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Original article

Synthesis of chromeno[3,4-*b*]indoles as Lamellarin D analogues : A novel DYRK1A inhibitor class

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ABSTRACT

A library of substituted chromeno[3,4-*b*]indoles was developed as Lamellarin isosters. Synthesis was achieved from indoles after a four-step pathway sequence involving *C*-3 iodination, a Suzuki cross-coupling reaction, and a one pot deprotection/lactonisation step. Twenty final compounds were tested in order to determine their activity against topoisomerase I and kinases, the two major biological activities of Lamellarins. One newly synthesized derivative exhibited a strong topoisomerase activity comparable to reference compounds such as campthotecin and Lamellarin with only a weak kinase inhibition. Two other lead compounds were identified as new nanomolar DYRK1A inhibitors and several other drugs affected the kinases in the sub-micromolar range. These results will enable us to use the chromeno[3,4-*b*]indole as a pharmacophore to develop potent treatments for neurological or oncological disorders in which DYRK1A is fully involved.

1. Introduction

Lamellarins are natural marine products isolated from molluscs, ascidians, and sponges. Since the first isolation of Lamellarins by Faulkner in 1985, more than 30 related polyaromatic pyrrole alkaloids have been thus extracted [1,2]. This family has been the subject of numerous studies due to its promising activity [3]. Among this family, Lamellarins B and D differ only in the number and position of the OH and OMe groups on a common pyrrolo[2,1-*a*]isoquinoline scaffold.

Lamellarin D, which displays unselective kinase inhibition (CDK1, CK5, GSK3, PIM1 and DYRK1A, …) in the sub-nanomolar range, is a strong topoisomerase I poison. It also exhibits strong cytotoxic activity against cancer cell lines [4] and has been identified as a potent anticancer agent.

Synthetic efforts have been undertaken to use this natural scaffold to design new anticancer agents. Total synthesis, the synthesis of analogues [5] or the design of hybrids, combining for example Lamellarin D and Combretastatin A4 architectures, have been described in attempts to improve their physicochemical properties and inhibitory potencies [6].

In our research, we envisioned simplification of the synthetic model in order to discriminate the two activities and keep the kinase inhibition thanks to a fine tuning of the natural structure. The main modification was to replace the pyrrole moiety with an indole skeleton and design new chromeno[3,4-*b*]indoles. We kept the C, B, and A parts of Lamellarin D unchanged (Fig. 1). The most powerful substituents for activities on ring A, i.e the OH and OCH_3 groups, were also kept. The indole phenyl ring G will play the role, by fusion, of the E, D, and F Lamellarin rings. To increase the molecular diversity and the size of our library, various chemical groups (*inter alia* phenyl substituents) were added to the structure. Such modifications could be useful to modulate potential activities.

Surprisingly, access to our envisioned chromeno[3,4-*b*]indol-6(7*H*)-one has seldom been described [7]. This fused heterocycle is

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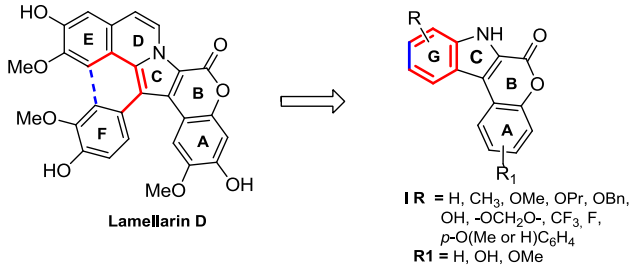


Fig. 1. Lamellarin D and general structure of chromenoindoles **I**.

synthesized in only a few steps starting from 3-iodoindole methyl (or ethyl) carboxylates **III** and 2-boron phenol protected derivatives **IV** by a Suzuki coupling reaction/lactonisation/deprotection sequence, without any indole protective group (Fig. 2).

Herein, we present the building of the indole library and the synthesis of phenol boronic acids or esters and potassium trifluoroborate salts. Then, each step leading to the final type **I** derivatives is disclosed. The library of final compounds is next used in kinase and topoisomerase assays. SAR are reported and molecular modelling illustrates the strong DYRK1A inhibition.

2. Chemistry

2.1. Synthesis of the 3-iodo-1H-indole-2-methyl carboxylate library

In order to synthesize chromenoindoles bearing substituents on the indole core, we surmised that the necessary 1*H*-indole-2-carboxylate derivatives could be obtained through a Hemetsberger reaction (Scheme 1) [8].

Starting from previously protected hydroxybenzaldehydes or commercially available benzaldehydes and ethyl azidoacetate, we prepared (Table 1, entries 1–9, step a) the corresponding methyl 3-aryl-2-azidoacrylates **1**–**9** in moderate to good yields (51–90%), following a general procedure involving NaOMe at low temperature.

The indole scaffold building was carried out from methyl 3-aryl-2-azidoacrylates by heating in xylene, according to standard protocols to afford the desired methyl 1*H*-indole-2-carboxylates **10**–**19** [9]. Yields were generally good, except for azidoacrylates bearing an electron-withdrawing group (entries 4, 6). Note that 3-trifluoromethyl-phenylazidoacrylate **6** led to a separable mixture of 5- and 7-substituted indoles **15** and **16** (entry 6, step b). Two methods were next used to perform *C*-3 iodination on the newly obtained indoles **10**–**19** and commercially available indole ethyl esters **20**–**23**.

In some cases, the standard iodination involving iodine/DMF in basic media failed or gave poor yields. An alternative is to use a mixture of NCS and NaI in DMF at room temperature, though this increases the reaction time considerably. Iodo derivatives were mainly isolated in satisfying yields, except in the case of **31** and **36** for which the purification steps proved to be more problematic.

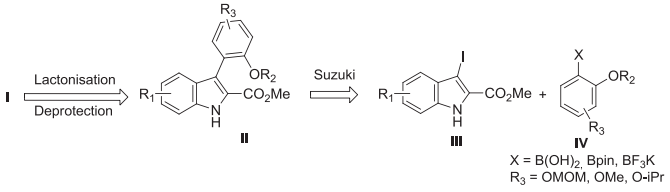


Fig. 2. Retrosynthetic scheme.

The 3-iodo indoles **39** and **40** were prepared following another pathway. Bromo derivatives **14** and **19** were first functionalized through a Suzuki cross-coupling reaction (Scheme 2) using 4-methoxyphenylboronic acid in the presence of 10 mol % $Pd(PPh_3)_4$ in a ternary mixture (toluene/ethanol/saturated aqueous solution of sodium bicarbonate). Compounds **37** and **38** were isolated after 4 h in 90% and 72% yields respectively. A further KOH/I_2 iodination at room temperature led after 1.5 h to the corresponding 3-iodo indoles **39** and **40** in fairly good yields.

2.2. Preparation of 2-boron phenol derivatives

The second objective of this work concerns the formation of functionalized boronic acids or esters or potassium trifluoroborates on protected (poly)phenols (Scheme 3). Methyl, MOM and *i*-Pr ethers were chosen as protective groups so as to be able to remove them selectively or simultaneously in a single step at the end of the synthesis. Compounds **41** and **42** were synthesized according to published procedures [20]. Due to difficulties during the purification of **42**, this boronic acid was converted into its corresponding trifluoroborate potassium salt **43** in 80% yield, by a KHF_2 treatment.

Boronic acid **44** was obtained through the protection of 3-methoxyphenol [21], followed by its borylation *via* the corresponding lithium anion formation and its quenching with $B(OMe)_3$ as an electrophile. Finally, pinacolato boronic ester **45** was also prepared starting from 2,4-bis(methoxymethoxy)bromobenzene, through a palladium-catalyzed reaction involving the presence of KOAc, $PdCl_2$(dppf) and $(BPin)_2$ in 61% yield [22].

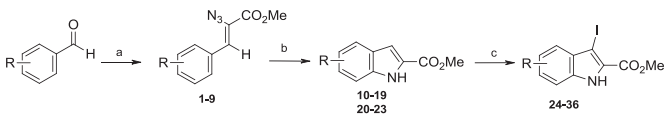
2.3. Palladium cross-coupling reactions

Having thus obtained 3-iodo-1*H*-indole-2-carboxylates **24**–**36**, **39**–**40** and the boron derivatives **41**–**45** or commercially available boronic acids, we next performed several Suzuki-Miyaura coupling reactions (Scheme 4, Table 2) using previously optimized conditions [23].

Starting from bis halogeno derivatives **28**, we were unable to discriminate the reactivity of 3-iodo and 4-bromo atoms. A complex and inseparable mixture of mono and di arylated derivatives was obtained, whatever the amount of boron derivative used. The Suzuki-Miyaura cross-coupling applied to 7-trifluoromethyl-3-iodoindole **30**, and 2-methoxyphenyl boronic acid **A** seemed to take place smoothly but after treatment only 67% of starting material **30** could be recovered as pure product. In all the other reactions, whatever the nature of the indole substituents (i.e. bulky, electron donor/acceptor) and their position (*C*4-*C*6), variations in yields were mainly due to difficulties during the column chromatography purification step.

