.5, 118.7, 113.2, 103.3, 65.4, 61.6, 55.8, 14.5 ppm. IR (ATR): ν_{max} = 3292, 2976, 1678, 1505, 1248, 1202, 1158, 1019, 771, 671 cm⁻¹. MS (EI) *m/z* = 299 (M⁺, 100), 75 (18), 76 (15), 101 (13), 102 (13), 119 (33), 130 (10), 144 (26), 146 (14), 284 (23), 300 (15), 345 (56). HRMS (ESI): calcd. for C₁₂H₁₃INO₃ [M+H]⁺ 345.9940; found 345.9936.

Methyl 3-iodo-7-methoxy-1*H*-benzo[*g*]indole-2-carboxylate 5e: Method (B). White solid (9.36 g, 91 %); m.p. 263-265 °C; *R*_f = 0.41 (EtOAc/PE, 20:80). ¹H NMR (300 MHz, DMSO-*d*₆): δ = 8.72 (d, *J* = 9 Hz, 1 H), 7.54 (d, *J* = 9 Hz, 1 H), 7.43 (s, 1 H), 7.42 (d, *J* = 12 Hz, 1 H), 7.25 (dd, *J* = 9 Hz, *J* = 2.5 Hz, 1 H), 3.93 (s, 3 H), 3.89 (s, 3 H) ppm. ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 160.7, 157.5, 133.7, 133.4, 125.9, 124.9, 123.9, 122.2, 121.6, 117.2, 116.5, 108.6, 68.6, 55.3, 51.7 ppm. IR (ATR): ν_{max} = 3299, 1685, 1435, 1168, 824, 663 cm⁻¹. MS (EI) *m/z* = 382 (16), 381 (M⁺, 97), 350 (16), 349 (84), 224 (10), 196 (10), 195 (16), 194 (100), 174 (10), 169 (33), 152 (22), 127 (11), 126 (25), 125 (25), 99 (11), 97 (11), 76 (12), 75 (15), 63 (11), 51 (52). HRMS (ESI): calcd. for C₁₅H₁₃INO₃ [M+H]⁺ 381.9940; found 381.9930.

Methyl 4-bromo-3-iodo-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylate 5f: Method (B). White solid (9.73 g, 95 %); m.p. 229-231 °C; *R*_f = 0.34 (EtOAc/PE, 50:50). ¹H NMR (300 MHz, acetone-*d*₆): δ = 13.08 (s, 1H), 8.07 (d, *J* = 5.7 Hz, 1 H), 7.53 (d, *J* = 5.7 Hz, 1 H), 3.92 (s, 3 H). ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 160.2, 142.1, 141.2, 135.7, 129.7, 123.6, 108.7, 63.9, 52.2. IR (ATR): ν_{max} = 2955, 1713, 1654, 1250, 1184, 940 cm⁻¹. HRMS (ESI): calcd. for C₉H₇BrIN₂O₂ [M+H]⁺ 380.87301; found 380.87241; calcd. for C₉H₅BrIN₂O₂ [M-H]⁺ 378.85846, found 378.85915.

Ethyl 1-(3-iodoprop-2-yn-1-yl)-1*H*-indole-2-carboxylate 6': Method (A). solid (2.2 g, 38 %). Purification by column chromatography (eluent EtOAc/PE, 5:95). ¹H NMR (300 MHz, CDCl₃) δ = 7.69 (d, *J* = 8.0 Hz,

1H), 7.49 (d, $J = 8.2$ Hz, 1H), 7.44 - 7.33 (m, 2H), 7.20 (t, $J = 7.4$ Hz, 1H), 5.58 (s, 2H), 4.40 (q, $J = 7.1$ Hz, 2H), 1.42 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) $\delta = 162.0, 139.0, 127.0, 126.2, 125.6, 122.8, 121.2, 111.5, 110.6, 89.2, 72.1, 60.9, 35.7, 14.4$. HRMS (ESI): calcd. for $\text{C}_{14}\text{H}_{13}\text{INO}_2$ $[\text{M}+\text{H}]^+$ 353.9991; found. 353.9976.

General procedure for *N*-alkylation: In a two-necked round bottom flask, 0.82 g of NaH 60 % (1.3 equiv., 20.6 mmol) were dissolved in 15 mL of DMF, and 1 equiv. of compound **5** (15.8 mmol) in 10 mL of DMF were added drop by drop using a syringe at 0 °C under argon. The mixture was stirred for 30 min at room temperature. 1.3 equiv. of propargyl bromide 80 % (20.6 mmol) or tosylate were diluted with DMF and added to the mixture drop by drop using a syringe at 0 °C under argon. After 4 h of stirring at room temperature, the mixture was hydrolyzed by 10 mL of NH_4Cl , extracted by diethyl ether (7 × 20 mL), and the organic phase was washed with NaCl (6 × 10 mL), dried by MgSO_4 and evaporated under vacuum. The product is obtained pure or the residue was purified by column chromatography (eluent EtOAc/hexane).

The following products are already described and in accordance with the literature : Ethyl 1-(prop-2-ynyl)-1*H*-indole-2-carboxylate **6i**^[14]; 1-(but-2-ynyl)-1*H*-indole-2-carboxylic acid **6k**.^[14]

Ethyl 3-iodo-1-(prop-2-yn-1-yl)-1*H*-indole-2-carboxylate 6a: Yellow solid (5.3 g, 95 %); m.p. 84-86 °C; $R_f = 0.67$ (EtOAc/hexane, 20:80). ^1H NMR (300 MHz, CDCl_3): $\delta = 7.59$ (d, $J = 9$ Hz, 1 H), 7.46-7.44 (m, 2 H), 7.30-7.25 (m, 1 H), 5.40 (d, $J = 3$ Hz, 2 H), 4.49 (q, $J = 8$ Hz, 2 H), 2.27 (t, $J = 2.5$ Hz, 1 H), 1.51 (t, 3H, $J = 6$ Hz) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 161.2, 138.3, 130.7, 127.6, 126.7, 124.3, 122.0, 110.7, 78.6, 72.5, 69.0, 61.6, 35.2, 14.3$ ppm. IR (ATR): $\nu_{\text{max}} = 3277, 2985, 2121, 1690, 1609, 1568$ cm^{-1} . HRMS (ESI): calcd. for $\text{C}_{14}\text{H}_{13}\text{O}_2\text{NI}$ $[\text{M}+\text{H}]^+$ 353.9991; found 353.9904.

Methyl 7-iodo-5-(prop-2-yn-1-yl)-5*H*-[1,3]dioxolo[4,5-*f*]indole-6-carboxylate 6b: White solid (6.09 g, 97%); m.p. 180-182 °C; $R_f = 0.49$ (EtOAc/hexane, 20:80). ^1H NMR (300 MHz, CDCl_3): $\delta = 6.94$ (s, 1 H), 6.87 (s, 1 H), 6.02 (s, 2 H), 5.34 (d, $J = 3$ Hz, 2 H), 3.96 (s, 3 H), 2.28 (t, $J = 2.5$ Hz, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 161.4, 149.3, 145.5, 134.6, 126.2, 125.5, 101.9, 101.7, 90.7, 78.4, 72.7, 69.1, 51.7, 35.5$ ppm. IR (ATR): $\nu_{\text{max}} = 3260, 3001, 2952, 2895, 2123, 1690, 1509, 1495, 1480$ cm^{-1} . HRMS (ESI): calcd. for $\text{C}_{14}\text{H}_{11}\text{INO}_4$ $[\text{M}+\text{H}]^+$ 383.9727; found 383.9719.

Ethyl 3-iodo-5-methoxy-1-(prop-2-yn-1-yl)-1*H*-indole-2-carboxylate 6c: Brown solid (5.75 g, 95 %); m.p. 108-110 °C; $R_f = 0.62$ (EtOAc/PE, 20:80). ^1H NMR (300 MHz, acetone- d_6): $\delta = 7.57$ (d, $J = 9$ Hz, 1 H), 7.12 (dd, $J = 9$ Hz, 3 Hz, 1 H), 6.95 (d, $J = 3$ Hz, 1 H), 5.47 (d, $J = 3$ Hz, 2 H), 4.45 (q, $J = 7$ Hz, 2 H), 3.89 (s, 3H), 2.80 (t, $J = 2.5$ Hz, 1 H), 1.47 (t, $J = 7.5$ Hz, 3 H) ppm. ^{13}C NMR (75 MHz, acetone- d_6): $\delta = 161.4, 156.9, 134.3, 131.8, 128.9, 118.7, 113.2, 104.3, 79.8, 73.8, 67.7, 61.9, 55.9, 35.7, 14.5$ ppm. IR (ATR): $\nu_{\text{max}} = 3277, 2923, 1689, 1500, 1257, 1021, 772, 681$ cm^{-1} . HRMS (ESI): calcd. for $\text{C}_{15}\text{H}_{15}\text{INO}_3$ $[\text{M}+\text{H}]^+$ 384.0091; found 384.0092.

Ethyl 5-fluoro-3-iodo-1-(prop-2-yn-1-yl)-1*H*-indole-2-carboxylate 6d: White solid (5.51 g, 94 %); m.p. 249-251 °C; $R_f = 0.66$ (EtOAc/PE, 20:80). ^1H NMR (300 MHz, CDCl_3): $\delta = 7.42$ (dd, $J = 3$ Hz, 9 Hz, 1 H), 7.29-7.16 (m, 3 H), 5.39 (d, $J = 3$ Hz, 2 H), 4.49 (q, $J = 7$ Hz, 2 H), 2.28 (t, $J = 2.2$ Hz, 1 H), 1.51 (t, $J = 7.5$

Hz, 3 H) ppm. ^{13}C NMR (75 MHz, DMSO- d_6): δ = 160.2, 158.4 (d, $J_{\text{C-F}}$ = 238 Hz), 134.7, 130.4 (d, $J_{\text{C-F}}$ = 9 Hz), 129.4, 115.3 (d, $J_{\text{C-F}}$ = 26 Hz), 113.6 (d, $J_{\text{C-F}}$ = 9 Hz), 107.6 (d, $J_{\text{C-F}}$ = 25 Hz), 79.2, 75.1, 68.7, 61.5, 35.3, 14.05 ppm. ^{19}F NMR (252 MHz, CDCl_3): δ = -121.37 (td, J = 9 Hz, J = 4 Hz). IR (ATR): ν_{max} = 3284, 2983, 1686, 1497, 1380, 1263, 1161 cm^{-1} . HRMS (ESI): calcd. for $\text{C}_{14}\text{H}_{12}\text{FINO}_2$ $[\text{M}+\text{H}]^+$ 371.9891; found 371.9892.

Methyl 3-iodo-7-methoxy-1-(prop-2-yn-1-yl)-1H-benzo[g]indole-2-carboxylate 6e: White solid (5.06 g, 74 %); m.p.: 197-199 °C; R_f = 0.52 (EtOAc/PE, 20:80). ^1H NMR (300 MHz, CDCl_3): δ = 8.60 (d, J = 12 Hz, 1 H), 7.60-7.51 (m, 2 H), 7.34-7.28 (m, 2 H), 5.69 (d, J = 3 Hz, 2 H), 4.02 (s, 3H), 3.97 (s, 3H), 2.47 (t, J = 2.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 161.7, 157.6, 135.9, 134.6, 126.9, 126.8, 124.1, 123.6, 123.1, 117.4, 116.9, 109.4, 79.2, 73.9, 71.5, 55.5, 51.8, 39.1. IR (ATR): ν_{max} = 3278, 1697, 1467, 1258, 1174, 690 cm^{-1} . HRMS (ESI): calcd. for $\text{C}_{18}\text{H}_{15}\text{INO}_3$ $[\text{M}+\text{H}]^+$ 420.0091; found 420.0092.

