Tetrahedron 64 (2008) 11012–11019

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of new fused and substituted benzo and pyrido carbazoles via C-2 (het)arylindoles

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ARTICLE INFO

Article history:
Received 8 July 2008
Received in revised form 10 September 2008
Accepted 30 September 2008
Available online 8 October 2008

ABSTRACT

In the course of a program aimed at designing new antitumor agents, we were interested in the synthesis of new substituted benzo and pyrido carbazoles. The synthesis was performed through an efficient four-step sequence from a 2-trimethylstannylindole derivative and via C-2 (het)arylindoles. The synthetic sequence was developed using two palladium mediated reactions including, at the end of the synthesis, a direct (het)arylannulation, which led to the desired heterocycles.

1. Introduction

Indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole alkaloids form a class of compounds endowed with potent antitumor, antiviral and/or antimicrobial activities.[1] During the past decade, two natural models named rebeccamycin and staurosporin have been modified in order to establish fine structure–activity relationships. Structural modifications of rebeccamycin scaffold led to topoisomerase I inhibitors such as NB-506 and J-107088, which were advanced to clinical trials.[2–4]

Concerning the staurosporin and its derivative UCN-01, strong but unselective inhibition of protein kinases was found.[5,6]

In order to simplify the complex glycosylated models, some groups focused their efforts on the arcyriaflavin skeleton (Fig. 1).[7,8] Many synthetic challenges were next explored to modify the indolocarbazolic structure. In this area, we replaced the indole moeity by 5 or 7-azaindoles units and reported the synthesis and the biological results of 5 or 7-aza-indolocarbazoles.[9] We also recently described the synthesis of naphtho and benzo carbazoles.[10]

From the beginning of the indolocarbazoles story, numerous pathways were developed to build bis indolic derivatives. The most representative consisted in the Grignard addition of indolyl lithium or magnesium salts on the 2,3-dibromomaleimide **23**.[11] The second classical way consisted in the preparation of indolyl-3 glyoxylate and 3-indolyl acetamide, which led under basic conditions to similar bis indolic maleimides.[12] In both pathways the final annulation step, leading to indolocarbazole skeleton, could be performed either by photochemical irradiation or by [4+2] cycloaddition thus generating a C–C bond between the two C-2 indolic positions.

Alternatively, the Sanchez's group and our team successfully proposed an original route **A**. Starting from (het)Ar glyoxylate or acetamide, boron or stannyl derivatives, mono indolyl compounds of type **II** were prepared and a C-2 indolic palladium-assisted arylation achieved the synthesis of the non-substituted (het)aryl derivatives **I** (R=H).[10,13] This global strategy (Fig. 2) appeared as a major simplification for parented indolocarbazole synthesis without any photochemical step. Nevertheless limitations appeared to obtain trisubstituted (het)Ar derivatives **II** (R≠H).

The generalization of route **A** would imply the preparation of derivatives **II** bearing: (i) a leaving group X (halogen atom or triflate), (ii) the appropriate substituent R in the *ortho* position to X, and (iii) a useful function Fc for cross coupling ($B(OH)_2$, SnR_3,…). Immediately this challenge appeared as difficult.

So, we elaborated an alternative retrosynthetic scheme, starting from indole derivative **3**, including two palladium catalyzed reactions (route **B**). Very recently, a related strategy was reported to design pyridocarbazoles.[14a] The synthesis involved, in a first step, a Suzuki cross coupling reaction between indoles and an halogenopyridine.[14b] Nevertheless, the final annulation was performed exclusively under photochemical irradiation.

Our synthetic route **B** allowed the preparation of substituted carbazoles of type **I** and involved the use of 2-phenyl (or 2-pyridinyl) substituted indoles, which were obtained from the *N*-benzenesulfonyl-2-trimethylstannyl indole **3** and the halogeno derivatives **IV** through a Stille reaction. After protective group removal and condensation of the dibromo maleimide **23**, the intermediates **V** were obtained. The final step was devoted to the bond formation between the C-sp^2 of the maleimide moiety and the (het)Ar fragment. This was performed by a second palladium catalyzed Heck type arylation reaction. As in route **A** the central ring formation is achieved by a C-2 cyclization on the indole ring, this route **B** may be considered as an anti-clockwise building of (het)arylcarbazoles. In order to complete our studies, each step was

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0040-4020/$ – see front matter © 2008 Published by Elsevier Ltd.
doi:10.1016/j.tet.2008.09.101

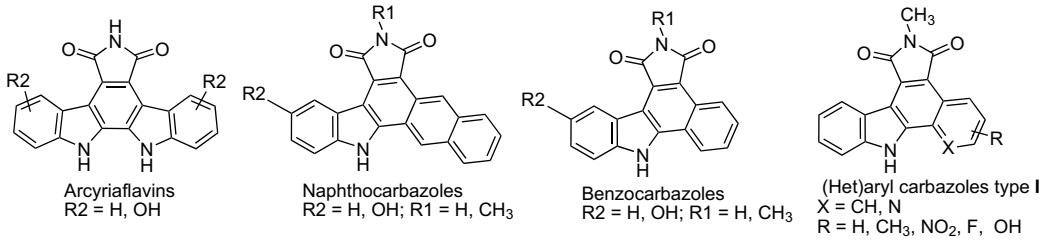


Figure 1. Some representative indolocarbazole related compounds.

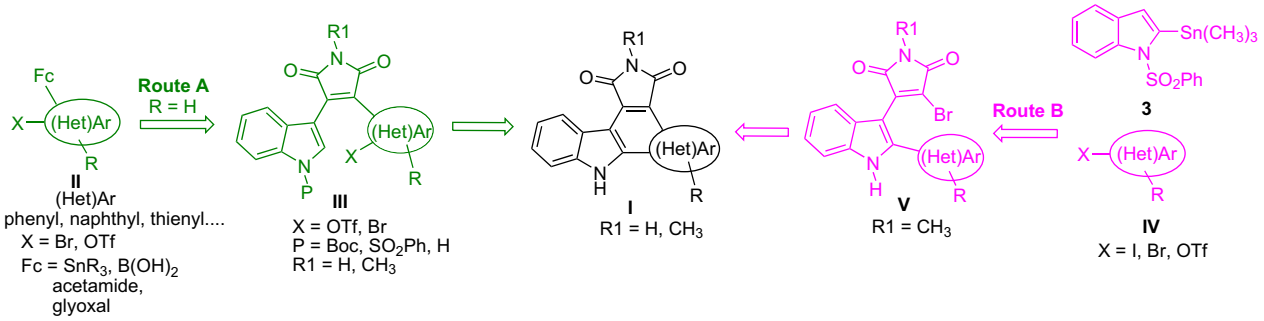


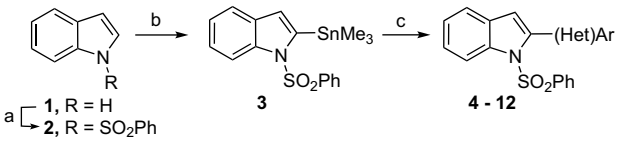
Figure 2. Two routes toward indolocarbazoles and (het)arylcarbazoles.

optimized in the presence of various substituents either on the phenyl or pyridine ring.