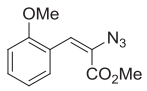
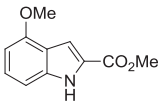
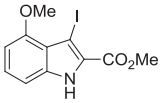
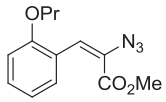
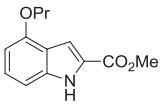
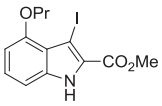
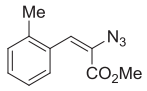
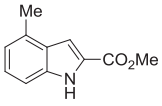
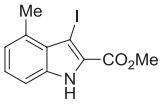
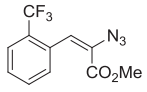
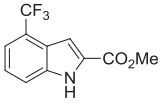
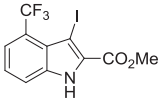
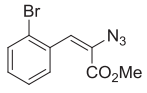
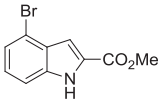
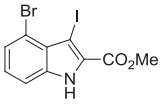
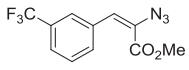
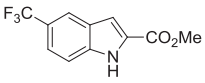
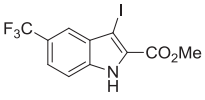
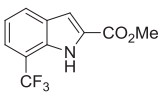
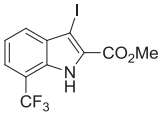
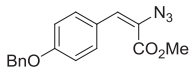
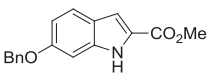
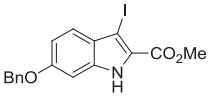
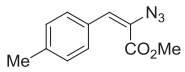
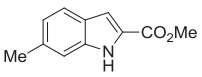
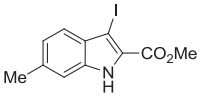
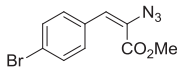
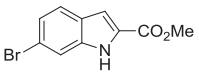
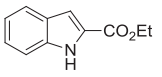
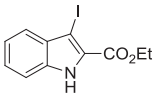
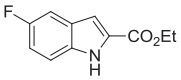
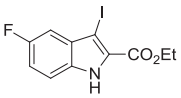
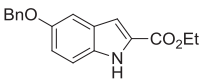
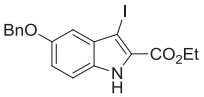
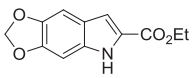
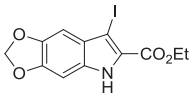
2.4. Ether deprotection and formation of type I lactones

Three methods employing acidic reagents were used in order to cleave the ether groups and achieve a "one pot" annellation reaction leading to lactones **I** (Table 3). Methoxy groups were removed by treating the ethers **46**–**48**, **50**, **51**, **56**, **57** and **61** with hydrobromhydric acid for several hours (*Method* ***A***, entries 1–3, 5–6,

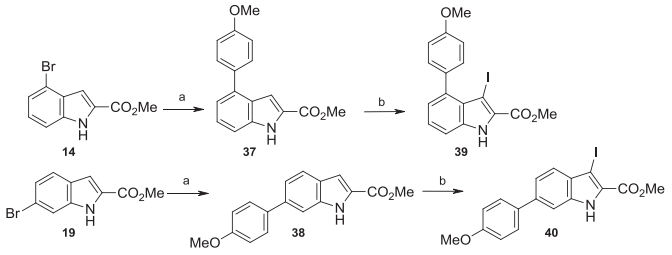


Scheme 1. a) NaOMe (2.0 eq.), MeOH, −20 °C, $N_3CH_2COOC_2H_5$ (1.0 eq.), 2 h then 0 °C, 12 h; b) xylene, reflux, 2 h leading to **10**–**23**; c) *Method* ***A*** : I_2, KOH (4.0 eq.), DMF, r.t., 1.5 h or *Method* ***B*** : NCS (1.2 eq.), NaI (1.2 eq.), DMF (0.3 M), 0 °C for 1 h then r.t. for 12 h.

Table 1
3-iodo-1*H*-indole-2-carboxylate **III** synthesis.

Entry	Product of step a	N°, yield	Product of step b	N°, yield	Product of step c	N°, yield
1		**1**, 78% [10]		**10**, 76% [11]		**24**, *Method* ***A***, 70% [11]
2		**2**, 57%		**11**, 94%		**25**, *Method* ***B***, 75%
3		**3**, 63% [12]		**12**, 67% [13]		**26**, *Method* ***B***, 70%
4		**4**, 76%		**13**, 21%		**27**, *Method* ***B***, 75%
5		**5**, 65% [14]		**14**, 74% [14]		**28**, *Method* ***A***, 70%
6		**6**, 48%		**15**, 28%		**29**, *Method* ***B***, 74%
				**16**, 17%		**30**, *Method* ***B***, 75%
7		**7**, 90% [16]		**17**[a]		**31**, *Method* ***B***, 21%
8		**8**, 65% [17]		**18**, 53% [9b]		**32**, *Method* ***A***, 60%
9		**9**, 65% [9b]		**19**, 54% [9b]	–	–
10	–	–		**20**[b]		**33**, *Method* ***A***, 81% [18]
11	–	–		**21**[b]		**34**, *Method* ***A***, 93% [19]
12	–	–		**22**[b]		**35**, *Method* ***A***, 60% [19]
13	–	–		**23**[b]		**36**, *Method* ***B***, 30%

[a] The crude product **17** was used in the following step without any purification.
[b] Commercially available.



Scheme 2. a) 4-MeOC$_6$H$_4$B(OH)$_2$ (2.0 eq.), Pd(PPh$_3$)$_4$ 10 mol%, Toluene/EtOH/aq. sat. NaHCO$_3$ 3/2/1.5, reflux, 4 h, **37** 90%, **38** 72%; b) KOH, DMF, r.t., 1.5 h, **39** 75%, **40** 73%.

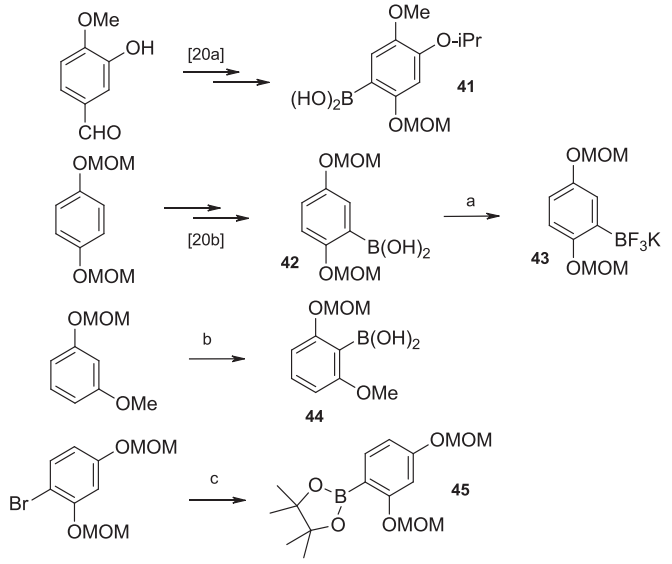
11–13, 16). Note that the methyl ether groups can alternatively be removed with BBr_3 at low temperature in dichloromethane but opened structures (esters or acids) and lactones are concomitantly formed, thus decreasing the interest of this method.

A single tetra deprotection/cyclization step of **58** was attempted but whatever the acidic conditions (HBr or BBr_3) used, only complex mixtures were obtained. The same behaviour was observed starting from the methylenedioxy indole derivative **65**, indicating the sensitivity of the cyclic ether substitution in such conditions.

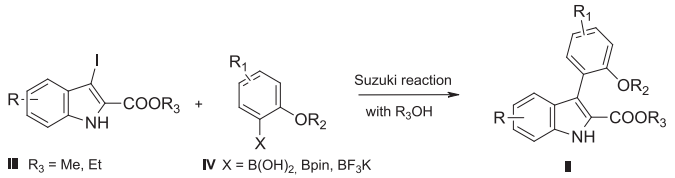
MOM release was achieved starting from **49**, **52**–**55**, **59**–**60**, **62**–**65** with hydrochloric acid in refluxing EtOH (*Method **B***, entries 4, 7–10, 14–15, 17–20). Methyl ether and methylenedioxy groups survived these mild conditions, and compounds **69**, **84** and **85** were obtained in satisfactory yields (entries 4, 19, 20). Nevertheless starting from **61**, compound **81** was obtained in only 22% yield and degradation mainly occurred, while starting from **62**, the attempted compound **82** was not pure enough to be fully characterized.

The last assay we tried concerned the sequential deprotection of **58** (Scheme 5). Hydrochloric acid (*Method **B***) removed the MOM ether protective group and gave lactone **58a** in 40% yield; finally a second reaction using BCl_3 led to the fully deprotected **78** derivative in 32% yield.

As a benzyl group protected the indole part of **31**, we envisaged the preparation of the benzyl analogue of boron derivative **45**



Scheme 3. a) KHF_2 (1M), MeOH, 0 °C to r.t., 4 h, 80%; b) i) *n*-BuLi (1.2 eq.), THF, reflux, 2 h; ii) B(OMe)$_3$ (1.2 eq.), r.t., 1 h; iii) satd. aq. NH_4Cl, **44** 40% c) KOAc (4.0 eq.), Pd(dppf)Cl_2.CH_2Cl_2 10 mol%, (BPin)$_2$ (1.0 eq.), toluene, reflux, 12 h, 61%.



Scheme 4. Pd(PPh$_3$)$_4$ 10 mol%, R$_3$OH, toluene, aq. sat. NaHCO$_3$, reflux, 4–8 h. Whatever the starting boron species were, yields were quite similar. Note that methanol was replaced by ethanol for the coupling reactions using ethyl esters **33**–**36** to prevent potential transesterifications (entries 1–4, 11–13, 15, 20).

which could offer us homogeneous full deprotection/lactonization as a last single step under Pd(C) catalyzed hydrogenation. Pinacaloto boronic ester **86** was thus prepared from 3,5-bis(benzyloxy) bromobenzene as described for **45** in 62% yield. Afterwards, the coupling reactions procedure (see Scheme 4) afforded the opened structure derivative **87** in a satisfactory yield of 55%, and finally the chromenoindole **82** was obtained by hydrogenolysis, followed by a basic treatment (*Method **D***) in 51% yield.