Methyl 4-bromo-3-iodo-1-(prop-2-yn-1-yl)-1H-pyrrolo[3,2-c]pyridine-2-carboxylate 6f: Beige solid (5.54 g, 81 %); m.p. 162-164 °C; R_f = 0.28 (EtOAc/PE, 50:50). ^1H NMR (300 MHz, CDCl_3): δ = 8.21 (d, J = 5.9 Hz, 1 H), 7.42 (d, J = 5.9 Hz, 1 H), 5.28 (d, J = 2.5 Hz, 2 H), 4.04 (s, 3 H), 2.35 (t, J = 2.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 161.3, 143.1, 137.9, 123.7, 106.2, 105.7, 76.9, 73.9, 73.8, 65.3, 52.6, 35.9 ppm. IR (ATR): ν_{max} = 3275, 2129, 1707, 1440, 1179, 1120 cm^{-1} . HRMS (ESI): calcd. for $\text{C}_{12}\text{H}_9\text{BrIN}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 419.8920; found 419.8911.

Ethyl 1-(but-2-yn-1-yl)-3-iodo-1H-indole-2-carboxylate 6g: White solid (3.30 g, 57 %); m.p. 96-98 °C; R_f = 0.7 (EtOAc/PE, 20:80). ^1H NMR (300 MHz, CDCl_3): δ = 7.58 (dt, J = 8 Hz, J = 1 Hz, 1 H), 7.48-7.40 (m, 2 H), 7.29-7.23 (m, 1 H), 5.33 (q, J = 3 Hz, 2 H), 4.49 (q, J = 7 Hz, 2 H), 1.74 (t, J = 2.3 Hz, 3 H), 1.51 (t, J = 6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 161.2, 138.3, 130.6, 127.7, 126.4, 124.1, 121.9, 110.9, 80.3, 74.0, 68.2, 61.5, 35.6, 14.3, 3.6 ppm. IR (ATR): ν_{max} = 2976, 1691, 1452, 1260, 1192, 739. HRMS (ESI): calcd. for $\text{C}_{15}\text{H}_{15}\text{INO}_2$ $[\text{M}+\text{H}]^+$ 368.0142; found 368.0141.

Ethyl 3-iodo-1-(3-phenylprop-2-yn-1-yl)-1H-indole-2-carboxylate 6h: Yellow oil (5.02 g, 74 %); R_f = 0.7 (EtOAc/PE, 20:80). ^1H NMR (300 MHz, CDCl_3): δ = 7.61 (d, J = 6 Hz, 1 H), 7.54 (d, J = 6 Hz, 1 H), 7.46 (t, J = 7.5 Hz, 1 H), 7.37-7.23 (m, 6 H), 5.62 (s, 2 H), 4.51 (q, J = 8 Hz, 2 H), 1.52 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 161.2, 138.4, 131.8, 130.6, 128.5, 128.3, 127.7, 126.6, 124.2, 122.4, 122.0, 110.9, 84.2, 84.0, 68.6, 61.6, 36.0, 14.3 ppm. IR (ATR): ν_{max} = 2981, 1698, 1240, 1191, 741, 690. HRMS (ESI): calcd. for $\text{C}_{20}\text{H}_{17}\text{INO}_2$ $[\text{M}+\text{H}]^+$ 430.0298; found 430.0299.

Ethyl 1-(3-phenylprop-2-yn-1-yl)-1H-indole-2-carboxylate 6j: Yellow oil (4.65 g, 97 %); R_f = 0.86 (EtOAc/PE, 20:80). ^1H NMR (300 MHz, CDCl_3): δ = 7.70 (d, J = 9 Hz, 1 H), 7.61 (d, J = 9 Hz, 1 H), 7.41-7.18 (m, 8 H), 5.68 (s, 2 H), 4.41 (q, J = 7 Hz, 2 H), 1.43 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 162.2, 139.2, 131.9, 128.4, 128.3, 127.2, 126.3, 125.4, 122.8, 122.7, 121.1, 111.4, 111.0, 84.3, 83.8, 60.9, 34.8, 14.5 ppm. IR (ATR): ν_{max} = 2981, 1702, 1455, 1192, 748. HRMS (ESI): calcd. for $\text{C}_{20}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 304.1332; found 304.1330.

General procedure for saponification

In a round bottom flask, indole ester **6** (1 equiv., 7.5 mmol) was dissolved in 20 mL of ethanol before the addition of 10.5 g of 12% aq. KOH (3 equiv., 22.5 mmol) slowly. The mixture was stirred and heated at 45 °C. After 3 h, the mixture was cooled on an ice bath and acidified with 25 mL of HCl (1 M) to obtain pH = 1. The precipitate obtained was filtered on a Büchner funnel and washed with hexane.

Only the 1-(but-2-ynyl)-1*H*-indole-2-carboxylic acid **7i** was already described and is in accordance with the literature.^[14, 44]

3-Iodo-1-(prop-2-yn-1-yl)-1*H*-indole-2-carboxylic acid 7a: Beige solid (2.38 g, 98 %); m.p. 196-198 °C; $R_f = 0.08$ (EtOAc/hexane, 20:80). ¹H NMR (300 MHz, acetone-*d*₆): $\delta = 7.67$ (d, $J = 8.5$ Hz, 1 H), 7.56 (d, $J = 8$ Hz, 1 H), 7.49 (t, $J = 7.5$ Hz, 1H), 7.30 (t, $J = 7.5$ Hz, 1 H), 5.57 (d, $J = 3$ Hz, 2 H), 2.82 (t, $J = 3$ Hz, 1 H) ppm. ¹³C NMR (75 MHz, DMSO-*d*₆): $\delta = 162.0, 137.9, 129.9, 128.8, 126.1, 123.1, 121.8, 111.5, 79.6, 74.7, 68.9, 34.7$ ppm. IR (ATR): $\nu_{\max} = 3277, 3052, 2985, 2121, 1690, 1610, 1568$ cm⁻¹. HRMS (ESI): calcd. for C₁₂H₉O₂NI [M+H]⁺ 325.9678; found 325.9598.

7-Iodo-5-(prop-2-yn-1-yl)-5*H*-[1,3]dioxolo[4,5-*f*]indole-6-carboxylic acid 7b: White solid (2.49 g, 90 %); m.p. 226-228 °C; $R_f = 0.08$ (EtOAc/ hexane, 20:80). ¹H NMR (300 MHz, acetone-*d*₆): $\delta = 7.16$ (s, 1 H), 6.89 (s, 1 H), 6.19 (s, 1 H), 5.51 (d, $J = 3$ Hz, 2 H), 2.81 (t, $J = 3$ Hz, 1 H) ppm. ¹³C NMR (75 MHz, DMSO-*d*₆): $\delta = 161.7, 148.4, 144.8, 134.0, 127.0, 124.5, 101.5, 100.5, 91.6, 79.6, 74.7, 69.3, 35.0$ ppm. IR (ATR): $\nu_{\max} = 3279, 3261, 2894, 2579, 2506, 2123, 1667, 1509, 1495, 1480$ cm⁻¹. HRMS (ESI): calcd. for C₁₃H₇INO₄ [M-H]⁺ 367.9425; found 367.9424.

3-Iodo-5-methoxy-1-(prop-2-yn-1-yl)-1*H*-indole-2-carboxylic acid 7c: Beige solid (2.39 g, 90 %); m.p. 214-216 °C; $R_f = 0.21$ (EtOAc/PE, 20:80). ¹H NMR (300 MHz, CDCl₃): $\delta = 7.39$ (d, $J = 9$ Hz, 1 H), 7.14 (dd, $J = 2.5$ Hz, $J = 9$ Hz, 1 H), 7.14 (dd, $J = 3, 9$ Hz, 1 H), 6.96 (d, $J = 3$ Hz, 1 H), 5.42 (d, $J = 3$ Hz, 2H), 3.91 (s, 3 H), 2.28 (t, $J = 3$ Hz, 1 H) ppm. ¹³C NMR (75 MHz, DMSO-*d*₆): $\delta = 161.9, 155.3, 133.1, 130.3, 128.9, 117.3, 112.8, 103.1, 79.6, 74.7, 68.1, 55.4, 34.8$ ppm. IR (ATR): $\nu_{\max} = 3258, 2922, 2512, 1663, 1500, 1263, 1170, 1024, 845$. HRMS (ESI): calcd. for C₁₃H₁₁INO₃ [M+H]⁺ 355.9778; found 355.9777.

5-Fluoro-3-iodo-1-(prop-2-yn-1-yl)-1*H*-indole-2-carboxylic acid 7d: White solid (2.21 g, 86 %); m.p. 229-231 °C; $R_f = 0.06$ (EtOAc/PE, 20:80). ¹H NMR (300 MHz, DMSO-*d*₆): $\delta = 7.76$ -7.71 (m, 1 H), 7.32 (t, $J = 9$ Hz, 1 H), 7.19 (d, $J = 8.5$ Hz, 1 H), 5.46 (bs, 2 H), 3.30 (bs, 1 H) ppm. ¹³C NMR (75 MHz, DMSO-*d*₆): $\delta = 161.7, 158.3$ (d, $J_{C-F} = 237$ Hz), 134.6, 130.5, 130.3, 115.0 (d, $J_{C-F} = 25$ Hz), 113.4 (d, $J_{C-F} = 12$ Hz), 107.3 (d, $J_{C-F} = 25$ Hz), 79.4, 74.9, 67.9 (d, $J_{C-F} = 5$ Hz), 35.0 ppm. IR (ATR): $\nu_{\max} = 3282, 2836, 1666, 1500, 1257, 1164, 799$. HRMS (ESI): calcd. for C₁₂H₆FINO₂ [M-H]⁺ 341.9432; found 341.9438.

3-Iodo-7-methoxy-1-(prop-2-yn-1yl)-1*H*-benzo[*g*]indole-2-carboxylic acid 7e: Beige solid (1.61 g, 53 %); m.p. 217-219 °C; $R_f = 0.01$ (EtOAc/PE: 20/80). ¹H NMR (300 MHz, DMSO-*d*₆): $\delta = 8.59$ (d, $J = 9.3$ Hz, 1 H), 7.64 (d, $J = 8.8$ Hz, 2 H), 7.54-7.49 (m, 2 H), 7.33 (dd, $J = 9.2$ Hz, $J = 2.5$ Hz, Hz, 1 H), 5.78 (bs, 2 H), 3.91 (s, 3 H), 3.44 (bs, 1 H) ppm. ¹³C NMR (75 MHz, DMSO-*d*₆): $\delta = 162.1, 157.0, 135.2, 133.3, 127.9, 125.9, 124.1, 123.3, 122.4, 117.1, 116.4, 109.4, 79.8, 76.2, 71.4, 55.3, 38.2$ ppm. HRMS (ESI): calcd. for C₁₇H₁₁IINO₃ [M-H]⁺ 403.9783; found 403.9797.

4-Bromo-3-iodo-1-(prop-2-yn-1-yl)-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid 7f: White solid (1.76 g, 58 %); m.p. 233-235 °C; $R_f = 0$ (EtOAc/PE, 50:50). ^1H NMR (300 MHz, DMSO- d_6): $\delta = 8.17$ (d, $J = 6.0$ Hz, 1 H), 7.86 (d, $J = 6.0$ Hz, 1 H), 5.38 (d, $J = 2$ Hz, 2 H), 3.41 (t, $J = 2$ Hz, 1 H) ppm. ^{13}C NMR (75 MHz, DMSO- d_6): $\delta = 162.3, 142.9, 142.4, 136.2, 123.0, 107.8, 107.6, 78.9, 76.3, 64.7, 35.9$ ppm. IR (ATR): $\nu_{\text{max}} = 3239, 2900\text{-}2412, 1206, 1126, 1070, 804$ cm^{-1} . HRMS (ESI): calcd. for $\text{C}_{11}\text{H}_7\text{BrIN}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 405.8763; found 405.8755.

1-(But-2-yn-1-yl)-3-iodo-1H-indole-2-carboxylic acid 7g: White solid (2.51 g, 99 %); m.p. 218-220 °C; $R_f = 0.17$ (EtOAc/PE, 20:80). ^1H NMR (300 MHz, acetone- d_6): $\delta = 7.63$ (d, $J = 8.4$ Hz, 1 H), 7.55 (dm, $J = 8.1$ Hz, 1 H), 7.46 (t, $J = 7.2$ Hz, 1 H), 7.28 (t, $J = 8$ Hz, 1 H), 5.47 (q, $J = 2.4$ Hz, 2 H), 1.69 (t, $J = 2.4$ Hz, 3 H) ppm. ^{13}C NMR (75 MHz, acetone- d_6): $\delta = 162.4, 139.2, 131.3, 129.4, 127.0, 124.2, 122.6, 112.2, 80.3, 75.2, 68.1, 35.8, 3.1$ ppm. IR (ATR): $\nu_{\text{max}} = 2507, 1665, 1266, 738$ cm^{-1} . HRMS (ESI): calcd. for $\text{C}_{13}\text{H}_9\text{INO}_2$ $[\text{M}-\text{H}]^+$ 337.9683; found 337.9689.