2. Results and discussion

2.1. Synthesis of bis 2-(het)aryl indolic derivatives

Lithiation of 1-benzenesulfonyl indole **2** (obtained from indole **1**, Scheme 1) was first carried out in presence of *n*-BuLi (1.2 equiv) at −78 °C during 1 h followed by addition of trimethylstannyl chloride (1.5 equiv).[15] After 1 h, compound **3** was isolated in only 37% yield. Replacing *n*-BuLi by LDA (1.5 equiv) and warming up the mixture to −30 °C for 45 min led to quantitative anion formation. After cooling again to −78 °C the electrophile (1.7 equiv) was added and the reaction mixture was allowed to reach room temperature. This optimized conditions afforded, after 2 h, the desired trimethylstannyl derivative **3** in a very good yield (83%).



Scheme 1. *Reagents and conditions*: (a) $PhSO_2Cl$ (1.1 equiv), NaH (1.2 equiv), THF, 0 °C to rt, 6 h, 86%; (b) LDA (1.5 equiv), THF, −78 °C to −30 °C, 45 min then $ClSn(CH_3)_3$ (1.7 equiv), −78 °C to rt, 2 h, 83%; (c) for conditions see Table 1.

Stille reactions involving **3** were, surprisingly, scarcely described in the literature. In presence of 2-bromopyridine (2.5 equiv), $Pd(PPh_3)_4$ (10%), and CuI (20%), the reaction led in refluxing THF to compound **4** after 3 days in 65% yield (Table 1, entry 1a). Starting material **3** was never fully consumed and a small amount of **3** was isolated after the purification step (10%). Switching the solvent for DMA had no effect on the yield but decreased the reaction time to 5 h (entry 1b). Postulating that the high temperature enhanced the degradation of the reaction mixture, the reaction was next conduced at 100 °C and after 6 h the compound **4**[16] was quantitatively isolated (entry 1c).

We next applied these last conditions [i.e., $Pd(PPh_3)_4$ (10%), CuI (20%), DMA, 100 °C] to the 2-bromo-6-methoxypyridine. After 14 h the desired compound **5** was isolated without any difficulty in a 70% yield (entry 2). Some limitations occurred starting from 2-bromopyridine *N*-oxide and 2-chloro-6-(*O*-MOM)-pyridine (entries 3 and 4), only homocoupling of **3**, leading to bis-(benzenesulfonyl[2,2′]indole) **6**, occurred.[17]

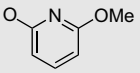
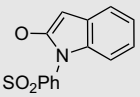
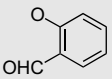
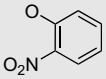
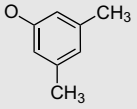
Nevertheless, compound **6** was not detected in the phenyl series. Compound **7**[18] was quantitatively obtained after 12 h (entry 5a) from the volatile bromobenzene (10.0 equiv) and in 78% yield after only 4 h (entry 5b) by using iodobenzene (3 equiv). Unfortunately, the electro-withdrawing groups (EWG) in position 2 of the phenyl halide (entries 6–9) diminished the efficiency of the cross coupling reaction. Indeed starting from 1-bromo-2-fluorobenzene, compound **8** was isolated in only 25% yield (entry 6a). Since an increase of the reaction time was inefficient, we modified the amount of halide (10.0 equiv) and thus the yield of **8** enhanced to 75% (entry 6b). We next performed the reaction with 1-fluoro-2-iodobenzene (3.0 equiv) and after 6 h, compound **8** was obtained in 82% yield (entry 6c).

Starting from 2-bromobenzaldehyde (3.0 equiv), the resulting mixture led after purification to **9**[19] in 45% yield. In this case, a simple increase of the reaction time to 16 h enhanced the yield to 89% (entries 7a, b). The other assays performed with 2-bromobenzonitrile and 2-bromonitrobenzene were also realized in 16 h to provide compounds **10** and **11**[20] in 84 and 88% yield, respectively (entries 8 and 9). Despite the presence of EWG, the desired products were obtained in very good yields increasing the quantity of halide and more specifically the reaction times. As a next assay, we used the 1-bromo-3,5-dimethylbenzene, and after 12 h, the reaction was completed to afford **12** in 78% yield (entry 10).

2.2. Deprotection and introduction of the maleimide moiety on C-3 of indole

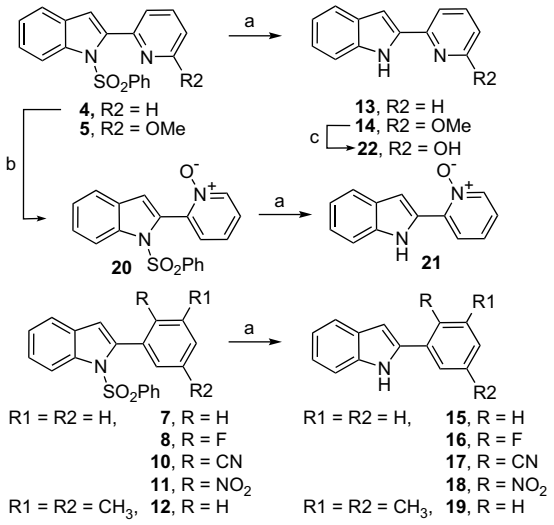
To perform the C-3 Michael addition, the indolic nitrogen must be free of substituent. So the benzenesulfonyl group was removed, using Bu_4NF in refluxing THF (Scheme 2). The only reaction

Table 1
Experimental conditions for Stille reactions using **3**

Entry		(Het)ArX	Equivalent	Conditions	Time	(Het)Ar	Yield[a]
1	a	2-Bromopyridine	3.0	$Pd(PPh_3)_4$ (10%), CuI (20%), THF, reflux	3 days		**4** (65%)
	b			$Pd(PPh_3)_4$ (10%), CuI (20%), DMA, reflux	5 h		**4** (65%)
	c			$Pd(PPh_3)_4$ (10%), CuI (20%), DMA, 100 °C	6 h		**4** (quant.)
2		2-Bromo-6-methoxy-pyridine	3.0	$Pd(PPh_3)_4$ (10%), CuI (20%), DMA, 100 °C	14 h		**5** (70%)
3		2-Bromo-pyridine-*N*-oxide	3.0	Idem	12 h		**6** (46%)
4		2-Choro-6-(*O*-MOM)pyridine[b]	3.0	Idem	24 h		**6** (46%)
5	a	Bromobenzene	10.0	Idem	12 h		**7** (quant.)
	b	Iodobenzene	3.0		4 h		**7** (78%)
6	a	1-Bromo-2-fluorobenzene	3.0	Idem	16 h		**8** (25%)
	b	1-Bromo-2-fluorobenzene	10.0		16 h		**8** (75%)
	c	1-Fluoro-2-iodobenzene	3.0		6 h		**8** (82%)
7	a	2-Bromobenzaldehyde	3.0	Idem	8 h		**9** (45%)
	b				16 h		**9** (89%)
8		2-Bromobenzonitrile	3.0	Idem	16 h		**10** (84%)
9		2-Bromonitrobenzene	3.0	Idem	16 h		**11** (88%)
10		1-Bromo-3,5-dimethylbenzene	3.0	Idem	12 h		**12** (78%)[c]

[a] Yields are given for isolated products, which were fully characterized by IR, MS, ^1H, and ^{13}C NMR.
[b] This compound was selectively obtained from 6-chloro-1*H*-pyridin-2-one and MOMCl (1.1 equiv) in THF at room temperature in presence of NaH (1.5 equiv) during 2 h in 72% yield.
[c] A small amount of **12** was lost during the purification step.

providing degradation occurred with the formylated derivative **9**. Starting materials **4**, **5**, **7**, **8**, **10**–**12** led without any difficulties to compounds **13**–**19**, after a few hours and with a slight excess of Bu_4NF, in very good yields.[16,20–24]



Scheme 2. *Reagent and conditions*: (a) Bu_4NF (1.5 equiv), THF, reflux, **13** (4 h, quant.), **14** (1 h 30 min, 94%), **15** (3 h, quant.), **16** (2 h, 91%), **17** (2 h, 88%), **18** (1 h 30 min, 94%), **21** (3 h, 81%), **19** (Bu_4NF 2.5 equiv, 1 h 30 min, 87%); (b) *m*-CPBA (1.2 equiv), $CHCl_3$, rt, 12 h, 79%; (c) H_2O/HBr 30% in acetic acid 1:1, reflux, 6 h, 89%.