3. Biological activities

As Lamellarin derivatives inhibit several protein kinases, we evaluated our final derivatives on three representative kinases, CDK5, GSK3 and DYRK1A. We then measured DNA interaction and conducted a topoisomerase poisoning assay with our derivatives.

3.1. Kinase assays

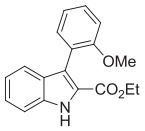
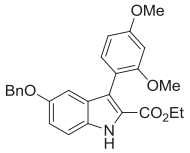
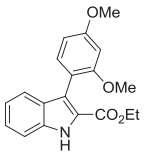
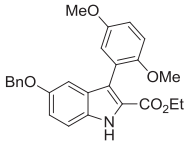
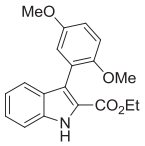
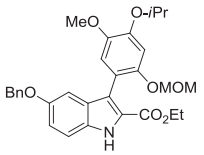
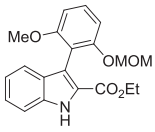
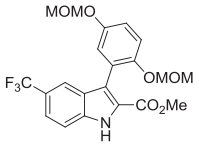
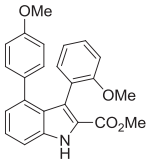
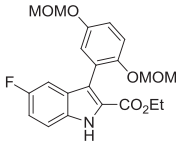
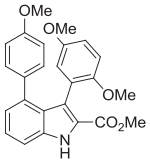
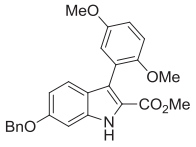
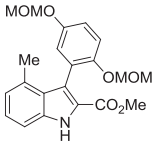
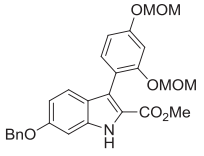
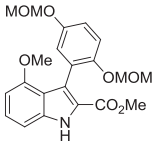
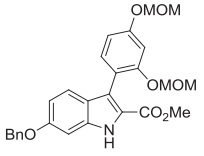
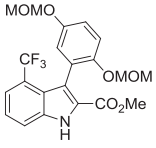
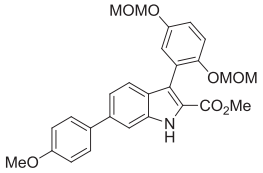
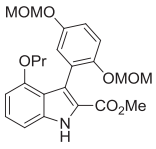
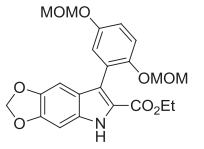
Whatever the kinase used, when the phenyl ring A was nude or possessed a methyl ether (Table 4, entries 1–3), there was no kinase inhibition; the presence of hydroxyl groups on phenyl ring A seems to be crucial in order to develop a kinase effect. Compounds **67** and **68** (entries 4, 7), which are hydroxylated analogues of the non-active compound **66**, both exhibited significant inhibition of kinase activity. For **68**, a nanomolar IC_{50} against DYRK1A was measured with a high selectivity towards the other two enzymes. Activity and selectivity depended on the position of the hydroxy group on ring A. The *C*-2 position is more favourable than the *C*-3 (**68** versus **67**, entries 7, 4). Having thus identified a lead, we pursued the SAR exploration with the G indole ring.

All the modifications at the indole *C*-11 position decreased the efficiency of the derivatives (entries 3, 10–12). Small OMe and Me groups were partially tolerated (**72** and **73**, entries 8, 9) and DYRK1A inhibition increased proportionally with the electro-donating character. By contrast, bulky and lipophilic groups are totally forbidden (**71** and **74**, entries 11, 12).

The best results were obtained in *C*-10 substituted chromenoindole: thus, compound **77** (entry 13) was identified as the most active molecule with respect to kinase activity that was designed in this series. At only 67 nM, DYRK1A was inhibited by 50%. As previously mentioned, a lipophilic group spontaneously decreased kinase inhibition (**79**, entry 16) whereas the small fluorine atom partially maintained the efficiency of the tested compound **80** (entry 15).

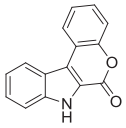
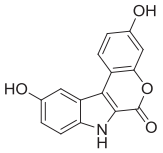
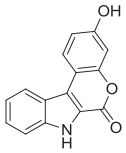
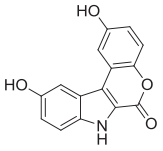
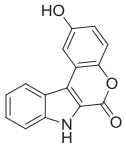
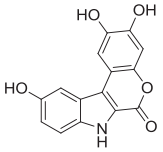
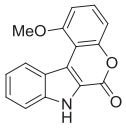
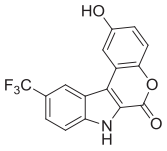
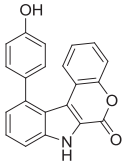
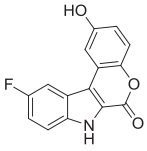
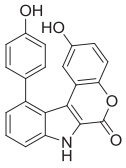
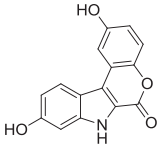
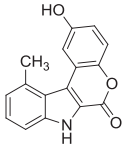
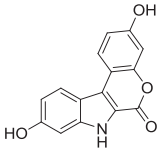
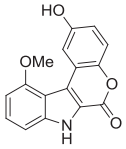
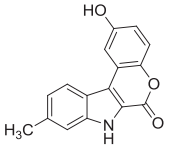
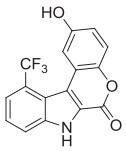
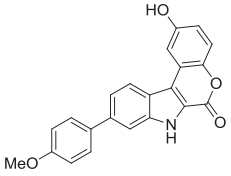
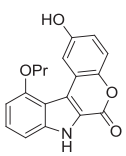
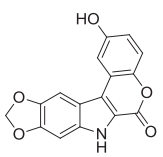
The introduction of a substituent at the *C*-9 position led to a strong decrease in inhibition and gave the inactive molecules **81**–**85** (entries 6, 17, 18–20). In summary, DYRK1A inhibition is conditioned by the position of two groups attached to the crucial chromenoindole **I** phenyl rings A and G in the *C*-2 or *C*-3 and *C*-10 positions. The planar chromenoindole **I** skeleton leads to a strong inhibition of the enzyme interfering with the ATP competition. Docking studies (see section 4) will explain this result.

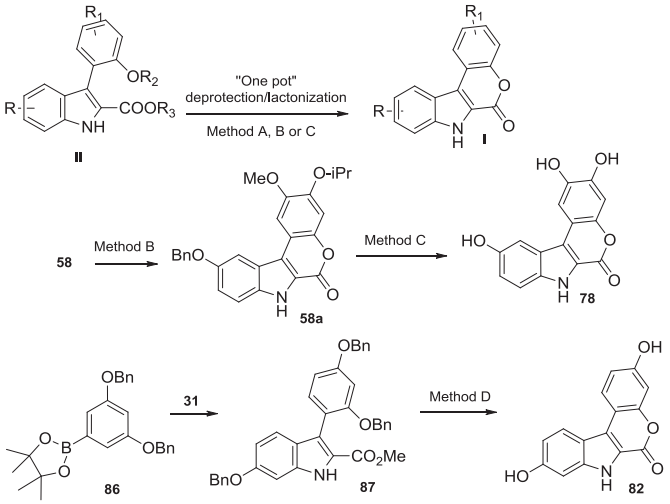
Table 2
Synthesis of type **II** compounds.

Entry	Starting materials **III**/**IV**	Product **II**	N°, time, yield	Entry	Starting materials **III**/**IV**	Product **II**	N°, time, yield
1	**33**/**A**		**46**, 6 h, 91%	11	**35**/**B**		**56**, 8 h, 70%
2	**33**/**B**		**47**, 6 h, 70%	12	**35**/**C**		**57**, 8 h, 63%
3	**33**/**C**		**48**, 6 h, 78%	13	**35**/**41**		**58**, 7 h, 76%
4	**33**/**44**		**49**, 7 h, 74%	14	**29**/**43**		**59**, 7 h, 40 %[a]
5	**39**/**A**		**50**, 3 h, 82%[a]	15	**34**/**42**		**60**, 7 h, 82%
6	**39**/**C**		**51**, 4 h, 80%[a]	16	**31**/**C**		**61**, 7 h, 60%[a]
7	**26**/**43**		**52**, 5 h, 45%[a]	17	**31**/**45**		**62**, 6 h, 68%[a]
8	**24**/**43**		**53**, 5 h, 35%[a]	18	**32**/**43**		**63**, 7 h, 90%[a]
9	**27**/**43**		**54**, 5 h, 60%[a]	19	**40**/**43**		**64**, 7 h, 60 %[a]
10	**25**/**43**		**55**, 7 h, 77%[a]	20	**36**/**43**		**65**, 7 h, 60%

[a] Ethanol was replaced by methanol. **A** 2-methoxyphenyl boronic acid; **B** 2,4-dimethoxyphenyl boronic acid; **C** 2,5-dimethoxyphenyl boronic acid.

Table 3
Synthesis of type **I** compounds.