3-Iodo-1-(3-phenylprop-2-yn-1-yl)-1H-indole-2-carboxylic acid 7h: Yellow solid (2.91 g, 97 %); m.p. 211-213 °C; $R_f = 0.18$ (EtOAc/PE, 20:80). ^1H NMR (300 MHz, acetone- d_6): $\delta = 7.74$ (d, $J = 8.3$ Hz, 1 H), 7.56 (d, $J = 8.1$ Hz, 1 H), 7.50 (t, $J = 7.2$ Hz, 1 H), 7.37-7.28 (m, 6 H), 5.79 (s, 2 H) ppm. ^{13}C NMR (75 MHz, acetone- d_6): $\delta = 162.4, 139.3, 132.3, 131.4, 129.4, 129.3, 127.2, 124.4, 123.2, 122.8, 112.2, 85.5, 84.2, 68.5, 36.3$ ppm. IR (ATR): $\nu_{\text{max}} = 2589, 1663, 1434, 742, 688$. HRMS (ESI): calcd. for $\text{C}_{18}\text{H}_{11}\text{INO}_2$ $[\text{M}-\text{H}]^+$ 399.9839; found 399.9844.

1-(3-Phenylprop-2-yn-1-yl)-1H-indole-2-carboxylic acid 7j: Pale pink solid (1.81 g, 88 %); m.p. 186-188 °C; $R_f = 0.28$ (EtOAc/PE, 20:80). ^1H NMR (300 MHz, CDCl_3): $\delta = 7.74$ (d, $J = 8.5$ Hz, 1 H), 7.62 (d, $J = 8.5$ Hz, 1 H), 7.53 (d, $J = 1$ Hz, 1 H), 7.45 (t, $J = 8$ Hz, 1 H), 7.38-7.35 (m, 2 H), 7.28-7.20 (m, 4 H), 5.69 (s, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 165.3, 139.8, 132.0, 128.5, 128.3, 126.3, 126.2, 125.6, 123.2, 121.4, 113.6, 111.1, 84.1, 34.9$ ppm. IR (ATR): $\nu_{\text{max}} = 687, 740, 1264, 1444, 1654, 2929$. HRMS (ESI): calcd. for $\text{C}_{18}\text{H}_{12}\text{NO}_2$ $[\text{M}-\text{H}]^+$ 274.0873; found 274.0878.

3-Iodo-1-(propa-1,2-dienyl)-1H-indole-2-carboxylic acid 8:

In a round bottom flask, indole ester **6a** (1 equiv., 8.5 mmol) was dissolved in 3 mL of ethanol before the addition of 143 mg of KOH 23% (3 equiv., 2.5 mmol) slowly. The mixture was stirred and heated at 70 °C. After 3 h, the mixture was cooled in an ice bath and acidified with 5 mL of HCl (1 M) to obtain pH = 1. The precipitate obtained was filtered on Büchner and washed with hexane. White solid (240 mg, 87%); m.p. 158 °C. ^1H NMR (300 MHz, CDCl_3): $\delta = 7.83\text{-}7.73$ (m, 2 H), 7.50 (d, $J = 8.0$ Hz, 1 H), 7.42 (t, $J = 7.7$ Hz, 1 H), 7.29 (t, $J = 7.4$ Hz, 1 H), 5.73 (d, $J = 6.5$ Hz, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 203.7, 161.9, 137.1, 130.3, 129.4, 126.3, 123.3, 122.3, 112.4, 96.8, 86.8, 70.1$ ppm. HRMS (ESI): calcd. for $\text{C}_{12}\text{H}_9\text{O}_2\text{NI}$ $[\text{M}+\text{H}]^+$ 325.9678; found 325.9593.

General procedure for iodo-cyclization: In a round bottom flask containing the compound **7** (1 equiv., 3 mmol) and 10 mL of THF were added 0.95 g of sodium carbonate (3 equiv., 9 mmol), 1.14 g of iodine (1.5 equiv., 4.5 mmol) and 0.51 g of silver nitrate (1 equiv., 3 mmol). The mixture was stirred overnight at room temperature. The medium was hydrolyzed by saturated solution of $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL) then extracted by dichloromethane (4 × 15 mL). The organic phase was washed with NaCl (3 × 10 mL), dried

with MgSO₄ and evaporated under vacuum. Compound were isolated by column chromatography on silica gel using 5/95: ethyl acetate/petroleum ether as eluent.

(E)-10-Iodo-3-(iodomethylene)-3,4-dihydro-1H-[1,4]oxazino[4,3-*a*]indol-1-one 10a: Yellow-brown solid (1.16 g, 86 %); m.p. 184-186 °C; *R*_f = 0.32 (EtOAc/hexane, 20:80). ¹H NMR (300 MHz, CDCl₃): δ = 7.63 (d, *J* = 8.2 Hz, 1 H), 7.53 (t, *J* = 8.1 Hz, 1 H), 7.42 (d, *J* = 8.3 Hz, 1 H), 7.34 (t, *J* = 8.1 Hz, 1 H), 6.37 (t, *J* = 1 Hz, 1 H), 5.13 (d, *J* = 1 Hz, 2 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 153.8, 146.6, 136.7, 131.2, 128.1, 124.2, 122.9, 120.2, 110.5, 69.5, 64.0, 43.6 ppm. IR (ATR): ν_{max} = 3078, 2922, 1739, 1635, 1513 cm⁻¹. HRMS (ESI): calcd. for C₁₂H₇O₂Nl₂ [M+H]⁺ 451.8638; found 451.8635.

(E)-10-Iodo-7-(iodomethylene)-6,7-dihydro-9H-[1,3]dioxolo[4,5-*f*][1,4]oxazino[4,3-*a*]indol-9-one 10b: White solid (0.60 g, 41 %); m.p. 213 °C; *R*_f = 0.40 (EtOAc/hexane, 20:80). ¹H NMR (300 MHz, DMSO-*d*₆): δ = 7.78 (d, *J* = 0.5 Hz, 1 H), 7.32 (d, *J* = 0.5 Hz, 1 H), 6.93 (t, *J* = 1 Hz, 1 H), 6.57 (s, 2 H), 5.26 (d, *J* = 3 Hz, 2 H) ppm. ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 153.3, 149.4, 146.8, 145.5, 132.8, 125.3, 118.8, 101.7, 99.6, 91.4, 69.0, 64.8, 43.6 ppm. IR (ATR): ν_{max} = 3083, 2911, 1735, 1640, 1519, 1499 cm⁻¹. HRMS (ESI): calcd. for C₁₃H₈O₄Nl₂ [M+H]⁺ 495.8537; found 495.8534.

6,7-Diiodo-5-(prop-2-yn-1-yl)-5H-[1,3]dioxolo[4,5-*f*]indole 10b': beige solid (0.34 g, 25 %); m.p. 198 °C. ¹H NMR (300 MHz, CDCl₃): δ = 6.89 (s, 1 H), 6.83 (s, 1 H), 5.98 (s, 2 H), 4.95 (d, *J* = 2.5 Hz, 2 H) 2.34 (t, *J* = 2.5 Hz, 1H) ppm. ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 145.4, 143.7, 132.3, 125.5, 110.9, 99.1, 94.0, 92.1, 78.7, 75.4, 73.3, 38.6 ppm. HRMS (ESI): calcd. for C₁₂H₇O₂Nl₂ [M]⁺ 450.8566; found 450.8554.

(E)-10-Iodo-3-(iodomethylene)-8-methoxy-3,4-dihydro-1H-[1,4]oxazino[4,3-*a*]indol-1-one 10c: Pale brown solid (1.32 g, 92 %); m.p. 214-216 °C; *R*_f = 0.62 (EtOAc/PE, 20:80). ¹H NMR (300 MHz, CDCl₃): δ = 7.32 (d, *J* = 9 Hz, 1 H), 7.17 (dd, *J* = 9 Hz, 2.4 Hz, 1 H), 6.93 (d, *J* = 3 Hz, 1 H), 6.35 (t, *J* = 1 Hz, 1 H), 5.09 (d, *J* = 1 Hz, 2 H), 3.92 (s, 3 H) ppm. ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 155.7, 153.6, 146.8, 131.8, 130.8, 120.4, 119.2, 113.1, 102.1, 67.8, 64.9, 55.4, 43.5 ppm. IR (ATR): ν_{max} = 3066, 1728, 1511, 1319, 1080, 814 cm⁻¹. HRMS (ESI): calcd. for C₁₉H₉I₂NO₃ [M+H]⁺ 481.8744; found 481.8746.

(E)-8-Fluoro-10-iodo-3-(iodomethylene)-3,4-dihydro-1H-[1,4]oxazino[4,3-*a*]indol-1-one 10d: Yellow solid (1.12 g, 80 %); m.p. 185-187 °C; *R*_f = 0.5 (EtOAc/PE, 20:80). ¹H NMR (300 MHz, CDCl₃): δ = 7.41 (m, 1 H), 7.27-7.33 (m, 2 H), 6.39 (t, *J* = 1.2 Hz, 1 H), 5.11 (d, *J* = 1.5 Hz, 1 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 159.4 (d, *J*_{C-F} = 240 Hz), 153.7, 146.3, 133.4, 131.8 (d, *J*_{C-F} = 9 Hz), 121.6, 117.7 (d, *J*_{C-F} = 27 Hz), 111.9 (d, *J*_{C-F} = 8 Hz), 108.7 (d, *J*_{C-F} = 23 Hz), 68.4 (d, *J*_{C-F} = 7 Hz), 64.4, 43.8 ppm. ¹⁹F NMR (188 MHz, CDCl₃) δ = -119.25 (td, *J* = 8.6 Hz, *J* = 4.2 Hz) ppm. IR (ATR): ν_{max} = 3067, 1735, 1510, 1152, 1066, 853 cm⁻¹. HRMS (ESI): calcd. for C₁₂H₆FI₂NO₂ [M+H]⁺ 469.8544; found 469.8544.

(Z)-7-Iodo-10-(iodomethylene)-3-methoxy-10,11-dihydro-8H-benzo[*g*][1,4]oxazino[4,3-*a*]indol-8-one 10e: solid (0.33 g, 21 %); m.p. 219-221 °C. (EtOAc/EP, 20:80). ¹H NMR (300 MHz, DMSO-*d*₆): δ = 8.38 (d, *J* = 9.1 Hz, 1 H), 7.67 (d, *J* = 9.1 Hz, 1 H), 7.58 (d, *J* = 2.5 Hz, 1 H), 7.50 (d, *J* = 9.1 Hz, 1 H), 7.39 (dd, *J* = 9.1 Hz, 2.5 Hz, 1 H), 6.66 (s, 1 H), 5.76 (m, 2 H), 3.93 (s, 3 H) ppm. ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 157.6,

153.7, 146.3, 135.5, 132.2, 126.6, 123.7, 123.3, 121.7, 118.30, 117.5, 116.3, 109.8, 66.0, 55.4, 54.9, 47.3 ppm. HRMS (ESI): calcd. for $C_{17}H_{11}I_2NO_3$ $[M+H]^+$ 531.8907; found 531.8920.

2,3-Diiodo-7-methoxy-1-(prop-2-yn-1-yl)-1H-benzo[g]indole 10e':

White solid (0.9 g, 61 %); m.p. 209-211 °C; R_f = 0.65 (EtOAc/EP, 20:80). 1H NMR (300 MHz, $CDCl_3$): δ = 8.41 (d, J = 9.1 Hz, 1 H), 7.48 (s, 2 H), 7.32-7.27 (m, 2 H), 5.45 (d, J = 2.5 Hz, 1 H), 3.96 (s, 3 H), 2.47 (t, J = 2.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.6, 133.4, 132.7, 128.0, 122.7, 122.5, 121.9, 117.6, 116.9, 108.7, 92.5, 77.8, 75.9, 74.8, 55.5, 43.4 ppm. IR (ATR): ν_{max} = 3237, 2115, 1383, 1231, 1036, 852 cm^{-1} . HRMS (ESI): calcd. for $C_{16}H_{11}I_2NO$ $[M]^+$ 486.8930; found 486.8948.