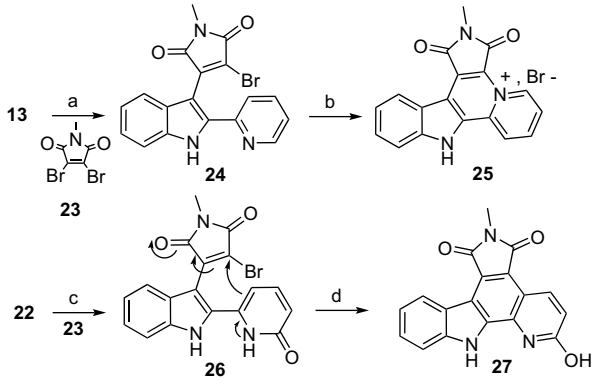
In the previous Stille reaction, we were unable to obtain directly the 2-(*N*-benzenesulfonylindolyl)-pyridin-*N*-oxide **20** from **3**. As an alternative, we prepared **20** from compound **4** in presence of *m*-CPBA in $CHCl_3$ at room temperature during 12 h in 74% yield (Scheme 2). The benzenesulfonyl group of **20** was next removed using 1.5 equiv of Bu_4NF in refluxing THF without any difficulties and compound **21** was isolated in 81% yield. In addition, the hydroxylated compound **22** was obtained from **14** in refluxing aqueous HBr solution in 89% yield (all assays with BBr_3 from **5** and **14** failed). Compound **22** exists as a mixture of tautomers.

The next step consisted in the regioselective Michael addition[9] on the 3,5-dibromo-*N*-methylmaleimide **23** at C-3 indolic position. In this new series, all reactions were performed with 2.2 equiv of LiHMDS between −20 °C and room temperature but it appeared that results depended also on the nature of the C-2 indolic substitution.[10,11]

2.2.1. Reactions with C-2 pyridinyl indoles

Compound **24** was the only product observed on TLC during the Michael reaction of **13** and **23** (Scheme 3). But after hydrolysis and heating to remove the volatiles, another strong polar yellow product **25** appeared. Nevertheless after a fast silica gel pad filtration, the highly sensitive derivative **24** was only isolated in the moderate yield of 43%. To identify the by-product, the crude material was dissolved in DMA and the mixture was heated to reflux for 30 min; after cooling, **25** was filtered and isolated in a 80% yield. Its formation is certainly due to the nucleophilic addition of the pyridine nitrogen atom on the maleimide Michael acceptor by a spontaneous intramolecular 1,4-addition followed by bromide

elimination. It must be pointed out that Bregman[14] indicated the formation of a pyridinium salt as traces (no data reported) during the photocyclisation of analogous derivative; here **25** was obtained according to a quasi spontaneous nucleophilic displacement. The structure of **25** is supported by NMR data and HRMS.

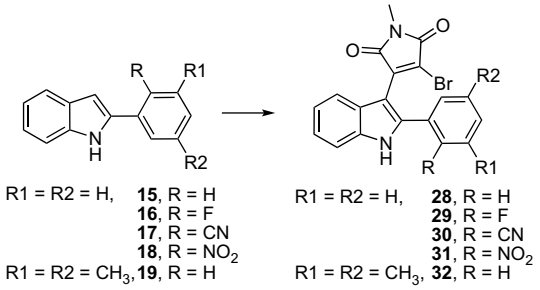


Scheme 3. *Reagent and conditions*: (a) LiHMDS (2.2 equiv), THF, −20 °C, 45 min then **23** (1.3 equiv), −20 °C to rt, 1 h, 43%; (b) DMA, 120 °C, 30 min, 80%; (c) LiHMDS (3.2 equiv), THF, −20 °C, 45 min then **23** (1.3 equiv), −20 °C to rt, 1 h, 58%; (d) DMSO, 50 °C, 48 h, quant.

Starting from the *N*-oxide derivative **21**, degradation occurred whereas the reaction of the pyridine **22** led to the expected compound **26** in 58% yield. This last reaction required 3.2 equiv of base. The two first equivalents formed the dianion of **22** whereas the third one achieved the aromatization step after the nucleophilic addition on **23**. Under basic media or after hydrolysis, the intramolecular reaction due to the pyridinic nitrogen atom was not observed. The tautomeric equilibrium pyridinone/hydroxypyridine decreased also the nucleophilicity of the nitrogen atom. In order to promote the cyclization, compound **26** was stirred in at room temperature for 48 h but surprisingly **27** was the sole isolated compound in a quantitative manner. The corresponding pyridinium salt was not observed.

2.2.2. Reactions with C-2 phenyl indoles

Michael condensations were next regioselectively carried out in C-3 position of indole, starting from the 2-phenylated indoles **15**–**19**, under the previously reported conditions (Scheme 4). Starting from **15** and **16**, the reaction led without any difficulty to compounds **28**[1b] and **29**, respectively, both in very good yields. From **19** the attempted product **32** was isolated in 75% yield after the increase of the amounts of base (3.0 equiv) and compound **23** (2.0 equiv).



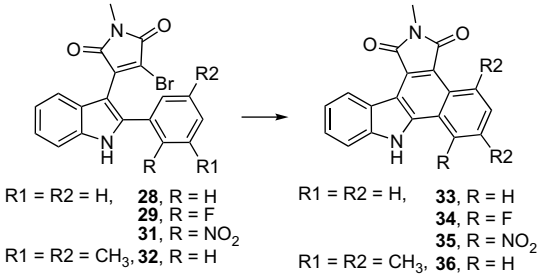
Scheme 4. *Reagent and conditions*: LiHMDS, THF, −20 °C then **23**, −20 °C to rt, **28** (75%), **29** (92%), **32** (75%), **30** (65%), **31** (38%).

The presence of the cyano and nitro groups decreased dramatically the reactivity of the lithiated indole. From **17**, using 2.2 equiv of base and 1.3 equiv of maleimide **23**, the product **30** was isolated in only 56% yield. By modifying the amount of base (3.0 equiv), the amount of **23** (2.0 equiv), and the reaction time (5 h), **30** was finally obtained in a yield of 65%.

The effect of the EWG was reinforced with the nitro derivative **18**, limiting the formation of compound **31**, which was obtained in a poor 38% yield. One hypothesis to explain this result consisted in the stabilization of the nitrogen indolic anion by an intramolecular 6-center ring including the electronegative group. The reactivity of the C-3 center decreased considerably.