Entry	Compound **II**, conditions, time, yield	Product of type **I**	N°	Entry	Compound **II**, conditions, time, yield	Product of type **I**	N°
1	**46**, *Method* ***A***, 6 h, 80%		**66**	11	**56**, *Method* ***A***, 24 h, 70%		**76**
2	**47**, *Method* ***A***, 24 h, 66%		**67**	12	**57**, *Method* ***A***, 24 h, 65%		**77**
3	**48**, *Method* ***A***, 24 h, 74%		**68**	13	**58**, *Method* ***C***, 3 h, 32%		**78**
4	**49**, *Method* ***B***, 12 h, 90%		**69**	14	**59,** *Method* ***B***, 12 h, 50%		**79**
5	**50**, *Method* ***A***, 24 h, 50%		**70**	15	**60,** *Method* ***B***, 12 h, 80%		**80**
6	**51**, *Method* ***A***, 24 h, 54%		**71**	16	**61,** *Method* ***A***, 24 h, 22%		**81**
7	**52**, *Method* ***B*** 12 h, 93%		**72**	17	**62,** *Method* ***B***, failed **87,** *Method* ***D***, 24 h,51%		**82**
8	**53,** *Method* ***B***, 12 h, 93%		**73**	18	**63,** *Method* ***B***, 12 h, 73%		**83**
9	**54**, *Method* ***B***, 12 h, 50%		**74**	19	**64,** *Method* ***B***, 12 h, 80%		**84**
10	**55**, *Method* ***B***, 1 h, 76%		**75**	20	**65**, Method **B**, 12 h, 70%		**85**



Scheme 5. *Method* ***A*** : HBr, AcOH, reflux then sat. aqueous $NaHCO_3$; *Method* ***B*** : sat. HCl (g) solution of EtOH, reflux; *Method* ***C*** : BCl_3 (10.0 eq.), CH_2Cl_2, -78 °C, 30 min to r.t.. *Method* ***D***: H_2, Pd(C) 10% EtOH, then K_2CO_3 (4.0 eq.), THF, r.t., 12 h. For Suzuki conditions starting from **31** and **86** see also Scheme 4.

3.2. Topoisomerase inhibition and DNA binding

The structure of the newly synthesised chromenoindoles is close to Lamellarin D which has been proven to be a topoisomerase I inhibitor. For these reasons, these compounds were tested for their topoisomerase I inhibition but also for their DNA binding. First of all, the chromenone family does not present any interaction with DNA (data not shown). As shown in Fig. 3, supercoiled plasmid DNA was treated with human topoisomerase I in the presence of the reference compounds (camptothecin and Lamellarin) or compounds **67**, **68**, **71**, **76, 77** in graded concentrations. The DNA relaxation/cleavage products were resolved by electrophoresis. Inhibition of topoisomerase I was clearly specifically detected with the reference compounds (CPT, LmD), which produced a marked level of DNA double stranded breaks (Fig. 3). Among all the compounds tested, only the chromenoindole **76** was found to really stabilize the drug-DNA complex with an increase in the nicked band. This stabilization progressed with the concentration of the drug. It was moderate at 20 μM (The Nck bands were respectively 16%; 26% and 22% with **76**, CPT and LmD) and strong at 100 μM, comparable to the reference compounds (the Nck bands were respectively 21%; 27% and 21% with **76**, CPT and LmD at 100 μM). The result from this topoisomerase assay formally established that compound **76** is a strong topoisomerase I poison *in vitro*, with a weak DNA interaction.

4. Molecular modelling

In order to compare the putative binding modes of Lamellarin D and of our best synthesised inhibitor compound with the binding site of DYRK1A, docking studies were carried out. These molecular modelling experiments used a model based on the most recent 3anr DYRK1A structure available in the Protein Data Bank [24]. The co-crystallized ligand, 7-methoxy-1-methyl-9*H*-pyrido[3,4-*b*]indole, was docked again in order to validate our approach. Superimposition of our best docked pose on the crystal structure gave an RMSD deviation, based on heavy atoms, of 0.12Å.

3D structures of Lamellarin D and compound **77** were then generated and submitted to Glide [25] according to the previous protocol. The results of these docking experiments were sorted in accordance with the Glide docking score and the first ranked poses of **77** and Lamellarin D are here compared. These 2 compounds adopt a similar probable binding mode, as illustrated in Fig. 4.

5. Conclusion

We designed new chromeno[3,4-*b*]indoles as indole Lamellarin isosteres. Their synthesis involved a palladium-catalyzed reaction/deprotection/lactonization sequence as key steps. Twenty final compounds were designed in order to explore the SAR of each compound on kinase and topoisomerase I, the two main activities of Lamellarins. By drug variations, we found that these two effects could be separated by fine modifications on the two phenyl rings of the chromenoindole scaffold. Both activities are linked to the presence of some aryl hydroxy groups.

The *C*-3 and *C*-10 bis hydroxylated chomenoindole **76** exhibited strong topoisomerase I inhibition with only a weak sub-nanomolar kinase effect. Each modulation of these two key points led to a lack of topoisomerase activity. In addition, in an attempt to correlate this result with cellular effects, we measured the cytotoxic effect on sensitive (CEM) and topoisomerase I resistant cell lines (CEM/C2) and the measured activities could not be related to topoisomerase cellular effects (IC_{50} values of **76**, LmD and CPT on CEM cells were respectively: 38.5 ± 0.07, 15 ± 4 and 0.005 ± 0.005).

When a hydroxy group is positioned in *C*-2, the topoisomerase inhibition is lost but an interesting selective DYRK1A inhibition was observed. Without any other substituent or the addition of a hydroxyl group in *C*-10, we obtained two lead compounds **68** and **77** (IC_{50} 74 and 76 nM respectively). By varying the nature and position of the two aryl functions, five additional derivatives were found to inhibit the DYRK1A kinase in the sub-nanomolar range with a preservation of selectivity (i.e. CDK, GSK3). Molecular modelling docking studies revealed a Lamellarin-like binding mode with the ATP active site. The lack of toxicity and strong kinase inhibition will enable us to use the chromeno[3,4-*b*]indole as a pharmacophore to develop potent treatments for neurological or oncological disorders in which DYRK1A is fully involved.

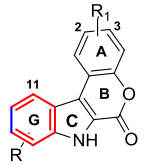
6. Experimental section

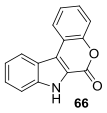
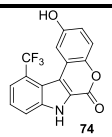
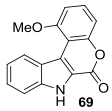
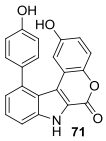
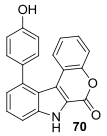
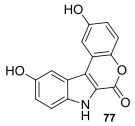
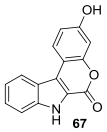
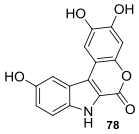
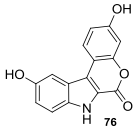
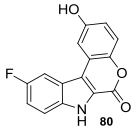
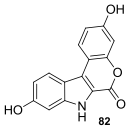
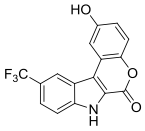
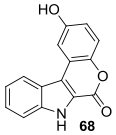
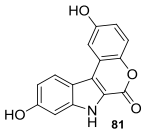
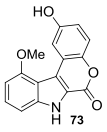
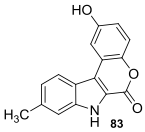
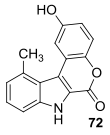
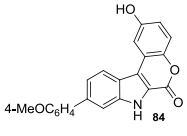
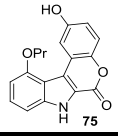
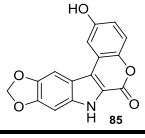
^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 250 or 400 MHz instrument using $CDCl_3$ or DMSO-*d*6. The chemical shifts are reported in ppm (δ scale) and all coupling constants (J) values are in hertz (Hz). The splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and dd (doublet doublet). Melting points are uncorrected. IR absorption spectra were obtained on a Perkin Elmer PARAGON 1000 PC and values were reported in cm^{-1}. MS spectra (Ion Spray) were performed on a Perkin Elmer Sciex PI 300. HRMS were performed on a Bruker maXis mass spectrometer by the "Fédération de Recherche" ICOA/CBM (FR2708) platform. Monitoring of the reactions was performed using silica gel TLC plates (silica Merck 60 F254). Spots were visualised by UV light at 254 nm and 356 nm. Column chromatographies were performed using silica gel 60 (0.063–0.200 mm, Merck).

6.1. General procedure for the synthesis of methyl 3-aryl-2-azidoacrylate *1*–*9*

To a solution of NaOMe (4.0 eq.) in MeOH at −20 °C was added a solution of the aldehyde derivative (1.0 eq.) and ethyl azidoacetate (4.0 eq.) in MeOH (1.0 M). The addition was carried out slowly to allow the resulting heat to dissipate and to maintain the internal

Table 4
Kinase activity of type **I** compound.[a]



Entry	Product **I**	DYRK1A	CDK5	GSK3	Entry	Product **I**	DYRK1A	CDK5	GSK3
1	 66	>10	>10	>10	11	 74	2.1	> 10	≥ 10
2	 69	> 10	> 10	> 10	12	 71	≥ 10	≥ 10	> 10
3	 70	≥ 10	≥ 10	> 10	13	 77	**0.067**	**0.72**	**0.31**
4	 67	**0.5**	4.7	**0.44**	14	 78	1.5	>10	1.3
5	 76	**0.3**	4.2	**0.42**	15	 80	**0.21**	8.4	2.5
6	 82	3.2	10	10	16		≥ 10	≥ 10	≥ 10
7	 68	**0.074**	2.7	**0.38**	17	 81	4.3	> 10	> 10
8	 73	**0.35**	≥ 10	3.3	18	 83	3.3	> 10	> 10
9	 72	**0.66**	> 10	5.9	19	 84	> 10	> 10	> 10
10	 75	1.7	> 10	8.1	20	 85	1.8	16	> 10

[a] IC_{50}values are reported in μM.