(E)-9-Bromo-10-iodo-3-(iodomethylene)-3,4-dihydro-1H-pyrido[3',4':4,5]pyrrolo[2,1-c][1,4]oxazin-

1-one 10f: Yellow solid (0.82 g, 52 %); m.p. 255-257 °C; R_f = 0.12 (EtOAc/EP, 20:80). 1H NMR (300 MHz, $CDCl_3$): δ = 8.28 (d, J = 5.8 Hz, 1 H), 7.41 (d, J = 5.8 Hz, 1 H), 6.45 (t, J = 1.1 Hz, 1 H), 5.12 (d, J = 1.1 Hz, 2H) ppm. ^{13}C NMR (75 MHz, $DMSO-d_6$): δ = 153.3, 145.7, 143.0, 140.6, 136.3, 123.5, 123.2, 107.7, 67.6, 65.6, 43.9 ppm. IR (ATR): ν_{max} = 1737, 1220, 1097, 985, 736 cm^{-1} . HRMS (ESI): calcd. for $C_{11}H_6BrI_2N_2O_2$ $[M+H]^+$ 531.7730, found 531.7726.

(E)-10-Iodo-3-(1-iodoethylidene)-3,4-dihydro-1H-[1,4]oxazino[4,3- α]indol-1-one 10g:

Yellow solid (1.10 g, 79 %); m.p. 194-196 °C; R_f = 0.66 (EtOAc/EP, 20:80). 1H NMR (300 MHz, $CDCl_3$): δ = 7.61 (d, J = 8.5 Hz, 1 H), 7.50 (t, J = 7.5 Hz, 1 H), 7.39 (d, J = 8 Hz, 1 H), 7.31 (t, J = 7.5 Hz, 1 H), 5.17 (q, J = 1.2 Hz, 2 H), 2.65 (t, J = 1.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.3, 140.5, 136.6, 131.2, 127.9, 124.1, 122.8, 120.6, 110.5, 83.8, 68.9, 46.1, 25.5 ppm. IR (ATR): ν_{max} = 2507, 1665, 1266, 738 cm^{-1} . HRMS (ESI): calcd. for $C_{13}H_{10}I_2NO_2$ $[M+H]^+$ 465.8795; found 465.8799.

(E)-10-iodo-3-(iodo(phenyl)methylene)-3,4-dihydro-1H-[1,4]oxazino[4,3- α]indol-1-one 10h:

Yellow solid (1.37 g, 87 %); m.p. 195-197 °C; R_f = 0.62 (EtOAc/EP, 20:80). 1H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, J = 8.2 Hz, 1 H), 7.58-7.52 (m, 1 H), 7.49-7.44 (m, 3 H), 7.40-7.27 (m, 3 H), 5.38 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.8, 140.6, 137.9, 136.7, 131.2, 129.9, 129.0, 128.4, 128.0, 124.2, 122.9, 120.3, 110.5, 86.2, 69.2, 47.0 ppm. IR (ATR): ν_{max} = 1737, 1220, 1097, 985, 736 cm^{-1} . HRMS (ESI): calcd. for $C_{18}H_{12}I_2NO_2$ $[M+H]^+$ 527.8951, found 527.8956.

General procedure for Stille Cross-coupling:

Monocoupling: In a schlenk tube, dried by a flame and under argon, compound **10** (1 equiv., 0.62 mmol) was introduced with 9 mg of $PdCl_2(CH_3CN)_2$ (5% mol) in 10 mL of DMF and the mixture was stirred for 15 min at room temperature before the addition of 0.24 g of organostannane (1.2 equiv., 0.74 mmol). The mixture was stirred at room temperature overnight, and 20 mL of ethylacetate and 10 mL of KF (1M) were added and the mixture was stirred for 1 h at room temperature. The precipitate obtained was filtered through a celite pad, washed by diethyl ether and water then the filtrate was extracted by diethyl ether (3 \times 20mL). The organic phase was washed by NaCl (2 \times 10 mL), dried by $MgSO_4$ and concentrated under vacuum. Compound were isolated by column chromatography on silica gel using 2/98: ethyl acetate/petroleum ether as eluent.

Bis coupling: In a schlenk tube, dried by a flame and under argon, compound **10** (1 equiv., 0.66 mmol) was introduced with 9.7 mg of $PdCl_2(CH_3CN)_2$ (5% mol) in 10 mL of DMF and the mixture was stirred

for 15 min at room temperature before the addition of 0.63 g of organostannane (3 equiv., 1.98 mmol). The mixture was stirred at room temperature overnight. 20 mL of ethylacetate and 10 mL of KF (1M) were added and the stirring was continued for an additional 1 h at room temperature, then the precipitate obtained was filtered through a celite pad, washed by diethyl ether and water. The filtrate was extracted by diethyl ether (3 × 20 mL) and the organic phase was washed with NaCl (2 × 10 mL), dried by MgSO₄ and concentrated under vacuum. Compound were isolated by column chromatography^[34] on silica gel using 2/98: ethyl acetate/petroleum ether as eluent.

(E)-3-Allylidene-10-iodo-3,4-dihydro-1H-[1,4]oxazino[4,3-*a*]indol-1-one 11a: Yellow solid (0.13 g, 61 %); m.p. 154-156 °C; *R*_f = 0.37 (EtOAc/PE, 20:80). ¹H NMR (300 MHz, CDCl₃): δ = 7.63 (d, *J* = 8.2 Hz, 1 H), 7.51 (t, *J* = 8.5 Hz, 1 H), 7.38 (d, *J* = 8.4 Hz, 1 H), 7.32 (t, *J* = 8 Hz, 1 H), 6.45 (ddd, *J* = 10.2 Hz, *J* = 11.5 Hz, *J* = 16.5 Hz, 1 H), 6.22 (d, *J* = 11.5 Hz, 1 H), 5.42 (d, *J* = 16.5 Hz, 1 H), 5.32 (d, *J* = 10.2 Hz, 1 H), 5.09 (s, 2 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 155.3, 142.4, 136.5, 131.2, 128.2, 127.8, 124.2, 122.7, 121.6, 121, 115.6, 110.4, 68.7, 39.5 ppm. IR (ATR): ν_{max} = 1720, 1513, 984, 896, 735 cm⁻¹. HRMS (ESI, positive mode): calcd. for C₁₄H₁₁O₂NI [M+H]⁺ 351.9829; found 351.9825.

(E)-10-Iodo-3-((E)-3-(trimethylsilyl)allylidene)-3,4-dihydro-1H-[1,4]oxazino[4,3-*a*]indol-1-one 11b: Yellow solid (99 mg, 38 %); m.p. 163-165 °C; *R*_f = 0.63 (EtOAc/PE, 20:80). ¹H NMR (300 MHz, CDCl₃): δ = 7.62 (d, *J* = 9 Hz, 1 H), 7.51 (t, *J* = 9 Hz, 1 H), 7.42 (d, *J* = 9 Hz, 1 H), 7.31 (t, *J* = 7.5 Hz, 1 H), 6.56 (dd, *J* = 10.5 Hz, *J* = 18 Hz, 1 H), 6.21 (d, *J* = 10.5 Hz, 1 H), 6.11 (d, *J* = 18 Hz, 1 H), 5.10 (d, *J* = 0.75 Hz, 2 H), 0.14 (s, 9 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 155.4, 142.0, 139.6, 136.6, 134.3, 131.3, 127.7, 124.3, 122.8, 121.8, 118.0, 110.4, 68.7, 39.7, -1.2 ppm. IR (ATR): ν_{max} = 2953, 2895, 1749, 1661, 1615, 1518 cm⁻¹. HRMS (ESI, positive mode): calcd. for C₁₇H₁₉O₂NiSi [M+H]⁺ 424.0224; found 424.0219.

(E)-3-Allylidene-8-fluoro-10-iodo-3,4-dihydro-1H-[1,4]oxazino[4,3-*a*]indol-1-one 11c: Pale yellow solid (0.16 g, 71 %); m.p. 163-165 °C; *R*_f = 0.45 (EtOAc/PE, 20:80). ¹H NMR (300 MHz, CDCl₃): δ = 7.38-7.23 (m, 3 H), 6.44 (ddd, *J* = 10.5 Hz, *J* = 11.2 Hz, *J* = 16.7 Hz, 1 H), 6.21 (d, *J* = 11.2 Hz, 1 H), 5.42 (d, *J* = 16.7 Hz, 1 H), 5.33 (d, *J* = 10.7 Hz, 1 H), 5.07 (s, 2 H) ppm. ¹³C NMR (CDCl₃, 75 MHz): δ = 159.3 (*J* = 239 Hz), 155.0, 142.1, 133.2, 131.8 (*J* = 10.4 Hz), 128.2, 128.0, 121.3, 117.3 (*J* = 27 Hz), 116.0, 111.7 (*J* = 10 Hz), 108.8 (*J* = 25 Hz), 67.6 (*J* = 5 Hz), 39.8 ppm. ¹⁹F NMR (188 MHz, CDCl₃): δ = -119.67 (td, *J* = 9 Hz, *J* = 5 Hz) ppm. IR (ATR): ν_{max} = 2970, 1724, 1515, 1224, 1159 cm⁻¹. HRMS (ESI, positive mode): calcd. for C₁₄H₁₀FINO₂ [M+H]⁺ 369.9734; found 369.9736.

(E)-7-Allylidene-10-iodo-6,7-dihydro-9H-[1,3]dioxolo[4,5-*f*][1,4]oxazino[4,3-*a*]indol-9-one 11d: Yellow solid (0.20 g, 83 %); m.p. 167-169 °C; *R*_f = 0.13 (EtOAc/PE, 20:80). ¹H NMR (300 MHz, CDCl₃): δ = 6.94 (s, 1 H), 6.75 (s, 1 H), 6.42 (ddd, *J* = 21 Hz, 18 Hz, 12 Hz, 1 H), 6.19 (d, *J* = 12 Hz, 1 H), 6.05 (s, 2 H), 5.41 (d, *J* = 18 Hz, 1 H), 5.31 (d, 1H, *J* = 12 Hz), 4.97 (s, 2 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 154.9, 150.2, 146.1, 142.4, 132.8, 128.2, 126.4, 120.8, 115.5, 101.9, 101.4, 89.8, 68.5, 39.8 ppm. IR (ATR): ν_{max} = 2892, 1720, 1315, 1162, 1070, 900, 839 cm⁻¹. HRMS (ESI, positive mode): calcd. for C₁₅H₁₁INO₄ [M+H]⁺ 395.9727; found 395.9726.

(E)-10-Iodo-8-methoxy-3-((E)-3-(trimethylsilyl)allylidene)-3,4-dihydro-1H-[1,4]oxazino[4,3-*a*]indol-1-one 11e: Yellow oil (134 mg, 48%); *R*_f = 0.72 (EtOAc/PE, 20:80). ¹H NMR (300 MHz, CDCl₃): δ = 7.17

(d, $J = 8.9$ Hz, 1 H), 6.97 (dd, $J = 8.9$ Hz, $J = 2.3$ Hz, 1 H), 6.72 (d, $J = 2.3$ Hz), 6.42 (dd, $J = 10.8$ Hz, $J = 18.1$ Hz, 1 H), 6.03 (d, $J = 11$ Hz, 1 H), 5.95 (d, $J = 18.1$ Hz, 1 H), 4.92 (s, 2H), 3.73 (s, 3 H), 0.00 (s, 9 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 156.2, 155.2, 142.0, 139.3, 134.3, 131.8, 131.6, 121.5, 119.9, 117.6, 111.5, 103.1, 67.3, 55.8, 39.7, -1.2$ ppm. HRMS (ESI, positive mode): calcd. for $\text{C}_{18}\text{H}_{21}\text{INO}_3\text{Si}$ $[\text{M}+\text{H}]^+$ 454.0335; found 454.0344.