2.3. Intramolecular Heck reaction

In the absence of pyridinyl derivatives, which require further studies, we focused our effort on the intramolecular Heck arylation reaction of compounds **28**–**32**, between the bromoalkene and the C-2 indolyl phenyl ring (Scheme 5). This reaction was first tried using compound **28** in presence of KOAc as a base, $Pd(PPh_3)_4$ (10%) as catalyst, in refluxing DMA.[13] After 12 h, only 10% of the desired products **33** were isolated. Based on our experimental knowledge, we performed the reaction using a catalytic amount of $Pd(OAc)_2$ (0.1 equiv), PPh_3 (0.2 equiv), and NaOAc (2.0 equiv) in presence of Bu_4NCl (1.0 equiv).[10] Nevertheless, after 12 h, in dioxane at 110 °C, the desired product **33** was obtained in a disappointing 15% yield.



Scheme 5. *Reagent and conditions*: AcONa (2.0 equiv), Bu_4NCl (1.0 equiv), PPh_3 (2.0 equiv), $Pd(OAc)_2$ (1.0 equiv), dioxane, 110 °C, **33** (7 h, 70%), **34** (5 h, 78%), **35** (6 h, 36%), **36** (7 h, 80%).

As described in our previous reports, we observed a linearity between the amount of the catalytic system and the yield of the reaction. So, after several assays, we used a stoichiometric amount of palladium acetate and after only 7 h the compound **33** was isolated in the best yield of 73%. Direct application of these conditions to **29** led without any surprise after 6 h to **34** in 78% yield. It should be noted that during the purification step of **29** or when the compound **29** was maintained in solution on air and light for 24 h, the compound **34** appeared on the TLC. So we deliberately maintained **29** in acetone in presence of silica gel and, after 12 h, 22% of **34** were isolated. Compound **29** was the sole compound able to spontaneously promote the [4+2] oxidative cycloaddition.

Benzannulation of **32** occurred after 7 h, the targeted product **36** was isolated in 80% yield. Direct application to the cyano compound **30** led only to degradation. Immediately during the heating phase, the solution turned off to red and degradation occurred. Starting from the nitro derivative **31**, compound **35** was obtained with the poor yield of 36%; the presence of strong EWG led also to modest results. So the electrophilic step involved in the Heck arylation mechanism is fully compromised in the presence of a strong electron-withdrawing group.

3. Conclusion

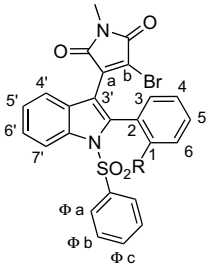
We here reported an efficient synthesis of new fused and substituted benzo and pyrido carbazoles. The reported strategy involved four efficient steps from the *N*-benzenesulfonyl-2-trimethylstannyl indole **3**. As an additional novelty, in the pyridine series, a new spontaneous cyclization occurring in C-3 was highlighted.

This reaction will be further studied and fully utilized for new substituted-pyridinyl series. As far as the phenyl series was concerned, the final reaction was completed following an intramolecular Heck reaction. Several efforts are in progress to apply this work and design potent bioactive molecules. Results will be reported in due course.

4. Experimental section

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance DPX 250 or 500 instruments using $CDCl_3$ or DMSO-d_6. The chemical shifts are reported in parts per million (δ scale) and all J values are in hertz. Melting points are uncorrected. IR absorption spectra were recorded on a Perkin–Elmer FT PARAGON 1000 PC and values were reported in cm^{-1}. MS spectra (Ion Spray) were performed on a Perkin–Elmer SCIEX API 300. HRMS were realized by the Centre Régional de Mesures Physiques de l'Ouest (CRMPO, Rennes) or by the Centre Régional de Mesure Physique (CRMP, Clermont-Ferrand). Monitoring of the reactions was performed using silica gel TLC plates silica Merck 60 F_{254}. Spots were visualized by UV light at 254 and 365 nm. Column chromatographies were performed using silica gel 60 (40–63 μm, Merck). Only the new products are described (not found on CAS-online) (Scheme 6).



Scheme 6. Atom labeling for NMR spectra assignation.

4.2. General procedure for Stille reaction

The reaction was performed in a 1–5 mmol scale. A solution containing the trimethylstannyl derivative **3** (1 mmol), the desired halide (3 equiv), CuI (0.2 equiv), and DMA (15 mL) was degassed by argon bubbling during 30 min. $Pd(PPh_3)_4$ (0.1 mmol) was then added in one portion and the reaction mixture immersed into a preheated oil bath at 100 °C for the desired time. After cooling, water (15 mL) and EtOAc (15 mL) were added, and the solution was filtered. The precipitate was washed with EtOAc (2×10 mL) and the aqueous layers were discarded. The combined organic layers were dried over $MgSO_4$, evaporated under reduced pressure, and the crude material was purified by flash chromatography on silica gel.

*4.2.1. 1-Benzenesulfonyl-2-(6-methoxypyridine-2-yl)-1H-indole (**5**)*

The reaction was performed with 2-bromo-6-methoxypyridine (3.0 equiv) for 14 h. Compound **5** was isolated after column chromatography purification (PE/EtOAc 2:8 then MeOH) as a white solid in 70% yield. R_f (petroleum ether/EtOAc 9:1) 0.25. Mp 106 °C; IR (KBr, cm^{-1}) ν 1598, 1423, 1361, 1094; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.80 (s, 3H, CH_3), 6.89 (dd, 1H, J=8.3, 0.6 Hz, H_5), 7.00 (d, 1H, J=0.5 Hz, $H_{3'}$), 7.27–7.31 (m, 2H, H_3, $H_{5'}$), 7.39 (ddd, 1H, J=8.5, 7.2, 1.2 Hz, $H_{6'}$), 7.51 (t, 2H, J=7.9 Hz, H_b), 7.58 (d, 1H, J=7.9 Hz, $H_{4'}$), 7.62 (tt, 1H, J=7.5, 1.3 Hz, H_c), 7.73 (dd, 2H, J=8.5, 0.2 Hz, H_a), 7.82 (dd, 1H, J=8.3, 7.2 Hz, H_4), 8.02 (dd, 1H, J=8.5, 0.8 Hz, $H_{7'}$); ^{13}C NMR (DMSO-d_6, 62.9 MHz): δ 53.1 (CH_3), 110.5 (CH), 114.2 (CH), 115.4 (CH), 118.4 (CH), 121.6 (CH), 124.5 (CH), 125.4 (CH), 126.4 (2CH), 129.3 (2CH), 129.6 (C), 134.3 (CH), 136.9 (C), 137.0 (C), 139.1 (C), 140.4 (C), 148.4 (C), 162.6 (C); HRMS (EI) calcd for $C_{20}H_{16}N_2O_3S$ 364.08816, found 364.0896 (M)$^{+\bullet}$.

*4.2.2. 1-Benzenesulfonyl-2-(2-fluoro-phenyl)-1H-indole (**8**)*

The reaction was performed with 2-iodofluorobenzene (3.0 equiv) during 6 h. Compound **8** was isolated after column chromatography purification (PE/EtOAc 9:1 then 8:2) as a white glassy solid in 82% yield. R_f (PE/EtOAc 9:1) 0.32. Mp 96 °C; IR (KBr, cm^{-1}) ν 1501, 1380, 1220, 1190, 605; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 6.90 (s, 1H, $H_{3'}$), 7.25–7.61 (m, 12H), 8.11 (d, 1H, J=8.5 Hz); ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 114.4 (CH), 115.2 (CH), 115.3 (C), 118.4 (C), 121.3 (CH), 123.9 (CH), 125.3 (CH), 126.2 (2CH), 124.3 (CH), 125.3 (CH), 126.2 (CH), 129.4 (2CH), 131.3 (CH), 131.7 (CH), 134.4 (CH), 136.8 (C), 158.2 (C), 162.1 (C); HRMS (EI) calcd for $C_{20}H_{15}FNO_2S$ 352.0819, found 352.0808 (M+1)$^+$.