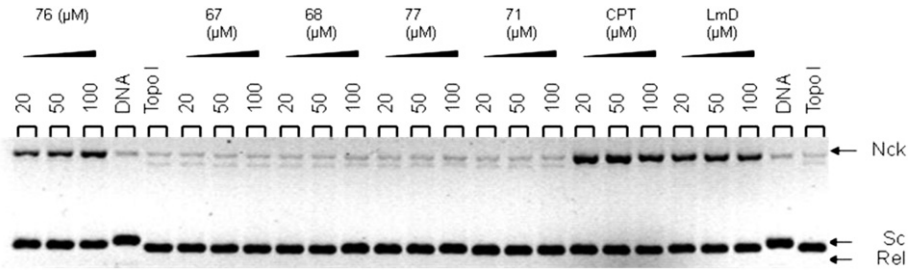


Fig. 3. Effects of novel derivatives on the relaxation of plasmid DNA by human topo I. Native supercoiled pUC19 (130 ng, lane DNA) was incubated with 4 units of topo1 in the absence (lane topo I) or presence of the tested compounds in the indicated concentrations (20–100 μM). Camptothecin (CPT) and Lamellarin D (LmD) were used in the same concentrations. DNA samples were separated by electrophoresis on a 1% agarose gel containing 1 μg/mL ethidium bromide. Gels were photographed under UV light. Nck, nicked; Sc, supercoiled; Rel, relaxed.

temperature at *ca* −20 °C. When the addition was completed, the reaction was stirred at −20 °C for 2 h and then allowed to warm to 0 °C overnight. During this time a fine precipitate generally started to form. The suspension was then poured onto ice and the azido derivative was collected by filtration, washed with cold water and petroleum ether, dried under reduced pressure and used without any further purification. Compounds **1**, **3**, **5**, **8**–**11** were previously described [9b,10,12,14,15–17].

*6.1.1. Methyl 2-azido-3-(2-propoxyphenyl)acrylate (**2**)*

Compound **2** was isolated as a white solid in 57% yield. Mp < 50 °C; IR (ATR diamond, cm^{-1}) ν 1383, 1516, 1720, 2140; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.06 (t, $J = 7.2$ Hz, 3H, CH_3), 1.89 (sext, $J = 7.2$ Hz, 2H, CH_2), 3.90 (s, 3H, OCH_3), 4.00 (t, $J = 7.2$ Hz, 2H, OCH_2), 6.89 (d, $J = 7.8$ Hz, 1H), 7.00 (t, $J = 7.8$ Hz, 1H), 7.35 (t, $J = 7.8$ Hz, 1H), 7.48 (s, 1H), 8.22 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.5 (CH_3), 22.5 (CH_2), 52.8 (OCH_3), 70.0 (OCH_2), 111.6 (CH), 120.0 (CH), 120.2 (CH), 122.3 (CH), 124.8 (CH), 130.5 (Cq), 130.8 (Cq), 157.2 (Cq), 164.3 (CO); MS (IS^+) *m/z* 262 $[M + H]^+$.

*6.1.2. Methyl 2-azido-3-(2-(trifluoromethyl)phenyl)acrylate (**4**)*

Compound **4** was isolated as a beige solid in 76% yield. Mp : 69 °C; IR (ATR diamond, cm^{-1}) ν 2112, 1700, 1240, 728; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.93 (s, 3H, OCH_3), 6.90 (s, 1H), 7.47–7.60 (m, 2H), 7.97–8.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 53.1 (CH_3), 123.3 (CH), 123.9 (q, $J = 270.7$ Hz, CF_3), 125.7 (CH), 127.0 (CH), 127.1 (CH), 128.9 (CH), 130.9 (q, $J = 32.1$ Hz, C–CF_3), 133.4 (Cq), 133.8 (Cq), 163.6 (CO); MS (IS^+) *m/z* 272 $[M + H]^+$.

*6.1.3. Methyl 2-azido-3-(3-(trifluoromethyl)phenyl)acrylate (**6**)*

Compound **7** was isolated as a yellow solid in 48% yield. Mp < 50 °C; IR (ATR diamond, cm^{-1}) ν 2130, 1718, 1383; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.93 (s, 3H, OCH_3), 6.90 (s, 1H), 7.46–7.59 (m, 2H), 7.99 (d, $J = 7.5$ Hz, 1H), 8.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 53.1 (OCH_3), 123.2 (CH), 123.9 (q, $J = 271.3$ Hz, C–CF_3), 126.0 (Cq), 127.0 (CH), 127.1 (Cq), 128.9 (CH), 130.9 (q, $J = 32.2$ Hz, CF_3), 133.4 (CH), 133.8 (CH), 163.6 (CO); MS (IS^+) *m/z* 272 $[M + H]^+$.

*6.2. General procedure for the synthesis of indoles (**10**–**19**)*

Methyl 3-aryl-2-azidoacrylate **1**–**11** (20.0 mmol) was added in one portion to a xylene refluxing solution (75 mL) which was heated for 2 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using a petroleum ether/EtOAc mixture as eluent. Compounds **12**, **18** and **19** were previously described [9b,13,14].

*6.2.1. Methyl 4-propoxy-1H-indole-2-carboxylate (**11**)*

Compound **11** was synthesized starting from **2** as a white solid in 94% yield. R_f 0.40 (petroleum ether/EtOAc 80/20); Mp 69 °C; IR (ATR diamond, cm^{-1}) ν 3320, 1750, 1693,1583; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.09 (t, $J = 7.0$ Hz, 3H, CH_3), 1.89 (sext, $J = 7.0$ Hz, 2H, CH_2), 3.94 (s, 3H, OCH_3), 4.07 (t, $J = 7.0$ Hz, 2H, OCH_2), 6.48 (d, $J = 8.0$ Hz, 1H), 6.99 (d, $J = 8.0$ Hz, 1H), 7.21 (t, $J = 8.0$ Hz, 1H), 7.37 (s, 1H), 8.99 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.6 (CH_3), 22.6 (CH_2), 51.9 (OCH_3), 69.5 (OCH_2), 100.6 (CH), 104.5 (CH), 106.7 (CH), 119.2 (Cq), 125.6

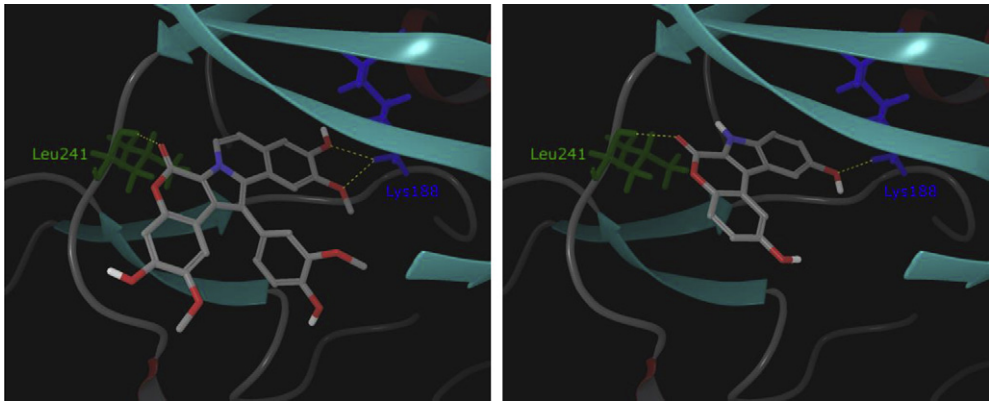


Fig. 4. Putative common binding mode of Lamellarin D (left) and 77 (right). Residues 164 to 166 are hidden for clarity, as well as nonpolar ligand hydrogens. H bonds are represented in dashed yellow lines with the residues Leu241 and Lys188 colour coded by property (hydrophobic and positive residues are green and blue respectively). Protein is shown as a ribbon, coloured according to its secondary structure. Both of them are involved in H-bond interactions connecting their carbonyl to the Leu241 CαH of the DYRK1A hinge region, and the oxygen atom of the ring G hydroxy to the side chain of Lys188. Furthermore our ligands are encompassed in a highly hydrophobic pocket (Fig. 5), generating a large number of hydrophobic interactions with the residues Ile165, Val173, Ala186, Val222, Phe238, Met240, Leu241, Leu294 and Val306 of the protein. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

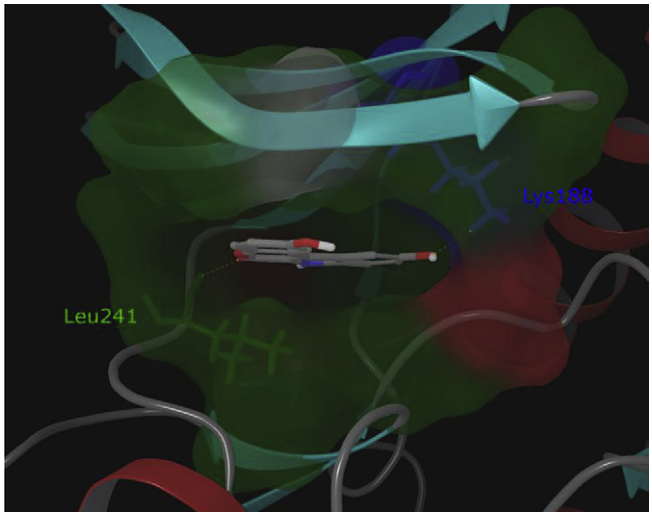


Fig. 5. Molecular surface designed from all the residues within 4 Å of the best pose of 77, highlighting the hydrophobic feature of the docking pocket. Molecular surface is colour coded according to the property of the related residue (green, red and blue for hydrophobic, negative and positive residues respectively). The common hydrophobic residues located within 4 Å of 77 and Lamellarin are Ile165, Val173, Ala186, Val222, Phe238, Met240, Leu241, Leu294 and Val306. The two H-bonded residues, Leu241 and Lys188, are also highlighted according to the previous colour code. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(Cq), 126.5 (CH), 138.3 (Cq), 154.1 (Cq), 162.4 (CO); MS (IS^+) *m/z* 234 $[M + H^+]$.