(E)-3-(But-3-en-2-ylidene)-10-iodo-3,4-dihydro-1H-[1,4]oxazino[4,3-*a*]indol-1-one 11f: Yellow solid (0.17 g, 74%); m.p. 235-237 °C; $R_f = 0.56$ (EtOAc/PE, 20:80). ^1H NMR (300 MHz, CDCl_3): $\delta = 7.62$ (d, $J = 9$ Hz, 1 H), 7.52-7.25 (m, 3 H), 6.63 (dd, $J = 10.9$ Hz, $J = 17$ Hz, 1 H), 5.46 (d, $J = 17$ Hz, 1 H), 5.34 (d, $J = 11$ Hz, 1 H), 5.13 (s, 2 H), 2.02 (s, 3 H) ppm. ^{13}C NMR (CDCl_3 , 75 MHz): $\delta = 155.6, 139.1, 136.5, 131.4, 131.2, 127.6, 124.2, 122.6, 120.3, 117.4, 110.5, 110.3, 68.1, 39.7, 11.1$. IR (ATR): $\nu_{\text{max}} = 2922, 1736, 1094, 730$ cm^{-1} . HRMS (ESI, positive mode): calcd. for $\text{C}_{15}\text{H}_{13}\text{INO}_2$ $[\text{M}+\text{H}]^+$ 365.9985; found 365.9980.

(Z)-10-Iodo-3-(1-phenylallylidene)-3,4-dihydro-1H-[1,4]oxazino[4,3-*a*]indol-1-one 11g: Yellow solid (0.11 g, 40%); m.p. 175-177 °C; $R_f = 0.62$ (EtOAc/PE, 20:80). ^1H NMR (300 MHz, CDCl_3): $\delta = 7.64$ (d, $J = 6$ Hz, 1 H), 7.55-7.35 (m, 5 H), 7.24 (d, $J = 9$ Hz, 2 H), 6.74 (dd, $J = 9$ Hz, $J = 16.5$ Hz, 1 H), 5.42 (d, $J = 9$ Hz, 1 H), 5.25 (s, 2 H), 5.10 (d, $J = 18$ Hz, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 154.9, 138.5, 136.5, 133.7, 131.8, 131.2, 130.0, 128.4, 128.0, 127.7, 126.4, 124.2, 122.7, 121.9, 121.3, 110.4, 68.3, 40.2$ ppm. IR (ATR): $\nu_{\text{max}} = 1733, 1227, 737, 696$. HRMS (ESI, positive mode): calcd. for $\text{C}_{20}\text{H}_{15}\text{INO}_2$ $[\text{M}+\text{H}]^+$ 428.0142; found 428.0141.

(E)-3-Allylidene-10-vinyl-3,4-dihydro-1H-[1,4]oxazino[4,3-*a*]indol-1-one 12a: Yellow solid (49 mg, 30 %); m.p. 127-129 °C; $R_f = 0.37$ (EtOAc/PE, 20:80). ^1H NMR (300 MHz, CDCl_3): $\delta = 8.08$ (d, $J = 8.2$ Hz, 1 H), 7.62 (dd, $J = 11.7$ Hz, $J = 18.2$ Hz, 1 H), 7.49 (t, $J = 7.5$ Hz, 1 H), 7.40 (d, $J = 9$ Hz, 1 H), 7.30 (t, $J = 6$ Hz, 1 H), 6.48 (ddd, $J = 10.3$ Hz, $J = 11.4$ Hz, $J = 16.5$ Hz, 1 H), 6.19 (d, $J = 11.3$ Hz, 1 H), 6.07 (dd, $J = 18.1$ Hz, $J = 1.5$ Hz, 1 H), 5.58 (dd, $J = 11.6$ Hz, $J = 1.5$ Hz, 1 H), 5.41 (d, $J = 18$ Hz, 1 H), 5.31 (d, $J = 10.5$ Hz, 1 H), 5.02 (s, 2 H), ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 156.2, 143.0, 136.4, 128.8, 128.4, 126.9, 125.4, 124.0, 123.2, 122.4, 120.6, 118.3, 118.2, 115.1, 110.1, 38.8$ ppm. IR (ATR): $\nu_{\text{max}} = 3060, 1714, 1523, 889, 734$ cm^{-1} . HRMS (ESI, positive mode): calcd. for $\text{C}_{16}\text{H}_{14}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 252.1019; found 252.1017.

(E)-7-Allylidene-10-vinyl-6,7-dihydro-9H-[1,3]dioxolo[4,5-*f*][1,4]oxazino[4,3-*a*]indol-9-one 12b: Yellow solid (51 mg, 26%); m.p. 206 °C; $R_f = 0.21$ (EtOAc/PE, 20:80). ^1H NMR (300 MHz, CDCl_3): $\delta = 7.54$ (dd, $J = 18$ Hz, 12 Hz, 1 H), 7.36 (s, 1 H), 6.77 (s, 1 H), 6.50-6.37 (m, 1 H), 6.17 (d, $J = 12$ Hz, 1 H), 6.04 (s, 2 H), 5.89 (d, $J = 18$ Hz, 1 H), 5.52 (d, $J = 12$ Hz, 1 H), 5.42-5.27 (m, 2 H), 4.90 (s, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 155.6, 149.3, 145.6, 142.9, 132.8, 128.9, 128.4, 124.3, 120.4, 119.8, 117.5, 114.9, 101.7, 100.4, 89.9, 39.0$ ppm. HRMS (ESI, positive mode): calcd. for $\text{C}_{17}\text{H}_{14}\text{NO}_4$ $[\text{M}+\text{H}]^+$ 296.0923; found 296.0926.

General procedure for Sonogashira Cross-coupling:

Monocoupling: In a schlenk tube dried by a flame and under argon, compound **10** (1 equiv., 0.66 mmol) and alkyne (1.5 equiv., 0.99 mmol) were introduced with 10 mL of DMF. The solution was cooled to 0 °C before the addition of 0.2 mL of Et_3N (2.2 equiv., 1.46 mmol) and the solution was stirred for 15 min at 0 °C. Then 12.7 mg of CuI (0.066 mmol, 10% mol), 17.3 mg of PPh_3 (0.066 mmol, 10% mol) and 7.4

mg of Pd(OAc)₂ (0.033 mmol, 5% mol) were added and the mixture was stirred at room temperature overnight.

30 mL of diethyl ether were added and the reaction medium was stirred for 5 min at room temperature, then 10 mL of NH₄Cl were added and the mixture was stirred for 5 min. The precipitate formed was filtered on celite and washed by diethyl ether and water, and the filtrate was extracted by diethyl ether (3 × 20 mL). The organic phase was washed by saturated solution of NH₄Cl (2 × 5 mL) and saturated solution of NaCl (2 × 10 mL), dried by MgSO₄ and evaporated under vacuum. Compound were isolated by column chromatography on silica gel using 5/95: ethyl acetate/petroleum ether as eluent.

Biscoupling: In a schlenk tube dried by a flame and under argon, 0.4 g of compound **10** (1 equiv., 0.88 mmol) were introduced with 0.3 mL of 1-hexyne (3 equiv., 2.64 mmol) in 10 mL of DMF. The mixture was cooled to 0 °C and 0.54 mL of Et₃N (4.4 equiv., 3.9 mmol) were added and the stirring was continued for 15 min at 0 °C before the addition of 17 mg of CuI (10% mol), 23 mg of PPh₃ (10 % mol) and 9.9 mg of Pd(OAc)₂ (10 % mol). The mixture was stirred at room temperature overnight. 30 mL of Et₂O were added and the mixture was stirred for 5 min followed by the addition of 10 mL of NH₄Cl and the stirring was continued for 5 min.

The precipitate was filtered on celite, washed with ether and water and the filtrate was extracted by diethyl ether (3 × 20 mL). The organic phase was washed by NH₄Cl (2 × 5 mL) and NaCl (5 × 10 mL), dried by MgSO₄ and evaporated under vacuum. Compound were isolated by column chromatography on silica gel using 5/95: ethyl acetate/petroleum ether as eluent.

(E)-3-(Hept-2-yn-1-ylidene)-10-iodo-3,4-dihydro-1H-[1,4]oxazino[4,3-*a*]indol-1-one 11h: Yellow solid (0.19 g, 74 %); m.p. 122-124 °C; *R*_f = 0.54 (EtOAc/PE, 10:90). ¹H NMR (300 MHz, CDCl₃): δ = 7.63 (d, *J* = 9 Hz, 1 H), 7.52 (t, *J* = 7.5 Hz, 1 H), 7.39 (d, *J* = 9 Hz, 1 H), 7.33 (t, *J* = 7.5 Hz, 1 H), 5.67 (s, 1 H), 5.16 (s, 2 H), 2.43 (t, *J* = 7.5 Hz, 2 H), 1.64-1.43 (m, 4 H), 0.97 (t, *J* = 7.5 Hz, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 154.5, 150.8, 136.8, 131.3, 127.9, 124.2, 122.8, 121.1, 110.5, 99.0, 96.5, 73.1, 69.2, 40.7, 30.8, 22.2, 19.5, 13.7 ppm. IR (ATR): ν_{max} = 1742, 1070, 735 cm⁻¹. MS (EI) *m/z* = 406 (20), 405 (M⁺, 100), 269 (26), 250 (31), 222 (13), 221 (11), 208 (17), 207 (13), 180 (13), 178 (13), 128 (68), 114 (27), 102 (11), 101 (56), 77 (17), 75 (22), 51 (19), 39 (10). HRMS (ESI, positive mode): calcd. for C₁₈H₁₇INO₂ [M+H] 406.0298; found 406.0296.

(E)-7-(Hept-2-yn-1-ylidene)-10-iodo-6,7-dihydro-9H-[1,3]dioxolo[4,5-*f*][1,4]oxazino[4,3-*a*]indol-9-one 11i: Yellow solid (0.25 g, 85 %); m.p. 164-166 °C; *R*_f = 0.84 (EtOAc/PE, 20:80). ¹H NMR (300 MHz, CDCl₃): δ = 6.94 (s, 1 H), 6.76 (s, 1 H), 6.06 (s, 1 H), 5.64 (m, 1 H), 5.04 (d, *J* = 1.2 Hz, 2 H), 1.61-1.46 (m, 4 H), 2.40 (dt, *J* = 6, 3 Hz, 2 H), 0.97 (t, *J* = 6 Hz, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 154.1, 150.8, 150.3, 146.1, 133.1, 126.4, 119.7, 102.0, 101.3, 98.9, 96.2, 89.9, 73.2, 68.9, 40.9, 30.8, 22.2, 19.6, 13.7 ppm. IR (ATR): ν_{max} = 2951, 1729, 1491, 1037, 945, 841, 736 cm⁻¹. HRMS (ESI, positive mode): calcd. for C₁₉H₁₇INO₄ [M+H]⁺ 450.0196; found 450.0196.

(E)-3-(Hept-2-yn-1-ylidene)-10-iodo-8-methoxy-3,4-dihydro-1H-[1,4]oxazino[4,3-*a*]indol-1-one 11j: Brown oil (0.14 g, 48 %); *R*_f = 0.61 (EtOAc/PE, 20:80). ¹H NMR (300 MHz, CDCl₃): δ = 7.27 (d, *J* = 9 Hz, 1 H), 7.15 (d, *J* = 9 Hz, 1 H), 6.90 (s, 1 H), 5.64 (s, 1 H), 5.10 (s, 2 H), 3.90 (s, 3 H), 2.42 (t, *J* = 6 Hz, 2 H), 1.61-1.46 (m, 4 H), 0.97 (t, *J* = 7.5 Hz, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 156.4, 154.3, 150.8,

132.2, 132.1, 121.0, 120.3, 111.6, 103.2, 99.0, 96.2, 73.1, 67.9, 55.9, 40.8, 30.8, 22.2, 19.5, 13.7 ppm. IR (ATR): ν_{\max} = 2928, 1734, 1512, 1449, 1167 cm^{-1} . MS (EI) m/z = 436 (21), 435 (M^+ , 100), 299 (28), 284 (10), 280 (22), 238 (15), 158 (21), 144 (12), 116 (13), 115 (19), 101 (12), 77 (17). HRMS (ESI, positive mode): calcd. for $\text{C}_{19}\text{H}_{19}\text{INO}_3$ [$\text{M}+\text{H}$] 436.0404; found 436.0404.