*4.2.3. 2-(1-Benzenesulfonyl-1H-indol-2-yl)-benzonitrile (**10**)*

The reaction was performed with 2-bromobenzonitrile (3.0 equiv) for 16 h. Compound **10** was isolated after column chromatography purification (PE/EtOAc 8:2) as tan solid in 84% yield. R_f (PE/EtOAc 9:1) 0.24. Mp 148–150 °C; IR (KBr, cm^{-1}) ν 2224, 1477, 1442, 1062, 748; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.05 (s, 1H, $H_{3'}$), 7.34 (t, 1H, J=7.6 Hz, $H_{5'}$), 7.46 (dt, 1H, J=7.9, 1.1 Hz, $H_{6'}$), 7.48–7.49 (m, 4H, H_a, H_b), 7.62–7.64 (m, 2H, $H_{4'}$, H_c), 7.68–7.71 (m, 2H, H_3, H_5), 7.83 (dt, 1H, J=7.7, 1.3 Hz, H_4), 7.98 (d, 1H, J=7.5 Hz, H_6), 8.15 (d, 1H, J=8.3 Hz, $H_{7'}$); ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 113.1 (C), 115.4 (CH), 115.6 (CH), 117.7 $(C)_{CN}$, 121.7 (CH), 124.7 (CH), 125.8 (CH), 126.3 (2CH), 129.6 (3CH+C), 131.6 (CH), 132.5 (CH), 132.7 (CH), 134.7 (CH), 135.2 (C),136.2 (C), 136.5 (C), 136.9 (C); HRMS (EI) calcd for $C_{21}H_{14}N_2O_2S$ 358.07760, found 358.0770 (M)$^{+\bullet}$.

*4.2.4. 1-Benzenesulfonyl-2-(3,5-dimethyl-phenyl)-1H-indole (**12**)*

The reaction was performed with 3,5-dimethylbromobenzene (3.0 equiv) for 12 h. Compound **12** was isolated after column chromatography purification (PE/EtOAc 5:5 then MeOH) as a white solid in a 78% yield. R_f (PE/EtOAc 9:1) 0.37. Mp 168 °C; IR (KBr, cm^{-1}) ν 3063, 1528, 1444, 1375, 744; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 2.36 (s, 6H), 7.04 (s, 1H), 7.32 (d, 1H, J=7.5 Hz), 7.45–7.52 (m, 5H), 7.58–7.64 (m, 2H), 7.68 (d, 2H, J=8.7 Hz), 7.85 (d, 1H, J=7.0 Hz), 7.99 (d, 1H, J=7.5 Hz), 8.18 (d, 1H, J=8.2 Hz); ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 20.1 ($2CH_3$), 115.3 (Cq), 117.5 (CH), 117.8 (CH), 119.9 (CH), 123.9 (CH), 126.8 (CH), 128.0 (CH), 128.4 (CH), 130.8 (2CH+Cq), 131.7 (Cq), 133.8 (CH), 134.6 (CH), 134.8 (CH), 136.8 (CH), 137.4 (Cq), 138.4 (Cq), 138.7 (Cq), 139.1 (Cq); HRMS (EI) calcd for $C_{22}H_{20}NO_2S$ 362.1215, found 362.1210 (M+1)$^+$.

4.3. General procedure for the deprotection step

The reaction was performed in a 1–5 mmol scale under argon. To a solution of the *N*-benzenesulfonylindoles **4**, **5**, **7**–**12**, **20** (1 mmol) in THF (12 mL) was added the desired amount of Bu_4NF (1 M in THF) at room temperature. The solution was heated to reflux for the desired time and after cooling water (10 mL) and EtOAc (10 mL) were added. The aqueous layers were extracted with EtOAc (3×10 mL) and the combined organic layers were washed with brine (2×10 mL) then dried over $MgSO_4$. The solvents were removed under reduced pressure and the crude material was purified by flash chromatography.

*4.3.1. 2-(6-Methoxypyridin-2-yl)-1H-indole (**14**)*

The reaction was performed with **5** for 1 h 30 min to afford after column chromatography purification (PE then PE/EtOAc 8:2) compound **14** as a white solid in 94% yield. R_f (PE/EtOAc 8:2) 0.85. Mp 139 °C; IR (KBr, cm^{-1}) ν 3435, 1593, 1465, 1416; ^{1}H NMR

(DMSO-d_6, 500 MHz): δ 4.03 (s, 3H, CH_3), 6.71 (d, 1H, J=8.1 Hz, H_3), 7.01 (dt, 1H, J=7.9, 0.8 Hz, $H_{5'}$), 7.12 (d, 1H, J=1.5 Hz, $H_{3'}$), 7.14 (dt, 1H, J=7.5, 1.0 Hz, $H_{6'}$), 7.50 (d, 1H, J=8.1 Hz, $H_{7'}$), 7.55–7.58 (m, 2H, $H_{4'}$, H_5), 7.75 (t, 1H, J=7.8 Hz, H_4), 11.68 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 53.2 (CH_3), 100.2 (CH), 108.6 (CH), 111.9 (CH), 112.5 (CH), 119.5 (CH), 120.6 (CH), 122.3 (CH), 128.4 (C), 136.9 (C), 137.0 (C), 139.8 (CH), 148.1 (C), 163.2 (C); HRMS (EI) calcd for $C_{14}H_{12}N_2O$ 224.09496, found 224.0947 $(M)^{+\bullet}$.

*4.3.2. 2-(1H-Indol-2-yl)benzonitrile (**17**)*

The reaction was performed with **10** for 2 h to afford after column chromatography purification (PE/EtOAc 9:1 to 7:3) compound **17** as a pale yellow solid in a 88% yield. R_f (PE/EtOAc 8:2) 0.43. Mp 150 °C; IR (KBr, cm^{-1}) ν 3323, 2232, 1559, 1482, 748; ^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm): 7.06 (dt, 1H, J=7.5, 0.9 Hz, $H_{5'}$), 7.13 (dd, 1H, J=2.1, 0.9 Hz, $H_{3'}$), 7.19 (ddd, 1H, J=8.1, 7.0, 1.0 Hz, $H_{6'}$), 7.47 (dd, 1H, J=8.1, 0.9 Hz, $H_{7'}$), 7.53 (dt, 1H, J=7.6, 1.2 Hz, H_5), 7.64 (d, 1H, J=7.9 Hz, $H_{4'}$), 7.83 (dt, 1H, J=7.7, 1.3 Hz, H_4), 7.90 (d, 1H, J=7.3 Hz, H_3), 7.96 (dd, 1H, J=7.8, 1.1 Hz, H_6), 11.68 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 102.7 (CH), 108.5 (C), 111.6 (CH), 119.0 $(C)_{CN}$, 119.8 (CH), 120.8 (CH), 122.7 (CH), 128.0 (CH), 128.1 (C), 128.3 (CH), 133.6 (CH), 133.7 (C), 134.6 (CH), 135.1 (C), 137.1 (C); HRMS (EI) calcd for $C_{15}H_{11}N_2$ 219.0922, found 219.0916 $(M+1)^+$.