*6.2.2. Methyl 4-trifluoromethyl-1H-indole-2-carboxylate (**13**)*

Compound **13** was synthesized starting from **4** as a white solid in 21% yield. R_f 0.60 (petroleum ether/EtOAc 80/20); Mp 70 °C; IR (ATR diamond, cm^{-1}) ν 3305 1694, 1098; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.98 (s, 3H, OCH_3), 7.29–7.31 (m, 1H), 7.57–7.58 (m, 2H), 8.01 (s, 1H), 9.13 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 52.2 (OCH_3), 109.3 (CH), 112.3 (CH), 122.6 (CH), 122.7 (Cq), 123.4 (q, $J = 270.0$ Hz, CF_3), 127.0 (CH), 128.8 (Cq), 131.2 (Cq), 137.8 (Cq), 161.9 (CO); MS (IS^+) *m/z* 244 $[M + H]^+$.

*6.2.3. Methyl-5-trifluoromethyl-1H-indole-2-carboxylate (**15**)*

Compound **15** was synthesized starting from **6** as a yellow solid in 28% yield. R_f 0.50 (petroleum ether/EtOAc 80/20); yield 28%; Mp 68 °C; IR (ATR diamond, cm^{-1}) ν 3323, 1690, 1526; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.99 (s, 3H, OCH_3), 7.29 (s, 1H), 7.51 (d, $J = 8.5$ Hz, 1H), 7.54 (d, $J = 8.5$ Hz, 1H), 8.01 (s, 1H), 9.35 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 52.3 (OCH_3), 109.4 (CH), 112.4 (CH), 120.5 (q, $J = 4.4$ Hz, CH), 121.8 (q, $J = 2.9$ Hz, CH), 123.4 (q, $J = 33.0$ Hz, C–CF_3), 124.9 (q, $J = 271.4$ Hz, CF_3), 126.6 (Cq), 128.8 (Cq), 137.9 (Cq), 168.1 (CO); MS (IS^+) *m/z* 244 $[M + H]^+$.

*6.2.4. Methyl-7-trifluoromethyl-1H-indole-2-carboxylate (**16**)*

Compound **16** was synthesized starting from **6** as a white solid in 17% yield. R_f 0.70 (petroleum ether/EtOAc 80/20); Mp 68 °C; IR (ATR diamond, cm^{-1}) ν 3334, 1678, 1578; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.97 (s, 3H, OCH_3), 7.21 (t, $J = 7.7$ Hz, 1H), 7.27 (d, $J = 2.4$ Hz, 1H), 7.58 (d, $J = 7.7$ Hz, 1H), 7.85 (d, $J = 7.7$ Hz, 1H), 9.18 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 52.2 (OCH_3), 108.2 (CH), 114.2 (q, $J = 33.2$ Hz, C–CF_3), 120.1 (CH), 122.8 (q $J = 4.7$ Hz, CH), 124.4 (q, $J = 272.5$ Hz, CF_3), 126.7 (CH), 128.5 (Cq), 128.9 (Cq), 132.1 (Cq), 161.7 (CO). MS (IS^+) *m/z* 244 $[M + H^+]$.

6.3. General procedures for iodination

*Method **A***: to a DMF solution (5 mL) of crushed pellets of KOH (4.0 eq.) and indole (1.0 eq.) at room temperature was dropwise added a solution of iodine (1eq) in DMF (3 mL). After 1.5 h, the mixture was poured onto a saturated aqueous solution (15 mL) of $NaHSO_3$, NH_4OH (30%, 2 mL) and water (15 mL). The solid was filtered, dried under reduced pressure and used without further purification. *Method **B***: to a solution of *N*-chlorosuccinimide (1.2 eq.) in DMF (0.3 M) was added sodium iodide (1.2 eq.) in small portion. The resulting brown solution was stirred at room temperature for 1 h before the slow addition at 0 °C of the corresponding indole (1.0 eq.) in DMF (0.3 M). The reaction mixture was stirred at room temperature overnight. A saturated aqueous solution of sodium thiosulfate and water were added and the mixture was stirred for 1 h. After filtration, the crude material was washed with cold water and cold petroleum ether to afford after drying under high vacuum the attempted 3-iodoindole which was used in the next step without any further purification. Compounds **24** (method B), **22**–**35** (method A) were previously described [11,18,19].

*6.3.1. Methyl-3-iodo-4-propoxy-1H-indole-2-carboxylate (**25**)*

Compound **25** was synthesized using *method B* from indole **11** and isolated as a pale brown solid in a 75% yield. Rf : 0.3 (petroleum ether/EtOAc 8/2); Mp 179 °C; IR (Ge-ATR, cm^{-1}) ν 3318 (NH), 3020, 3000, 1717 (C=O), 1576, 1095; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.18 (t, 3H, CH_3, $J = 12.0$ Hz), 1.89–2.03 (m, 2H, CH_2), 3.96 (s, 3H, CH_3), 4.06 (t, $J = 12.0$ Hz, 2H, CH_2), 6.49 (d, $J = 12.0$ Hz, 1H), 6.97 (d, $J = 12.0$ Hz, 1H), 7.20 (d, $J = 12.0$ Hz, 1H), 9.10 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 11.1 (CH_3), 22.4 (CH_2), 51.9 (OCH_3), 59.7 (Cq), 69.8 (OCH_2), 101.1 (CH), 104.3 (CH), 120.0 (Cq), 126.0 (Cq), 127.1 (CH), 137.8 (Cq), 154.6 (Cq), 161.2 (CO); MS (IS^+) *m/z* 360 $[M + H]^+$.

*6.3.2. Methyl-3-iodo-4-methyl-1H-indole-2-carboxylate (**26**)*

Compound **26** was synthesized using *method B* from indole **12** and isolated as a pale brown solid in a 70% yield. Rf 0.3 (petroleum ether/EtOAc 8/2); Mp 164 °C IR (Ge-ATR, cm^{-1}) ν 3300 (NH), 3020, 3000, 1717 (C=O), 1496, 1371, 1150; ^1H NMR (DMSO-*d*6, 400 MHz) δ 2.95 (s, 3H, CH_3), 3.97 (s, 3H, OCH_3), 6.91 (d, $J = 4.0$ Hz, 1H), 7.20 (t, $J = 8.0$ Hz, 1H), 7.29 (d, $J = 8.0$ Hz, 1H), 9.21 (br s, 1H, NH); ^{13}C NMR (DMSO-*d*6, 100.6 MHz) δ 20.4 (CH_3), 52.0 (CH_3), 62.1 (Cq), 110.2 (CH), 123.3 (CH), 126.0 (CH), 126.6 (Cq), 127.6 (Cq), 133.7 (Cq), 136.5 (Cq), 161.2 (CO); MS (IS^+) *m/z* 316 $[M + H]^+$.

*6.3.3. Methyl-3-iodo-4-(trifluoromethyl)-1H-indole-2-carboxylate (**27**)*

Compound **27** was synthesized using *method B* from indole **13** and isolated as a pale brown solid in a 75% yield. Rf : 0.3 (petroleum ether/EtOAc 8/2); Mp 192 °C; IR (Ge-ATR, cm^{-1}) ν 3312 (NH), 3020, 3000, 1700 (C=O), 1517, 1085; ^1H NMR (DMSO-*d*6, 400 MHz) δ 3.92 (s, 3H, OCH_3), 7.60–7.73 (m, 3H, H_{Ar}), 12.70 (br s, 1H, NH); ^{13}C NMR (DMSO-*d*6, 100.6 MHz) δ 51.9 (CH_3), 59.7 (Cq), 114.2 (CH), 119.8 (CH), 121.7 (CH), 126.0 (Cq), 127.1 (Cq), 137.8 (Cq), 154.6 (Cq),161.2 (CO); MS (IS^+) *m/z* 370 $[M + H]^+$.

*6.3.4. Methyl-3-iodo-4-bromo-1H-indole-2-carboxylate (**28**)*

Compound **28** was synthesized using *method A* from indole **14** and isolated as a white solid in a 70% yield. Rf 0.2 (petroleum ether/EtOAc 8/2); Mp 180 °C; IR (Ge-ATR, cm^{-1}) 3288 (NH, OH), 3020, 2988, 1700 (CO), 1600, 1498; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.99 (s, 3H, OCH_3), 7.14 (t, $J = 7.5$ Hz, 1H, H_{Ar}), 7.40 (t, $J = 6.2$ Hz, 2H, H_{Ar}), 9.40 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 52.4 (OCH_3), 112.0 (CH), 117.4 (Cq), 125.7 (Cq), 126.5 (CH), 127.0 (CH), 128.5 (Cq), 137.1 (Cq), 161.2 (CO); MS (IS^+) *m/z* 381 $[M + H]^+$.