(E)-10-Iodo-3-(4-methoxybut-2-yn-1-ylidene)-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indol-1-one 11k: Yellow-orange solid (70 mg, 27 %); m.p. 149-151 °C; R_f = 0.31 (EtOAc/EP, 20:80). ^1H NMR (300 MHz, CDCl_3): δ = 7.63 (d, J = 9 Hz, 1 H), 7.53 (t, J = 7.5 Hz, 1 H), 7.41 (d, J = 9 Hz, 1 H), 7.33 (t, J = 9 Hz, 1 H), 5.72 (t, J = 3 Hz, 1 H), 5.19 (s, 2 H), 4.32 (d, J = 3 Hz, 2 H), 3.45 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 153.8, 152.4, 136.6, 131.1, 127.9, 124.0, 122.8, 120.6, 110.5, 94.9, 93.3, 78.8, 69.5, 60.5, 58.0, 40.7 ppm. IR (ATR): ν_{\max} = 3050, 2953, 1744, 1670, 1614, 1518 cm^{-1} . HRMS (ESI, positive mode): calcd. for $\text{C}_{16}\text{H}_{12}\text{O}_3\text{NI}$ [$\text{M}+\text{H}$] 393.9934; found 393.9930.

(E)-10-Iodo-3-(3-phenylprop-2-yn-1-ylidene)-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indol-1-one 11l: Yellow solid (31 mg, 11 %); m.p. 127-129 °C; R_f = 0.77 (EtOAc/EP, 20:80). ^1H NMR (300 MHz, CDCl_3): δ = 7.76-7.27 (m, 9 H), 5.90 (s, 1H), 5.25 (s, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 154.1, 151.6, 136.8, 131.6, 131.3, 129.1, 128.7, 128.1, 124.3, 123.0, 122.6, 120.9, 110.6, 97.4, 95.9, 81.8, 69.6, 40.9 ppm. IR (ATR): ν_{\max} = 2922, 1736, 1512, 1090, 735 cm^{-1} . HRMS (ESI, positive mode): calcd. for $\text{C}_{20}\text{H}_{13}\text{INO}_2$ [$\text{M}+\text{H}$] $^+$ 425.9985; found 425.9985.

(E)-3-(Hept-2-yn-1-ylidene)-10-(hex-1-yn-1-yl)-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indol-1-one 12c: Yellow oil (0.11 g, 34 %); R_f = 0.72 (EtOAc/PE, 10:90). ^1H NMR (300 MHz, CDCl_3): δ = 7.83 (d, J = 6 Hz, 1 H), 7.50-7.44 (m, 1 H), 7.37 (d, J = 6 Hz, 1 H), 7.20-7.25 (m, 1 H), 5.64-5.62 (m, 1 H), 5.08 (s, 2 H), 2.60 (t, J = 6 Hz, 2 H), 2.42 (dt, J = 2.2 Hz, J = 7 Hz, 2 H), 1.74-1.42 (m, 8 H), 0.97 (t, J = 7 Hz, 3 H), 0.95 (t, J = 7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 154.0, 151.3, 135.8, 129.2, 127.4, 122.4, 122.2, 121.5, 110.2, 108.5, 100.2, 98.7, 96.0, 73.2, 71.9, 40.2, 30.9, 30.7, 22.1 (2C), 19.9, 19.5, 13.8, 13.7 ppm. IR (ATR): ν_{\max} = 2958, 2933, 1700, 1559, 739, 668 cm^{-1} . HRMS (ESI, positive mode): calcd. for $\text{C}_{24}\text{H}_{26}\text{NO}_2$ [$\text{M}+\text{H}$] $^+$ 360.1958; found 360.1959.

General procedure for Suzuki-Miyaura Cross-coupling:

Monocoupling: In a schlenk tube dried by a flame, and under argon, 0.2 g of compound **10a** (1 equiv., 0.44 mmol) were introduced with 10 mL of toluene and 2 mL of water. Then 0.12 g of potassium vinyltrifluoroborane (1.2 equiv, 0.53 mmol), 0.43 g of Cs_2CO_3 (3 equiv., 1.33 mmol) and 36 mg of PdCl_2dppf (0.1 equiv., 0.044 mmol) were added respectively. After 24 hours at 70 °C, 10 mL of HCl (1M) were added and the precipitate was filtered on Büchner then the filtrate was extracted by ethylacetate (3 × 20mL) and the organic phase was washed by NaCl (3 × 10mL), dried by MgSO_4 and concentrated under vacuum. Compound were isolated by column chromatography on silica gel using 2/98: ethyl acetate/petroleum ether as eluent.

Biscoupling: In a schlenk tube dried by a flame, and under argon, 0.2 g of compound **10a** (1 equiv., 0.44 mmol) were introduced with 10 mL of toluene and 2 mL of water. Then 0.13 g of potassium vinyltrifluoroborane (2.2 equiv., 0.97 mmol), 0.43 g of Cs_2CO_3 (3 equiv., 1.33 mmol) and 36 mg of PdCl_2dppf (0.1 equiv., 0.044 mmol) were added respectively. After 24 hours at 70 °C, 0.05 g of vinyltrifluoroborane and 0.02 g of PdCl_2dppf were added and the reaction was let for 3 days. 10 mL of

HCl (1M) were added and the precipitate was filtered on Büchner then the filtrate was extracted by ethylacetate (3 × 20 mL) and the organic phase was washed by NaCl (3 × 10 mL), dried by MgSO₄ and concentrated under vacuum. Compound were isolated by column chromatography on silica gel using 2/98: ethyl acetate/petroleum ether as eluent.

(E)-3-(Benzofuran-2-ylmethylene)-10-iodo-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indol-1-one 11m: Yellow solid (0.11 g, 57 %); m.p. 177-179 °C; *R_f* = 0.57 (EtOAc/PE, 20:80). ¹H NMR (300 MHz, CDCl₃): δ = 7.62-7.45 (m, 5 H), 7.37-7.23 (m, 3 H), 6.73 (s, 1 H), 6.49 (s, 1 H), 5.60 (s, 2 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 155.1, 154.8, 150.0, 143.5, 136.7, 131.2, 128.2, 127.8, 125.3, 124.1, 123.6, 122.8, 121.3, 121.2, 111.1, 110.5, 108.5, 104.4, 68.7, 41.0 ppm. IR (ATR): *v*_{max} = 2917, 2850, 1731, 1232, 1174, 1080, 734 cm⁻¹. HRMS (ESI, positive mode): calcd. for C₂₀H₁₃INO₃ [M+H]⁺ 441.9934; found 441.9931.

(E)-10-Iodo-3-(thiophen-2-ylmethylene)-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indol-1-one 11n: Yellow solid (37 mg, 21 %); m.p. 188-190 °C; *R_f* = 0.48 (EtOAc/PE, 20:80). ¹H NMR (300 MHz, CDCl₃): δ = 7.63 (d, *J* = 6 Hz, 1 H), 7.50 (t, *J* = 7.5 Hz, 1 H), 7.41-7.38 (m, 2 H), 7.32 (t, *J* = 9 Hz, 1 H), 7.11 (dd, *J* = 3.4 Hz, *J* = 5 Hz, 1 H), 7.04 (d, *J* = 3.4 Hz, 1 H), 6.80 (t, *J* = 0.9 Hz, 1 H), 5.32 (d, *J* = 3 Hz, 2 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 155.0, 142.0, 136.6, 134.7, 131.2, 128.6, 128.0, 127.8, 126.6, 124.2, 122.8, 110.4, 109.2, 68.7, 40.3 ppm. IR (ATR): *v*_{max} = 1731, 1086, 735 cm⁻¹. HRMS (ESI, positive mode): calcd. for C₁₆H₁₁INO₂S [M+H]⁺ 407.9549; found 407.9551.

(E)-3-((3,5-Dimethylisoxazol-4-yl)methylene)-10-iodo-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indol-1-one 11o: Yellow solid (18 mg, 12 %), m.p. 242-244 °C; *R_f* = 0.22 (EtOAc/PE, 20:80). ¹H NMR (300 MHz, DMSO-*d*₆): δ = 7.86 (d, *J* = 8 Hz, 1 H), 7.52-7.44 (m, 2 H), 7.29 (t, *J* = 7 Hz, 1 H), 6.27 (s, 1H), 5.09 (s, 2 H), 2.35 (s, 3 H), 2.14 (s, 3H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 165.9, 159.1, 154.8, 145.3, 136.4, 130.2, 127.0, 122.8, 122.4, 121.6, 112.3, 108.0, 101.9, 68.9, 40.2, 11.6, 10.0 ppm. IR (ATR): *v*_{max} = 1747, 1308, 1234, 1155, 1090, 745 cm⁻¹. HRMS (ESI, positive mode): calcd. for C₁₇H₁₄IN₂O₃ (M+H) 421.0043, found 421.0046.

(E)-8-fluoro-10-iodo-3-(pent-2-yn-1-ylidene)-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indol-1-one 13: To a solution of compound **10d** (1 equiv., 0.5 mmol) and pent-2-ynoic acid (3 equiv., 1.5 mmol) in DMF (3 mL), was added copper (I) iodide (0.025 mmol, 0.05 equiv.), palladium (II) acetate (0.1 equiv., 0.05 mmol), triphenylphosphine (0.1 equiv., 0.05 mmol) and triethylamine (2 equiv., 1 mmol) under argon atmosphere. The mixture was heated at 50 °C for 2 hours by microwave irradiation. After cooling to room temperature, the reaction mixture was diluted with water (10 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic phases were washed with brine (2 x 20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (90:10 PE/EtOAc) and afforded 0.14 g of compound **13** as yellow solid with 70% yield. m.p. 148 °C. ¹H NMR (300 MHz, CDCl₃): δ = 7.41-7.34 (m, 1 H), 7.33-7.27 (m, 2 H), 5.67 (bs, 1 H), 5.13 (s, 2 H), 2.43 (qd, *J* = 2.3 Hz, *J* = 7.5 Hz, 2 H), 1.24 (t, *J* = 7.5 Hz, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 159.4 (*J* = 241.2 Hz), 154.1, 150.4, 133.4, 131.8, 122.5, 117.4 (*J* = 24.63 Hz), 112.0 (*J* = 9.45 Hz), 108.8 (*J* = 27.52 Hz), 100.5, 96.8, 72.3, 68.0, 40.9, 14.0, 13.6 ppm. ¹⁹F NMR (188 MHz, CDCl₃) δ = -119.03 ppm. HRMS (ESI, positive mode): calcd. for C₁₆H₁₂IFNO₂ (M+H) 395.9897, found 395.9910.

Ethyl 1-(but-3-ynyl)-3-iodo-1*H*-indole-2-carboxylate 14a: 0.72 g of compound **4a** (1.2 equiv., 2.28 mmol) were introduced in a round bottom flask with 0.13 mg of 3-butyn-1-ol (1 equiv., 1.9 mmol) and 596 mg of PPh₃ (1.2 equiv., 2.28 mmol) in 20 mL of THF, 450 μ L of DIAD (1.2 equiv., 2.28 mmol) were added at 0 °C and the mixture was stirred at RT overnight. The solvent was evaporated under vacuum. Purification by flash chromatography (95:5 PE/EtOAc) afforded the compound **14a** as yellow oil (244 mg, 35%). *R_f* = 0.8 (EtOAc/PE, 5:95). ¹H NMR (300 MHz, CDCl₃) δ = 7.68 (d, *J* = 8.1 Hz, 1 H), 7.48 (d, *J* = 8.4 Hz, 1 H), 7.35 (t, *J* = 7.3 Hz, 1 H), 7.16 (t, *J* = 7.5 Hz, 1 H), 4.75 (t, *J* = 7.3 Hz, 2 H), 4.38 (q, *J* = 7.1 Hz, 2 H), 2.70 (dt, *J* = 7.3 Hz, *J* = 2.7 Hz, 2 H), 1.97 (t, *J* = 2.7 Hz, 1H), 1.43 (t, *J* = 7.1 Hz, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ = 162.1, 139.2, 127.5, 126.1, 125.2, 122.8, 120.9, 111.1, 110.6, 81.1, 70.6, 43.5, 29.8, 20.5, 14.5 ppm. IR (ATR): ν_{max} = 1703, 1436, 1185, 1119, 722, 541 cm⁻¹. HRMS (ESI, positive mode): calcd for C₁₅H₁₅INO₂ (M+H) 368.01420, found 368.02992.