*4.3.3. 2-(Pyridin-N-oxide-2-yl)-1H-indole (**21**)*

The reaction was performed with **20** during 3 h to afford after purification (CH_2Cl_2/MeOH 9:1) compound **21** in 81% yield as a yellow solid. R_f (CH_2Cl_2/MeOH 98:2) 0.19. Mp 120–124 °C (dec); IR (KBr, cm^{-1}) ν 3297, 3054, 1593, 1441, 1151, 747; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 7.02 (t, 1H, J=6.0, 8.1 Hz), 7.16 (t, 1H, J=8.1 Hz), 7.33 (td, 1H, J=7.5, 2.1 Hz), 7.46 (t, 1H, J=8.1 Hz), 7.53 (s, 1H), 7.61 (d, 2H, J=8.1 Hz), 8.18 (dd, 1H, J=8.1, 2.1 Hz), 8.37 (d, 1H, J=7.5 Hz) 12.33 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 105.7 (CH), 113.3 (CH), 120.6 (CH), 121.3 (CH), 123.8 (CH), 124.5 (CH), 125.1 (CH), 126.7 (CH), 127.8 (C), 132.1 (C), 136.8 (C), 140.8 (C), 141.4 (CH); HRMS (EI) calcd for $C_{13}H_{11}N_2O$ 211.0871, found 211.0867 $(M+1)^+$.

4.4. General procedure for Michael addition

The reaction was performed in a 0.3–2.0 mmol scale under argon. To a cooled solution (−20 °C) of deprotected indolyl compounds **13**, **15**–**19**, **22** (1 mmol) in THF (10 mL) was added the desired amount of LiHMDS (1 M in hexane). After 45 min the electrophile **23** in THF (10 mL for 1 mmol) was added and the reaction temperature adapted. After a few hours, the reaction was hydrolyzed with an aqueous hydrochloric solution (1 N, pH=2 or pH=7 with derivative **13**) and the resulting mixture was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, and the volatiles were removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel.

*4.4.1. 2-Methyl-1H-indolo[2,3-a]pyrrolo[3,4-c]quinolizinium-1,3-(2H)-dione bromide (**25**)*

The reaction was performed starting from **13** and **23** (2.3 equiv) with LiHMDS (2.2 equiv) at −20 °C to rt for 1 h. After hydrolysis and a rapid flash chromatography (PE/EtOAc 7:3) the very instable compound **24** could be isolated in a 43% yield as an orange solid. After hydrolysis and removing of the volatiles, the crude material containing in majority **24** was dissolved in DMA (30 mL) and the solution was heated at 120 °C for 30 min. After cooling, the reaction mixture was filtered and the solid was washed successively with THF (10 mL) and Et_2O (10 mL), and dried under reduced pressure to afford compound **25** as a yellow solid in 80% yield. R_f (MeOH) 0.01. Mp >250 °C; IR (KBr, cm^{-1}) ν 3033, 1750, 1725, 1528, 1426, 1350, 766; ^{1}H NMR (DMSO-d_6, 500 MHz, 80 °C): δ 3.31 (s, 3H), 7.47 (t, 1H, J=8.2 Hz), 7.64 (t, 1H, J=8.3 Hz), 8.01 (d, 1H, J=8.2 Hz), 8.34 (t, 1H, J=7.5 Hz), 8.66 (t, 1H, J=8.8 Hz), 8.92 (d, 1H, J=8.3 Hz), 9.26 (d, 1H, J=8.8 Hz), 10.56 (d, 1H, J=7.0 Hz), 14.26 (s, 1H); ^{13}C NMR (DMSO-d_6, 125.8 MHz, 80 °C): δ 24.5 (CH_3), 111.7 (C), 113.7 (CH), 113.9 (CH), 116.2 (CH), 119.3 (C), 122.7 (CH), 123.7 (CH), 124.8 (CH), 124.9 (CH), 131.1 (C), 132.7 (C), 133.3 (C), 134.9 (C), 138.0 (CH), 142.4 (C), 163.9 (CO), 165.1 (CO); HRMS (EI) calcd for $C_{18}H_{12}N_3O_2$ 302.0930, found 302.0915 $(M)^{+\bullet}$.

*4.4.2. 6-[3-(4-Bromo-1-methyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)-1H-indol-2-yl]-1H-pyridin-2-one (**26**)*

The reaction was performed starting from **22** and **23** (1.1 equiv) with LiHMDS (3.2 equiv) at −20 °C to rt for 1 h. After column chromatography purification (PE/EtOAc 8:2 then 7:3) compound **26** was isolated as an orange solid in 58% yield. R_f (PE/EtOAc 2:8) 0.16. Mp 201–204 °C (dec); IR (KBr, cm^{-1}) ν 3262, 2932, 1775, 1714, 1657, 1441, 1379, 738; ^{1}H NMR (DMSO-d_6, 250 MHz, 80 °C): δ 2.99 (s, 3H, CH_3), 6.49 (d, 1H, J=8.5 Hz, H_5), 7.00 (br s, 1H, H_3), 7.12 (dt, 1H, J=7.5, 1.0 Hz, $H_{5'}$), 7.25 (dt, 1H, J=7.4, 1.0 Hz, $H_{6'}$), 7.49–7.52 (m, 2H, $H_{4'}$, $H_{7'}$), 7.63 (t, 1H, J=7.9 Hz, H_4), 12.25 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62.5 MHz, HMBC): δ 24.4 (CH_3), 102.1 (C), 112.4 (CH), 120.5 (CH), 120.7 (CH), 123.4 (CH), 126.0 (C), 136.8 (CH), 140.2 (CH), 162.7 (CO), 167.1 (CO); HRMS (EI) calcd for $C_{18}H_{12}N_3O_3$ 318.08787, found 318.0872 $(M-Br)^{+\bullet}$.

*4.4.3. 3-Bromo-4-[2-(2-fluoro-phenyl)-1H-indol-3-yl]-1-methyl-pyrrole-2,5-dione (**29**)*

The reaction was performed starting from **16** and **23** (1.3 equiv) with LiHMDS (2.2 equiv) at −20 °C to rt for 45 min. After purification (PE/EtOAc 8:2) compound **29** was isolated as an orange solid in a 92% yield. R_f (PE/EtOAc 8:2) 0.20. Mp 183–185 °C; IR (KBr, cm^{-1}) ν 3528, 3282, 1752, 1697, 1466, 1419, 1222, 747; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 2.97 (s, 3H), 7.10 (t, 1H, J=7.5 Hz), 7.22–7.46 (m, 3H), 7.47–7.48 (m, 4H), 12.22 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 24.7 (CH_3), 106.4 (Cq), 113.1 (CH), 120.7 (CH), 120.9 (Cq), 123.0 (CH), 124.7 (C), 125.6 (C), 128.2 (CH), 130.5 (CH), 131.3 (CH), 133.0 (CH), 135.2 (C), 135.6 (C), 135.7 (C), 137.4 (CH), 148.0 (C), 163.7 (CO), 166.1 (CO); HRMS (EI) calcd for $C_{19}H_{12}BrFN_2O_2$ 399.0144, found 399.0148 $(M+1)^+$.