*6.3.5. Methyl-3-iodo-5-(trifluoromethyl)-1H-indole-2-carboxylate (**29**)*

Compound **29** was synthesized using *method B* from indole **15** and isolated as a pale brown solid in a 74% yield. Rf : 0.28 (petroleum ether/EtOAc 8/2); Mp 189 °C; IR (Ge-ATR, cm^{-1}) ν 3312 (NH), 3020, 3000, 1700 (CO), 1517, 1085; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.02 (s, 3H, OCH_3), 7.49 (d, J = 12.0 Hz, 1H, H_{Ar}), 7.59 (d, J = 12.0 Hz, 1H, H_{Ar}), 7.88 (s, 1H, H), 9.40 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 52.4 (CH_3), 66.6 (Cq), 65.6 (Cq),112.6 (CH), 121.7 (CH), 121.7 (CH), 123.1 (q, CF_3, J = 270.0 Hz), 124.5 (Cq), 128.9 (Cq), 130.8 (Cq), 137.3 (Cq), 155.0 (Cq), 160.8 (CO); MS (IS^+) m/z 370 $[M + H]^+$.

*6.3.6. Methyl-3-iodo-7-(trifluoromethyl)-1H-indole-2-carboxylate (**30**)*

Compound **30** was synthesized using *method B* from indole **16** and isolated as a white solid in a 75% yield. Rf 0.3 (petroleum ether/EtOAc 8/2); Mp : 103 °C; IR (Ge-ATR, cm^{-1}) ν 3328 (NH), 3020, 3000, 1700 (CO), 1594, 1520, 1438, 1061; ^1H NMR (DMSO-*d*6, 400 MHz) δ 4.02 (s, 3H, OCH_3), 7.31 (t, J = 8.0 Hz, 1H, H_{Ar}), 7.66 (d, J = 4.0 Hz, 1H, H_{Ar}), 7.78 (d, J = 8.0 Hz, 1H, H_{Ar}), 9.06 (br s, 1H, NH); ^{13}C NMR (DMSO-*d*6, 62.9 MHz) δ 51.4 (CH_3), 59.7 (Cq), 120.6 (CH), 124.2 (CH), 127.5 (CH), 126.0 (Cq), 127.1 (Cq), 137.8 (Cq), 154.6 (Cq), 160.6 (CO); MS (IS^+) m/z 370 $[M + H]^+$.

*6.3.7. Methyl-3-iodo-6-(benzyloxy)-1H-indole-2-carboxylate (**31**)*

Compound **31** was synthesized using *method B* from crude indole **17** and isolated as a pale brown solid in a 21% yield. Rf : 0.25 (petroleum ether/EtOAc 8/2); Mp 85 °C; IR (ATR diamond, cm^{-1}) ν 3409, 3314, 2360, 1669, 1621, 1570, 1505,1470; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.96 (s, 3H, OCH_3), 5.11 (s, 2H), 6.84 (d, J = 2.4 Hz, 1H), 6.97 (dd, J = 9.0 Hz, J = 2.4 Hz, 1H), 7.30–3.47 (m, 6H), 9.12 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 51.9 (OCH_3), 66.5 (Cq), 70.4 (CH_2), 94.9 (CH), 113.7 (CH), 124.4 (CH), 126.2 (Cq), 127.4 (Cq), 127.5 (2xCH), 128.1 (CH), 128.6 (2xCH), 136.6 (Cq), 136.9 (Cq), 158.9 (Cq), 161.2 (CO); HRMS Calcd for $C_{17}H_{14}NO_3NaI$: 429.9916. Found: 429.9918.

*6.3.8. Methyl-3-iodo-6-methyl-1H-indole-2-carboxylate (**32**)*

Compound **32** was synthesized using *method A* from indole **18** and isolated as a pale brown solid in a 60% yield. Rf : 0.31 (petroleum ether/EtOAc 8/2); Mp 170 °C; IR (Ge-ATR, cm^{-1}) ν 3326 (NH), 3030, 3000, 1700 (CO), 1502, 1432; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.48 (s, 3H, CH_3), 3.97 (s, 3H, OCH_3), 7.05 (d, J = 7.5 Hz, 1H, H_{Ar}), 7.20 (s, 1H, H_{Ar}), 7.42 (d, J = 7.5 Hz, 1H, H_{Ar}), 9.06 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 21.8 (CH_3), 52.0 (OCH_3), 66.2 (Cq), 111.5 (CH), 123.0 (CH), 123.8 (CH), 126.4 (Cq), 129.4 (Cq), 136.5 (Cq), 137.1 (Cq), 161.3(CO), MS (IS^+) m/z 408 $[M + H]^+$.

*6.3.9. Ethyl-7-iodo-5H-[1,3]dioxolo[4,5-f]indole-6-carboxylate (**36**)*

Compound **36** was synthesized using *method B* from indole **23** and isolated as a pale brown solid in a 30% yield. Rf : 0.35 (petroleum ether/EtOAc 8/2); Mp : 207 °C; IR (Ge-ATR, cm^{-1}) ν 3298 (NH), 3020, 3000, 1717 (CO), 1495, 1262; ^1H NMR (DMSO-*d*6, 250 MHz) δ 1.35 (t, J = 7.5 Hz, 3H, CH_3), 4.31 (q, J = 7.5 Hz, 2H, OCH_2), 6.03 (s, 2H, OCH_2O), 6.77 (s, 1H, H_{Ar}), 6.89 (s, 1H, H_{Ar}), 12.07 (br s, 1H, NH); ^{13}C NMR (DMSO-*d*6, 100.6 MHz) δ 14.2 (CH_3), 60.2 ($OCH_{2\ ester}$), 65.6 (Cq), 92.2 (CH), 99.4 (CH), 101.0 (CH_2), 125.1 (Cq), 125.4 (Cq), 132.6 (Cq), 144.3 (Cq), 147.8 (Cq), 159.9 (CO); MS (IS^+) m/z 360 $[M + H]^+$.

*6.4. Methyl-4-(4-methoxyphenyl)-1H-indole-2-carboxylate (**37**)*

To a solution containing 4-bromoindole **14** (1.0 g, 3.54 mmol) and 4-methoxyphenyl boronic acid (808 mg, 5.3 mmol) in a mixture of toluene (30 mL), ethanol (20 mL) and a saturated aqueous $NaHCO_3$ solution (15 mL), under vigorous stirring, was added $Pd(PPh_3)_4$ (0.4 g, 0.35 mmol). The mixture was plunged into a preheated oil bath at 130 °C and the reaction refluxed for 4 h. After cooling to r.t., the mixture was extracted with EtOAc (3 × 300 mL), the organic extracts washed with water (2 × 200 mL) and dried over magnesium sulphate. The volatiles were removed under reduced pressure and the residue was purified by column chromatography over silica gel using petroleum ether/EtOAc as eluent to yield 900 mg of compound **37** (90%) as a white solid. Rf : 0.3 (petroleum ether/EtOAc 8/2); Mp : 196 °C; IR (Ge-ATR, cm^{-1}) ν 3321 (NH), 3020, 3000, 1700 (CO), 1520, 1441, 834; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.87 (s, 3H, CH_3), 3.93 (s, 3H, CH_3), 7.02 (d, J = 7.5 Hz, 2H, H_{Ar}), 7.17 (t, J = 5.0 Hz, 1H, H_{Ar}), 7.36–7.39 (m, 3H, H_{Ar}), 7.60 (d, J = 10.0 Hz, 2H, H_{Ar}), 8.96 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 52.0 (OCH_3), 55.3 (OCH_3), 108.6 (CH), 110.4 (CH), 114.0 (2xCH), 120.1 (CH), 125.7 (CH), 125.9 (Cq), 127.1 (Cq), 129.7 (2xCH), 132.8(Cq), 136.1 (Cq), 137.4 (Cq), 159.1 (Cq), 162.4 (CO) MS (IS^+) m/z 282 $[M + H]^+$.

*6.5. Methyl-6-(4-methoxyphenyl)-1H-indole-2-carboxylate (**38**)*

Compound **38** was obtained as described for compound **37** starting from **19** as a white solid in a 72% yield. Mp 205 °C; IR (Ge-ATR, cm^{-1}) ν 3314 (NH), 3020, 3000, 1700 (CO), 1562, 1515, 1332, 832; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.85 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 6.99 (d, J = 10.0 Hz, 2H, H_{Ar}), 7.22–7.25 (m, 1H, H_{Ar}), 7.37 (d, J = 7.5 Hz, 1H, H_{Ar}), 7.54–7.59 (m, 3H, H_{Ar}), 7.71 (d, J = 7.5 Hz, 1H, H_{Ar}), 8.97 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 52.0 (OCH_3), 55.3 (OCH_3), 108.7 (CH), 109.4 (CH), 114.2 (CH), 114.7 (CH), 116.0 (CH), 120.7 (CH), 122.7 (CH), 126.3 (Cq), 127.3 (Cq), 128.3 (CH), 134.1 (Cq), 137.5 (Cq); 138.5 (Cq), 159.0 (Cq), 162.3 (CO); MS (IS^+) m/z 282 $[M + H]^+$.