Ethyl 3-iodo-1-(pent-4-ynyl)-1*H*-indole-2-carboxylate 14b: In a two-necked round bottom flask, 1.1 equiv. of NaH 60 % (3.48 mmol) were dissolved in 6 mL of DMF, and 1 equiv. of indole **4a** (3.16 mmol) in 5 mL of DMF were added drop by drop using a bromine bulb at 0 °C under argon. The mixture was stirred for 2 h at RT. 1.1 equiv. of 5-chloropent-1-yne (3.48 mmol) were added to the mixture drop by drop at 0 °C under argon and the mixture was heated at 70 °C overnight. The mixture was hydrolyzed by 10 mL of NH₄Cl, extracted by EtOAc (3 \times 20 mL), and the organic phase was washed with NaCl (6 \times 10 mL), dried by MgSO₄ and evaporated under vacuum. Compound **14b** was obtained as yellow oil (91 mg, 76%).

R_f = 0.71 (20:80 EtOAc/PE). ¹H NMR (300 MHz, CDCl₃): δ = 7.60 (d, *J* = 8.0 Hz, 1 H), 7.47 (d, *J* = 8.4 Hz, 1 H), 7.41 (t, *J* = 8.4 Hz, 1 H), 7.25 (t, *J* = 8.0 Hz, 1 H), 4.67 (t, *J* = 7.2 Hz, 2 H), 4.49 (q, *J* = 7.2 Hz, 2 H), 2.26 (dt, *J* = 7.2 Hz, *J* = 2.5 Hz, 2 H), 2.11 (t, *J* = 2.5 Hz, 1 H), 2.05 (quint, *J* = 7.2 Hz, 2 H), 1.53 (t, *J* = 7.1 Hz, 3 H) ppm. ¹³C NMR (CDCl₃, 75 MHz): δ = 161.2, 138.5, 130.3, 127.9, 126.2, 124.1, 121.6, 110.6, 83.3, 69.4, 67.5, 61.3, 44.8, 29.3, 16.0, 14.4 ppm. IR (ATR): ν_{max} = 2917, 2849, 1737, 1706, 1464, 1242 cm⁻¹. HRMS (ESI, positive mode): calcd for C₁₆H₁₇INO₂ (M+H) 382.02985, found 382.02983.

1-(But-3-ynyl)-3-iodo-1*H*-indole-2-carboxylic acid 15a:

General procedure of saponification with 60 mg of **14a**: Brown solid (50 mg, 91%); *R_f* = 0.19 (20:80 EtOAc/PE). ¹H NMR (300 MHz, CDCl₃): δ = 7.62 (d, *J* = 8.1 Hz, 1 H), 7.54-7.40 (m, 2H), 7.34-7.18 (m, 1 H), 4.81 (t, *J* = 7.1 Hz, 2 H), 2.75 (td, *J* = 7.0, *J* = 2.4 Hz, 2 H), 2.01 (t, *J* = 2.5 Hz, 1 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 166.2, 139.2, 130.7, 127.2, 126.7, 124.6, 122.2, 111.0, 80.7, 71.2, 71.1, 44.8, 20.6. IR (ATR): ν_{max} = 2917, 1677, 1437, 1119, 720 cm⁻¹. HRMS (ESI, positive mode): calcd for C₁₃H₁₁INO₂ (M+H) 339.98290, found 339.98275.

3-Iodo-1-(pent-4-ynyl)-1*H*-indole-2-carboxylic acid 15b: General procedure of saponification with 0.77 g of **14b**: White solid (0.7 g, 98%); m.p. = 191-193 °C; *R_f* = 0.19 (20:80 EtOAc/PE). ¹H NMR (300 MHz, CDCl₃): δ = 7.61 (d, *J* = 8.1 Hz, 1,H), 7.49 (d, *J* = 8.2 Hz, 1,H), 7.41-7.46 (m, 1,H), 7.23-7.28 (m, 1,H), 4.74 (t, *J* = 7.2 Hz, 2,H), 2.25 (dt, *J* = 6.5 Hz, 2.6 Hz, 2,H), 2.02-2.11 (m, 3,H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 165.7, 139.3, 130.6, 127.1, 126.7, 124.6, 122.0, 110.9, 83.3, 70.4, 69.6, 45.1, 29.5, 16.2 ppm. IR (ATR): ν_{max} = 3282, 2919-2504, 2163, 1666, 1263, 740 cm⁻¹. HRMS (ESI, positive mode): calcd for C₁₄H₁₃INO₂ (M+H) 353.99855, found 353.99821.

(E)-11-Iodo-3-(iodomethylene)-4,5-dihydro-1H,3H-[1,4]oxazepino[4,3-a]indol-1-one 16a: General procedure of iodocyclization with 140 mg of **15a**: Beige solid (79 mg, 41%); $R_f = 0.4$ (20:80 EtOAc/PE). m.p. = 192-194 °C. ^1H NMR (300 MHz, CDCl_3): $\delta = 7.59$ (d, $J = 8.3$ Hz, 1H), 7.47 (t, $J = 8.3$ Hz, 1H), 7.34 (d, $J = 8.2$ Hz, 1H), 7.27 (t, $J = 8.2$ Hz, 1H), 6.43 (t, $J = 1.5$ Hz, 1H), 4.50 (t, $J = 6.6$ Hz, 2H), 3.17 (td, $J = 6.6$ Hz, 1.5 Hz, 2H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 158.4, 151.4, 137.1, 130.5, 127.4, 127.3, 124.1, 122.2, 110.0, 77.4, 70.8, 40.8, 34.6$ ppm. IR (ATR): $\nu_{\text{max}} = 1717, 1350, 1061, 738$ cm^{-1} . HRMS (ESI, positive mode): calcd for $\text{C}_{13}\text{H}_{10}\text{I}_2\text{NO}_2$ (M+H) 465.87954, found 465.87909.

(E)-12-Iodo-3-(iodomethylene)-3,4,5,6-tetrahydro-1H-[1,4]oxazocino[4,3-a]indol-1-one 17b: General procedure of iodocyclization with 0.88 g of **15b**: Beige solid (33 mg, 28%); m.p. = 162-164 °C; $R_f = 0.38$ (20:80 EtOAc/PE). ^1H NMR (300 MHz, CDCl_3): $\delta = 7.51$ (d, $J = 8.1$ Hz, 1 H), 7.41 (t, $J = 8.5$ Hz, 1 H), 7.30-7.24 (m, 2 H), 5.73 (bs, 1 H), 4.41-4.34 (m, 2 H), 2.75 (t, $J = 6.5$ Hz, 2 H), 2.14-2.05 (m, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 159.4, 155.0, 137.3, 130.4, 129.5, 126.7, 123.6, 122.0, 110.0, 67.8, 67, 45.2, 31.9, 25.9$ ppm. IR (ATR): $\nu_{\text{max}} = 3048, 1725, 1632, 1077, 1036, 731$ cm^{-1} . HRMS (ESI, positive mode): calcd for $\text{C}_{14}\text{H}_{12}\text{I}_2\text{NO}_2$ (M+H) 479.89519, found 479.89536.

Ethyl 1-(prop-2-ynyl)-1H-pyrrole-2-carboxylate 19: General procedure of propargylation with 2.1 g of **18**: Colorless oil (1.92 g, 72%); $R_f = 0.73$ (20:80 EtOAc/PE). ^1H NMR (300 MHz, CDCl_3): $\delta = 7.11$ (dd, $J = 2.5$ Hz, $J = 1.8$ Hz, 1 H), 6.98 (dd, $J = 3.9$ Hz, $J = 1.8$ Hz, 1 H), 6.17 (dd, $J = 3.9$ Hz, $J = 2.5$ Hz, 1 H), 5.17 (d, $J = 2.5$ Hz, 2 H), 4.28 (q, $J = 7.1$ Hz, 2 H), 2.43 (t, $J = 2.5$ Hz, 1 H), 1.35 (t, $J = 7.1$ Hz, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 161.0, 127.8, 121.9, 118.3, 108.5, 78.3, 73.7, 59.9, 38.1, 14.3$ ppm. IR (ATR, cm^{-1}): $\nu_{\text{max}} = 3087, 1734, 1535, 1191, 867$. HRMS (ESI, positive mode): calcd for $\text{C}_{10}\text{H}_{12}\text{NO}_2$ (M+H) 178.08626, found 178.08634.

1-(Prop-2-ynyl)-1H-pyrrole-2-carboxylic acid 20: General procedure of saponification with 0.52 g of **19**: Pale yellow solid (0.39 g, 91%); $R_f = 0.21$ (20:80 EtOAc/PE); m.p. = 148-150 °C. ^1H NMR (300 MHz, CDCl_3): $\delta = 7.21$ (t, $J = 2.3$ Hz, 1 H), 7.13 (dd, $J = 4.0$ Hz, $J = 1.7$ Hz, 1 H), 6.22 (dd, $J = 4.0$ Hz, $J = 2.3$ Hz, 1 H), 5.17 (d, $J = 2.5$ Hz, 2 H), 2.45 (t, $J = 2.5$ Hz, 1 H) ppm. ^{13}C NMR (75MHz, CDCl_3): $\delta = 165.8, 129.3, 121.1, 120.9, 109.2, 78.1, 74.2, 38.5$ ppm. IR (ATR): $\nu_{\text{max}} = 3255, 2992-2548, 1654, 1260, 734$ ppm. HRMS (ESI, positive mode): calcd for $\text{C}_8\text{H}_8\text{NO}_2$ (M+H) 150.05496, found 150.05500.

(E)-3,4-Dihydro-3-(iodomethylene)pyrrolo[2,1-c][1,4]oxazin-1-one 21: General procedure of iodocyclization with 0.35 g of **20**: Brown solid (0.19 g, 30%); $R_f = 0.52$ (20:80 EtOAc/PE); m.p.= 88-90 °C. ^1H NMR (300 MHz, CDCl_3): $\delta = 7.14$ (dd, $J = 4.1$ Hz, $J = 1.5$ Hz, 1 H), 6.96-6.95 (m, 1H), 6.39 (dd, $J = 4.1$ Hz, 2.5 Hz, 1 H), 6.25 (t, $J = 1.2$ Hz, 1 H), 4.98 (d, $J = 1.2$ Hz, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 153.7, 147.3, 125.7, 118.2, 116.6, 112.0, 62.9, 45.6$ ppm. IR (ATR, cm^{-1}): $\nu_{\text{max}} = 1718, 1327, 1166, 735$. HRMS (ESI, positive mode): calcd for $\text{C}_8\text{H}_7\text{INO}_2$ (M+H) 275.95160, found 275.95138.