*4.4.4. 2-[3-(4-Bromo-1-methyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)-1H-indol-2-yl]-benzonitrile (**30**)*

The reaction was performed starting from **17** and **23** (2.0 equiv) with LiHMDS (3.2 equiv) at −20 °C to rt for 45 min. After purification (PE/EtOAc 8:2 then 7:3) compound **30** was isolated as an orange solid in a 65% yield. R_f (PE/EtOAc 8:2) 0.13. Mp 125–127 °C (dec); IR (KBr, cm^{-1}) ν 3320, 2223, 1774, 1710, 1382, 737; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.96 (s, 3H, CH_3), 7.18 (t, 1H, J=7.4 Hz, $H_{5'}$), 7.29 (t, 1H, J=7.2 Hz, $H_{6'}$), 7.54 (d, 1H, J=8.3 Hz, $H_{7'}$), 7.61–7.65 (m, 2H, $H_{4'}$, H_5), 7.68 (d, 1H, J=7.7 Hz, H_3), 7.82 (d, 1H, J=6.6 Hz, H_4), 7.97 (d, 1H, J=7.2 Hz, H_6), 12.45 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 25.1 (CH_3), 103.4 (C), 111.5 (C), 112.6 (CH), 118.6 (C), 121.1 (CH), 121.8 (CH), 121.9 (C), 123.8 (CH), 126.7 (C), 129.8 (CH), 131.5 (CH), 134.1 (CH), 134.6 (CH), 136.2 (C), 136.4 (C), 137.0 (C), 139.1 (C), 166.5 (CO), 168.6 (CO); HRMS (EI) calcd for $C_{20}H_{12}N_3O_2Br$ 405.01129, found 405.0116 $(M)^{+\bullet}$.

*4.4.5. 3-Bromo-1-methyl-4-[2-(2-nitro-phenyl)-1H-indol-3-yl]-pyrrole-2,5-dione (**31**)*

The reaction was performed starting from **18** and **23** (2.0 equiv) with LiHMDS (3.2 equiv) at −20 °C to rt for 5 h. After column chromatography purification (PE/EtOAc 8:2) compound **31** was isolated as an orange solid in a 38% yield. R_f (PE/EtOAc 8:2) 0.15. Mp 190–192 °C; IR (KBr, cm^{-1}) ν 3310, 3046, 1774, 1707, 1529, 1382, 983, 735; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 2.99 (s, 3H), 7.14 (t, 1H, J=7.5 Hz), 7.28 (t, 1H, J=7.8 Hz), 7.46 (d, 1H, J=8.1 Hz), 7.54–7.63 (m,

2H), 7.67 (t, 1H, J=7.2 Hz), 7.78 (s, 1H, J=7.2 Hz), 8.11 (d, 1H, J=7.8 Hz), 12.30 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 25.7 (CH_3), 103.4 (C), 113.0 (CH), 121.5 (CH), 122.4 (C), 122.8 (C), 124.1 (C), 126.2 (CH), 127.2 (CH), 128.0 (CH), 121.4 (CH), 131.4 (CH), 134.0 (CH), 134.8 (C), 136.6 (C), 137.6 (C), 138.8 (C), 149.3 (C), 167.1 (CO), 169.2 (CO); MS (IS): 426.5 ($(M+1)^+$, ^{79}Br), 428.5 ($(M+1)^+$, ^{81}Br).

4.4.6. 3-Bromo-4-[2-(3,5-dimethyl-phenyl)-1H-indol-3-yl]-1-methyl-pyrrole-2,5-dione (**32**)

The reaction was performed starting from **19** and **23** (2.0 equiv) with LiHMDS (3.0 equiv) at −20 °C to rt for 45 min. After purification on a silica gel column (PE/EtOAc 8:2) compound **32** was isolated as a red solid in 75% yield. R_f (PE/EtOAc 8/2) 0.65. Mp 194–196 °C; IR (KBr, cm^{-1}) ν 3380, 2934, 2854, 1710, 1618, 1450, 1384, 746; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 2.30 (s, 6H, CH_3), 2.97 (s, 3H), 7.01 (s, 1H), 7.09 (t, 1H, J=7.9 Hz), 7.18–7.23 (m, 3H), 7.45–7.48 (d, 2H, J=7.1 Hz), 12.11 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 19.7 ($2CH_3$), 23.4 (CH_3), 98.5 (C), 110.6 (CH), 118.9 (CH), 119.3 (CH), 120.9 (CH), 121.2 (C), 124.2 (C), 125.5 (2CH), 128.7 (C), 130.7 (CH), 135.0 (C), 136.6 (2C), 138.2 (2C), 164.8 (CO), 167.0 (CO); HRMS (EI) calcd for $C_{21}H_{18}BrN_2O_2$ 409.0552, found 409.0569 $(M+1)^+$.

4.5. General procedure for palladium assisted benzannulation

The reaction was performed in a 0.3–0.8 mmol scale. A solution containing the bromo derivative **28**, **29**, **31**, and **32** (0.5 mmol), Bu_4NCl (1.0 equiv), AcONa (2.0 equiv), PPh_3 (2.0 equiv) in dioxane (5 mL) was degassed by argon bubbling during 30 min. $Pd(OAc)_2$ (1.0 equiv) was then added in one portion and the reaction mixture was immersed into a preheated oil bath at 110 °C for the desired time. After cooling, water (15 mL) and EtOAc (15 mL) were added, and the solution was filtered. The precipitate was washed with EtOAc (3×10 mL) and the aqueous layers were discarded. The combined organic layers were dried over $MgSO_4$, evaporated under reduced pressure, and the crude material was purified by flash chromatography.

4.5.1. 2-(Methyl)-9-(fluoro)benzo[a]pyrrolo[3,4-c]carbazole-1,3-(2H,8H)dione (**34**)

The reaction was performed starting from **29** for 5 h. After purification (PE/EtOAc 8:2) compound **34** was isolated as a yellow solid in 75% yield. R_f (PE/EtOAc 8:2) 0.55. Mp 235–237 °C; IR (KBr, cm^{-1}) ν 3290, 3053, 1750, 1700, 1220, 765; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 3.11 (s, 3H, CH_3), 7.29–7.37 (d, 1H, J=7.5 Hz), 7.49–7.60 (m, 2H), 7.72–7.82 (m, 1H), 7.85 (d, 1H, J=8.2 Hz), 8.75 (d, 1H, J=8.2 Hz), 8.93 (d, 1H, J=7.8 Hz), 12.31 (s, 1H, NH). Compound was not soluble enough to perform a ^{13}C NMR experiment at 80 °C (125.8 MHz); HRMS (EI) calcd for $C_{19}H_{11}N_2O_2F$ 318.08046, found 318.0810 $(M)^{+\bullet}$.

4.5.2. 2-(Methyl)-9-(nitro)benzo[a]pyrrolo[3,4-c]carbazole-1,3-(2H,8H)dione (**35**)

The reaction was performed starting from **31** for 6 h. After purification (petroleum ether/EtOAc 8:2) compound **35** was isolated as an orange solid in 36% yield. R_f (PE/EtOAc 85:15) 0.38. Mp 196–198 °C; IR (KBr, cm^{-1}) ν 3420, 1752, 1702, 1516, 1340, 737; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 3.13 (s, 3H, CH_3), 7.41–7.51 (t, 1H, J=7.8 Hz), 7.85–7.94 (m, 3H), 7.94 (d, 1H, J=7.8 Hz), 9.01 (d, 1H, J=7.8 Hz), 9.37 (d, 1H, J=8.1 Hz), 12.76 (s, 1H, NH); ^{13}C DEPT NMR (DMSO-d_6, 125.8 MHz, 80 °C): δ 24.1 (CH_3), 112.8 (CH), 123.4 (CH), 124.4 (CH), 127.0 (CH), 127.6 (CH), 129.1 (CH), 131.8 (CH); HRMS (EI) calcd for $C_{19}H_{11}N_3O_4$ 345.07496, found 345.0748 $(M)^{+\bullet}$.

4.5.3. 2-(Methyl)-10,12-(dimethyl)benzo[a]pyrrolo[3,4-c]-carbazole-1,3-(2H,8H)dione (**36**)

The reaction was performed starting from **32** for 7 h. After purification (PE/EtOAc 8:2) compound **36** was isolated as an orange solid in a 80% yield. R_f (PE/EtOAc 85:15) 0.45. Mp 188–190 °C; IR (KBr, cm^{-1}) ν 3292, 1751, 1682, 1446, 1378, 1052, 743; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 2.48 (s, 3H), 2.93 (s, 3H, CH_3), 3.05 (s, 3H, CH_3), 7.29–7.34 (m, 2H), 7.48 (t, 1H, J=7.8 Hz), 7.67 (d, 1H, J=7.8 Hz), 8.22 (s, 1H), 7.87 (d, 1H, J=7.8 Hz), 12.63 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 22.8 (CH_3), 25.3 (CH_3), 27.3 (CH_3), 113.1 (CH), 113.2 (C), 120.6 (C), 121.5 (CH), 122.0 (CH), 122.9 (C), 125.6 (C), 125.9 (C), 126.2 (CH), 127.9 (CH), 130.3 (C), 134.6 (CH), 137.1 (C), 138.4 (C), 141.8 (Cq), 142.6 (Cq), 170.3 (CO), 170.4 (CO); HRMS (EI) calcd for $C_{21}H_{16}N_2O_2$ 328.12118, found 328.1213 $(M)^{+\bullet}$.

4.5.4. 1-Benzenesulfonyl-2-(pyridin-N-oxide-2-yl)-1H-indole (**20**)

To a solution of compound **4** (473 mg, 1.41 mmol) in $CHCl_3$ (20 mL) was portionwise added at 0 °C m-CPBA (400 mg, 70% in water, 1.62 mmol). The reaction mixture was stirred at room temperature for 12 h then a saturated aqueous solution of $NaHCO_3$ (20 mL) was added. The aqueous layers were extracted with EtOAc (3×20 mL) and the combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. After filtration the solvents were removed under reduced pressure and a flash chromatography (CH_2Cl_2/MeOH 98:2) afforded the compound **20** as a pale yellow solid (393 mg, 79%). R_f (CH_2Cl_2/MeOH 98:2) 0.15. Mp 204–206 °C (dec); IR (KBr, cm^{-1}) ν 1433, 1466, 1376, 1172, 1069, 756; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 7.04 (s, 1H), 7.24 (t, 1H, J=7.5 Hz), 7.32 (t, 1H, J=8.3 Hz), 7.49–7.63 (m, H), 7.72 (dd, 1H, J=2.2, 7.9 Hz), 7.81 (d, 1H, J=8.1 Hz), 7.92 (d, 2H, J=7.6 Hz), 8.39 (d, 1H, J=6.0 Hz); ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 116.9 (CH), 117.1 (CH), 124.9 (CH), 126.9 (CH), 128.0 (CH), 128.6 (CH), 128.8 (2CH), 132.0 (Cq), 132.3 (CH), 132.6 (3CH), 135.3 (C), 137.6 (CH), 138.9 (C), 140.5 (CH), 142.5 (C), 144.9 (C); HRMS (EI) calcd for $C_{19}H_{15}N_2O_3S$ 351.0807, found 351.0807 $(M+1)^+$.

4.5.5. 6-(1H-Indol-2-yl)-1H-pyridin-2-one (**22**)

A solution of compound **14** (300 mg, 1.34 mmol) water (15 mL), and an acetic HBr solution (15 mL, 30% in acetic acid) was refluxed for 6 h. After cooling at room temperature, a saturated aqueous $NaHCO_3$ solution was next slowly added till pH=7. After extraction with EtOAc (3×100 mL), the combined organic layers were washed with water (2×100 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The compound **22** was isolated as a pale yellow solid (249 mg, 89% yield). R_f (petroleum ether/EtOAc 8:2) 0.53. Mp >250 °C; IR (KBr, cm^{-1}) ν 3261, 1662, 1615, 1464, 798; ^{1}H NMR (DMSO-d_6, 500 MHz, 50 °C): 6.35 (d, 1H, J=8.7 Hz, H_5), 6.89 (br d, 1H, J=6.5 Hz, H_3), 7.03 (dt, 1H, J=7.5, 0.8 Hz, $H_{5'}$), 7.17 (dt, 1H, J=7.7, 1.1 Hz, $H_{6'}$), 7.21 (d, 1H, J=1.5 Hz, $H_{3'}$), 7.43 (d, 1H, J=8.3 Hz, $H_{7'}$), 7.54 (dd, 1H, J=8.8, 7.1 Hz, H_4), 7.57 (d, 1H, J=7.9 Hz, $H_{4'}$), 11.33 (br s, 2H, NH); ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 101.6 (CH), 103.8 (CH), 111.3 (CH), 115.1 (CH), 119.4 (CH), 120.4 (CH), 122.5 (CH), 127.7 (C), 132.1 (C), 137.0 (Cq), 140.0 (CH), 141.5 (C), 162.5 (C=O); HRMS (EI) calcd for $C_{13}H_{10}N_2O$ 210.07931, found 210.0803 $(M)^{+\bullet}$.

4.5.6. 5-Methyl-4,6-dioxopyrrolo[3,4-c]carbazole-[a-4,5] pyridinone (**27**)

A solution of compound **26** (100 mg, 0.251 mmol) in DMSO (2 mL) was stirred at room temperature for 48 h. The precipitate was filtered, washed with MeOH (3×1 mL) to afford compound **27** as an orange solid in a quantitative manner (79 mg). R_f (PE/EtOAc 2:8) 0.68. Mp 173–175 °C (dec); IR (KBr, cm^{-1}) ν 3384, 1756, 1675, 1438, 1384; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.04 (s, 3H), 6.74 (d, 1H, J=10.0 Hz, H_3), 7.33 (t, 1H, J=7.5 Hz, $H_{5'}$), 7.57 (t, 1H, J=7.7 Hz, $H_{6'}$), 7.68 (d, 1H, J=8.1 Hz, $H_{7'}$), 8.68 (d, 1H, J=9.7 Hz, H_4), 8.74 (d, 1H, J=8.1 Hz, $H_{4'}$), 11.85 (s, 2H, NH); ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 23.5 (CH_3), 93.5 (C), 111.4 (C), 112.0 (CH), 117.7 (C), 118.7 (C), 120.2 (C), 120.9 (CH), 123.3 (CH), 124.3 (CH), 128.1 (CH), 128.5 (C),

135.7 (CH), 140.3 (C), 161.2 (CO), 169.1 (CO); HRMS (EI) calcd for $C_{18}H_{11}N_3O_3$ 317.08004, found 317.0785 $(M)^{+\bullet}$.

Acknowledgements

We thank the Cancéropôle Grand Ouest and the Association pour la Recherche contre le Cancer (ARC) for the financial support of this work.

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