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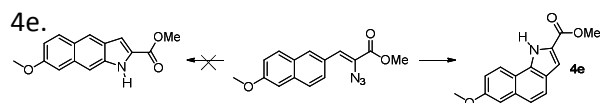
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- [1] a) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875–2911; b) S. Katayama, N. Ae, R. Nagata, *J. Org. Chem.* **2001**, *66*, 3474–3483; c) V. M. Lombardo, C. D. Thomas, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2013**, *52*, 12910–12914; *Angew. Chem.* **2013**, *125*, 13148–13152; d) T. C. Leboho, J. P. Michael, W. A. L. van Otterlo, S. F. van Vuuren, C. B. de Koning, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4948–4951; e) M. Bandini, A. Eichholzer, M. Tragni, A. Umani-Ronchi, *Angew. Chem. Int. Ed.* **2008**, *47*, 3238–3241; *Angew. Chem.* **2008**, *120*, 3282–3285. f) Z. Chen, X. Zeng, B. Yan, Y. Zhao, Y. Fu, *RSC Adv.* **2015**, *5*, 100251–100255; g) J. Liu, M. Shen, Y. Zhang, G. Li, A. Khodabocus, S. Rodriguez, B. Qu, V. Farina, C. H. Senanayabe, B. Z. Lu, *Org. Lett.* **2006**, *8*, 3573–3575; h) M. Lounasmaa, A. Tolvanen, *Nat. Prod. Rep.* **2000**, *17*, 175–191.
- [2] E. Deniz, M. Tomasulo, S. Sortino, F. Raymo, *J. Phys. Chem. C*, **2009**, *113*, 8491–8497.
- [3] S. Ayril-Kaloustian, N. Zhang, A. M. Venkatesan, T. S. Mansour, T. H. Nguyen, J. T. Anderson, U.S. Pat. Appl. Publ. **2009**, US 20090192147 A1.
- [4] a) W. T. Zimmerman, PCT Int. Appl. **1991**, WO 9110668 A1; b) W. T. Zimmerman, U.S. **1994**, US 5356862 A.
- [5] S. Inaba, K. Ishizumi, M. Akatsu, R. Kume, K. Mori, H. Yamamoto, Jpn. Tokkyo Koho **1974**, JP 49004238 B.
- [6] M. Fedouloff, F. Hossner, M. Voyle, J. Ranson, J. Powles, G. Riley, G. Sanger, *Bioorg. Med. Chem.* **2001**, *9*, 2119–2128.
- [7] a) J. A. Elvidge, F. S. Spring, *J. Chem. Soc.* **1949**, 2935–2942; b) J. Rokach, Y. Girard, J. G. Atkinson, *Can. J. Chem.* **1973**, *51*, 3765–3770; c) H. F. Schuster, G. M. Coppola, *J. Heterocycl. Chem.* **1994**, *31*, 1381–1384.
- [8] a) H. Yanai, T. Taguchi, *Chem. Comm.* **2012**, *48*, 8967–8969; b) C. O. Salas, R. A. Tapia, Y. Prieto, *Acta Cryst., Sect. E*: **2011**, *67*, o318.
- [9] L. Wei, L. Liu, J. Zhang, *Org. Biomol. Chem.* **2014**, *12*, 6869–6877.
- [10] S. P. Hiremath, G. R. Badiger, A. S. Jivanagi, M. G. Purohit, *Indian J. Chem., Sect. B* **1992**, *31B*, 583–589.
- [11] M. Bandini, A. Bottoni, A. Eichholzer, G. P. Miscione, M. Stenta, *Chem. Eur. J.* **2010**, *16*, 12462–12473; b) H. He, L.-X. Dai, S.-L. You, *Org. Biomol. Chem.* **2010**, *8*, 3207–3210.
- [12] V. A. Vaillard, R. A. Rossi, S. E. Martin, *Org. Biomol. Chem.* **2011**, *9*, 4927–4935.
- [13] J. K. Vandavasi, W.-P. Hu, G. C. Senadi, S. S. K. Boominathan, H.-Y. Chen, J.-J. Wang, *Eur. J. Org. Chem.* **2014**, *28*, 6219–6226.
- [14] S. Taskaya, N. Menges, M. Balci, *Beilstein J. Org. Chem.* **2015**, *11*, 897–905.
- [15] a) A. Putey, G. Fournet, B. Joseph, *Synlett* **2006**, 2755–2758; b) A. Putey, G. Fournet, O. Lozach, L. Perrin, L. Meijer, B. Joseph, *Eur. J. Med. Chem.* **2014**, *83*, 617–629.
- [16] S. Inack-Ngi, V. Guilloteau, M. Abarbri, J. Thibonnet, *J. Org. Chem.* **2011**, *76*, 8347–8354.
- [17] a) H. Hemetsberger, D. Knittel, *Monatsch. Chem.* **1972**, *103*, 194–204; b) D. Knittel, *Synthesis*, **1985**, 186–188; c) P. Roy, M. Boisvert, Y. Leblanc, *Org. Synth.* **2007**, *84*, 262–271.

[18] a) C. Poriel, M. Lachia, C. Wilson, J. R. Davies, C. J. Moody, *J. Org. Chem.* **2007**, *72*, 2978–2987. b) C. Neagoie, E. Vedrenne, F. Buron, J.-Y. Mérour, S. Rosca, S. Bourg, O. Lozach, L. Meijer, B. Baldeyrou, A. Lansiaux, S. Routier, *Eur. J. Med. Chem.* **2012**, *49*, 379–396.

[19] The thermolysis of the acrylate (Hemetsberger-Knittel method) leads exclusively to the product



[20] Y. Durust, A. Sagirli, B. M. Kariuki, D. W. Knight, *Tetrahedron* **2014**, *70*, 6012–6019.

[21] J. K. Vandavasi, W.-P. Hu, G. C. Senadi, S. S. K. Boominathan, H.-Y. Chen, J.-J. Wang *Eur. J. Org. Chem.* **2014**, *28*, 6219–6226.

[22] M. Sechi, M. Derrudas, R. Dallochio, A. Dessi, A. Bacchi, L. Sannia, F. Casta, M. Palomba, O. Ragab, C. Chen, R. Shoemaka, S. Sei, R. Dayam, N. Neamati, *J. Med. Chem.* **2004**, *47*, 5298–5310.

[23] A. Putey, F. Popowycz, B. Joseph *Synlett* **2007**, 419–422.

[24] A. Zakarian, A. Batch, R. A. Holton, *J. Am. Chem. Soc.* **2003**, *125*, 7822–7823.

[25] X. Zhang, Y. Zhou, H. Wang, D. Guo, D. Ye, Y. Xu, H. Jiang, H. Liu, *Adv. Synth. Catal.* **2011**, *353*, 1429–1437.

[26] M. Alvarez-Corral, M. Munoz-Dorado, I. Rodriguez-Garcia, *Chem. Rev.* **2008**, 3174–3198.

[27] CCDC 1496048, CCDC 1851526 and CCDC 1851393 contains the supplementary crystallographic data for **10a**, **16a** and **17b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data/request/cif.

[28] see supporting information (SI-2).

[29] P. Quinodoz, A. Quelhas, A.; K. Wright, B. Drouillat, J. Marrot, F. Couty, *Eur. J. Org. Chem.* **2017**, 2621–2626.

[30] a) T. Yao, R. C. Larock, *J. Org. Chem.* **2003**, *68*, 5936–5942; b) V. Dubrovskiy, N. A. Markina, R. C. Larock, *Comb. Chem. High Throughput Screening*, **2012**, *15*, 451–472; c) A. Gupta, B. L. Flynn, *J. Org. Chem.* **2016**, *81*, 4012–4019; d) H. Huang, X. Zhu, G. He, Q. Liu, J. Fan, H. Zhu, *Org. Lett.* **2015**, *17*, 2510–2513; e) R. Mancuso, C. C. Pomelli, F. Malafrente, A. Marino, C. Chiappe, B. Gabriele, *Org. Biomol. Chem.* **2017**, *15*, 4831–4841.

[31] V. L. Heasley, D. F. Shellhamer, L. E. Heasley, D. B. Yaeger, G. E. Heasley, *J. Org. Chem.* **1980**, *45*, 4649–4652.

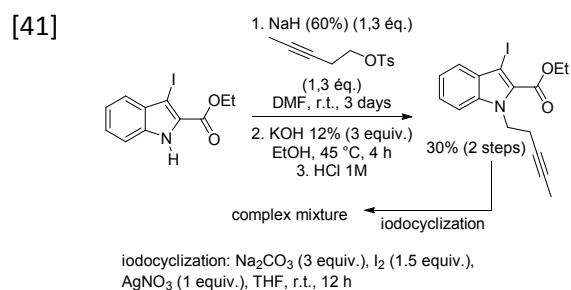
[32] a) J. K Stille, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508–524; b) D. Milstein, J. K. Stille, *J. Am. Chem. Soc.* **1979**, *101*, 4992–4998.

[33] a) M. Pereyre, J.-P. Quintard, A. Rahm, Tin in Organic Synthesis; Butterworths: London, **1987**; b) A. G. Davies, Organotin Chemistry; Wiley-VCH: Weinheim, **1997**; c) Tin in Organic Synthesis. In Tin Chemistry. Fundamentals, Frontiers, and Applications; A. G. Davies, M. Gielen, K. H. Pannell, E. R. T. Tiekink, Eds.; John Wiley & Sons, Ltd.: New York, **2008**; pp. 497–665; d) T. Hiyama, Organosilicon and relating Organotin Chemistry. In Organometallics in Synthesis, 3rd ed.; Schlosser, M., Ed.; J. Wiley & Sons: Hoboken, NJ, **2013**; pp. 373–544.

[34] M.M Heravi, L. Mohammadkhani, *J. Organometallic. Chem.* **869**, **2018**, 106–200.

[35] D. C. Harrowven, D. P. Curran, S. L. Kostiuik, I. L. Wallis-Guy, S. Whiting, K. J. Stenning, B. Tang, E. Packard, L. Nanson, *Chem. Commun.* **2010**, *46*, 6335–6337.

- [36] a) K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, 4467–4470; b) Y. Tohda, K. Sonogashira, N. Hagihara, *Synthesis*, **1977**, 777–778; c) K. Sonogashira, In *Metal-Catalyzed Cross-Coupling Reactions*, P. J. Stang, F. Diederich, Eds.; Wiley-VCH: Weinheim, **1998**, pp. 203–229.
- [37] a) A. Suzuki, *J. Organomet. Chem.* **1999**, 576, 147–168; b) A. Suzuki, In *Metal-Catalyzed Cross-Coupling Reactions* P. J. Stang, F. Diederich, Eds.; Wiley-VCH: Weinheim, **1998**, pp. 49–97; c) N. Miyaura, *Chem Rev.* **1995**, 95, 2457–2483; d) R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, 111, 1417–1492.
- [38] a) S. Darses, J.-P. Genet, *Chem. Rev.* **2008**, 108, 288–325; b) G. A. L. Molander, N. Ellis, *Acc. Chem. Res.* **2007**, 40, 275–286; c) C.-N. Zhou, H.-H. Xie, Z.-A. Zheng, Y.-C. Xiao, G. Li, Y.-H. Shen, W.-M. Peng, L. Wang, *Chem. Eur. J.* **2018**, 24, 5469–5473.
- [39] C. Maaliki, Y. Chevalier, E. Thiery, J. Thibonnet, *Tetrahedron Lett.* **2016**, 57, 3358–3362.
- [40] a) Mitsunobu, *Synthesis*, **1**, 1–28; b) K. C. Kumara Swamy, N. N. Bhuvan Kumar, E. Balaraman, K. V. P. Pavan Kumar, *Chem. Rev.* **2009**, 109, 2551–2651; c) S. S. Bhagwat, C. Gude, *Tetrahedron Lett.* **1994**, 35, 1847–1850.



- [42] M. A. Winnik, *Chem. Rev.* **1981**, 81, 491–524; b) J. Ackrell, F. Franco, R. Greenhouse, A. Guzman, J. M. Muchowski, *J. Heterocycl. Chem.* **1980**, 17, 1081–1085; c) F. Gatta, F. Ponti, *Boll. Chim. Farm.* **1981**, 120, 102–107; d) G. Mehta, V. Singh, *Chem. Rev.* **1999**, 99, 881–930; e) T. Iwai, H. Okochi, H. Ito, M. Sawamura, *Angew. Chem. Int. Ed.* **2013**, 52, 4239–4242; *Angew. Chem.* **2013**, 125, 4333–4336.
- [43] a) P. Gonzalez-Perez, L. Perez-Serrano, L. Casarrubios, G. Dominguez, J. Perez-Castells, *Tetrahedron Lett.* **2002**, 43, 4765–4767; b) M. L. Bannasar, E. Zulaica, S. Tummers, *Tetrahedron Lett.* **2004**, 45, 6283–6285; c) A. L. J. Beckwith, J. M. D. Storey, *J. Chem. Soc. Chem. Commun.* **1995**, 977–978; d) N. Chernyak, D. Tilly, Z. Li, V. Gevorgyan, *Chem. Commun.* **2010**, 46, 150–152; e) S. Naoe, T. Saito, M. Uchiyama, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2015**, 17, 1774–1777; f) Y. Liu, Y. Huang, H. Song, Y. Liu, Q. Wang, *Chem. Eur. J.* **2015**, 21, 5337–5340; g) B. Prasad, B. Y. Sreenivas, D. Rambabu, G. R. Krishna, C. M. Reddy, K. L. Kumar, M. Pal, *Chem. Commun.* **2013**, 49, 3970–3972.
- [44] S. Basceken, S. Kaya, M. Balci, *J. Org. Chem.* **2015**, 80, 12552–12561.