*6.6. Methyl-3-iodo-4-(4-methoxyphenyl)-1H-indole-2-carboxylate (**39**)*

Compound **39** was synthesized using the general procedure *Method **A*** for iodation from indole **37** and isolated as a white solid in a 75% yield. Rf : 0.3 (petroleum ether/EtOAc 8/2); Mp 210 °C; IR (Ge-ATR, cm^{-1}) ν 3316 (NH), 3020, 3000, 1700 (CO), 1520, 1496, 827; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.87 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.95–7.03 (m, 3H, H_{Ar}), 7.29–7.44 (m, 4H, H_{Ar}), 9.36 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 52.2 (OCH_3), 55.4 (OCH_3), 65.2 (Cq), 111.3 (CH), 112.9 (2xCH), 124.0 (CH), 125.6 (CH), 126.7 (Cq), 127.8 (Cq), 130.8 (Cq), 132.2 (2xCH), 136.6 (Cq),138.3 (Cq), 159.4 (Cq), 161.4 (CO); MS (IS^+) m/z 408 $[M + H]^+$.

*6.7. Methyl 3-iodo-6-(4-methoxyphenyl)-1H-indole-2-carboxylate (**40**)*

Compound **40** was synthesized using the general procedure for iodation *Method **A*** from indole **38** and isolated as a white solid in a 73% yield. Rf : 0.2 (petroleum ether/EtOAc 8/2); Mp 224 °C; IR (Ge-ATR, cm^{-1}) ν 3308 (NH), 3020, 3000, 1700 (CO), 1579, 1507, 1438, 829; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.87 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 7.00 (d, J = 7.5 Hz, 2H, H_{Ar}), 7.44–7.60 (m, 5H, H_{Ar}), 9.21 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 51.7 (OCH_3), 55.0 (OCH_3), 65.8 (Cq), 109.7 (CH), 114.2 (CH), 114.3 (CH), 120.5 (CH), 122.7 (CH), 127.0 (Cq), 127.7 (CH), 127.9 (CH), 129.5 (Cq), 132.7 (Cq), 137.4 (Cq), 137.9 (Cq), 158.8 (Cq), 160.6 (CO); MS (IS^+) m/z 408 $[M + H]^+$.

*6.8. 2,5-Bis(methoxymethoxy)phenyl trifluoroborate (**43**)*

To a solution of MeOH (3 mL) containing the crude boronic acid **42** (870 mg, 3.6 mmol) was added an aqueous 1M solution of KHF_2 at 0 °C (2 mL). After 4 h at r.t. under vigorous stirring, the precipitate

was filtered and washed with MeOH (1 mL) and then dried to afford compound **43** (690 mg) as a white solid which was used without any further purification in 80% yield. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.34 (s, 3H, CH_3), 3.35 (s, 3H, CH_3), 4.93 (s, 2H, CH_2), 5.03 (s, 2H, CH_2), 6.59–6.70 (m, 2H, H_{Ar}), 6.97 (s, 1H, H_{Ar}).

6.9. 2-Methoxy-6-(methoxymethoxy)phenylboronic acid (**44**)

To a solution of 1-methoxy-3-(methoxymethoxy)benzene (2.0 g, 11.0 mmol) in Et_2O (40 mL) a solution of *n*-BuLi in hexane 2.5M (5.28 mL, 13.2 mmol) was added and the mixture refluxed for 2 h. After cooling at room temperature $B(OCH_3)_3$ (1.47 mL, 13.2 mmol) was dropwise added and the mixture was stirred for 1 h. Addition of a saturated solution of NH_4Cl, extraction with EtOAc (3 × 60 mL), washing with water (2 × 30 mL), drying over $MgSO_4$ and evaporation left 800 mg of **44** as a pale yellow solid (40%) which was used without further treatment in cross-coupling reactions. ^{1}H NMR (DMSO-*d*6, 250 MHz) δ 3.32 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 5.06 (s, 2H, OCH_2), 6.51–6.62 (m, 2H, H_{Ar}), 7.17 (t, J = 7.5 Hz, 1H, H_{Ar}).

6.10. 2-(2,4-bis(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. (**45**)

To a solution of the 1-bromo-2,4-bis-methoxymethoxy-benzene (300 mg, 1.09 mmol, 1.0 eq.) in dry toluene (0.3 M, purged with Ar) were successively added potassium acetate (427 mg, 4.36 mmol), bis(pinacolato)diboron (276 mg, 1.09 mmol) and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) CH_2Cl_2 complex (335 mg, 0.11 mmol). The resulting mixture was stirred under reflux overnight and then concentrated. The residue was subjected to a quick silica gel flash chromatography (petroleum ether EtOAc 95/5 to 90/10) which afforded 215 mg of **45** as colourless oil (61%). R_f 0.50 (petroleum ether/EtOAc: 85/15); IR (Ge-ATR, cm^{-1}) ν 1350, 1377, 1427, 1572, 1603, 2976 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.32 (s, 12H), 3.46 (s, 3H), 3.52 (s, 3H), 5.17 (s, 2H), 5.18 (s, 2H), 6.69–6.73 (m, 2H), 7.64 (d, J = 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 24.8 (4 × CH), 56.1 (CH), 56.2 (CH), 83.2 (2x Cq), 94.2 (CH_2), 95.3 (CH_2), 104,4 (CH), 109.1 (CH), 138.0 (CH), 160.9 (Cq), 163.3 (Cq); HRMS Calcd for $C_{16}H_{25}BO_6Na$: 347.1642. Found: 347.1642.

6.11. Typical procedure for the Suzuki reaction leading to compound of type II (**46**–**65**)

To a solution of the boron derivative (2.0 eq.) in a mixture of toluene/EtOH (4/1, 0.3 M, purged with Ar) were added the methyl 3-iodo-4-methoxymethoxy-1*H*-indole-2-carboxylate derivative (1.0 eq.), tetrakis(triphenylphosphine)palladium(0) 10% and *ca* 2 mL of a saturated aqueous solution of $NaHCO_3$. The resulting mixture was stirred under reflux overnight, concentrated and then dissolved in EtOAc. The organic phase was separated and the aqueous layer was extracted with EtOAc. The combined organic phase was successively washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was finally subjected to a silica gel flash chromatography (petroleum ether/EtOAc) which afforded the desired compound.

6.11.1. Ethyl 3- (2-methoxyphenyl)-1H -indole- 2-carboxylate (**46**)

Compound **46** was synthesized using the general procedure for Suzuki reaction from **33** and 2-methoxyphenyl boronic acid **A** and isolated after 6 h as a white solid in a 91% yield. Mp 179 °C; IR (Ge-ATR, cm^{-1}) ν 3293 (NH), 3020, 3000, 1716 (C=O), 1554, 1500, 1426, 1064, 766; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.15 (t, 3H, CH_3, J = 7.0 Hz), 3.90 (s, 3H, OCH_3), 4.23 (q, 2H, OCH_2, J = 7.1 Hz), 6.99–7.14 (m, 3H, H_{Ar}), 7.29–7.37 (m, 5H, H_{Ar}), 8.95 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 14.1 (CH_3), 55.5 (OCH_3), 60.7 (OCH_2), 110.8 (CH), 111.8 (CH), 120.1 (CH), 120.6 (CH), 122.0 (Cq), 122.9 (Cq), 124.1 (Cq), 125.5 (CH), 128.2 (Cq), 128.8 (CH), 132.2 (CH), 132.2 (CH), 135.9 (Cq), 157.5 (Cq), 162.3 (CO); MS (IS^+) m/z 296 $[M + H]^+$.

6.11.2. Ethyl 3-(2,4-dimethoxyphenyl)-1H-indole-2-carboxylate (**47**)

Compound **47** was synthesized using the general procedure for Suzuki reaction from **33** to 2,4-dimethoxyphenyl boronic acid **B** and isolated after 6 h as a white solid in a 70% yield. R_f : 0.3 (petroleum ether/EtOAc 8/2); Mp 165 °C; IR (Ge-ATR, cm^{-1}) ν 3300 (NH), 3020, 2967, 1719 (C=O), 1503, 1465, 1381, 1073 : ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.17 (t, J = 6.9 Hz, 3H, CH_3), 3.67 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.25 (q, J = 7.1 Hz, 2H, OCH_2) 6.91–6.92 (m, 3H, H_{Ar}), 7.11 (t, J = 7.3 Hz, 1H, H_{Ar}), 7.29 (t, J = 7.0 Hz, 1H, H_{Ar}), 7.42 (d, J = 8.1 Hz, 1H, H_{Ar}), 7.5 (d, J = 7.8 Hz, 1H, H_{Ar}), 9.06 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 14.1 (CH_3), 55.8 (OCH_3), 56.2 (OCH_3), 60.7 (OCH_2), 111.8 (CH), 112.0 (CH), 113.5 (CH), 117.9 (CH), 119.5 (Cq), 120.7 (CH), 121.9 (CH), 123.9 (Cq), 124.2 (Cq), 125.5 (CH), 128.1 (Cq), 135.8 (Cq), 151.9 (Cq), 153.2 (Cq), 162.3 (CO); MS (IS^+) m/z 326 $[M + H]^+$.

6.11.3. Ethyl 3-(2,5-dimethoxyphenyl)-1H-indole-2-carboxylate (**48**)

Compound **48** was synthesized using the general procedure for Suzuki reaction from **33** to 2,5-methoxyphenyl boronic acid **C** and isolated after 6 h as a white solid in a 78% yield. R_f : 0.3 (petroleum ether/EtOAc 8/2); Mp 140 °C; IR (Ge-ATR, cm^{-1}) ν 3348 (NH), 3020, 3000, 1717 (C=O), 1557, 1465, 1404, 1063; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.17 (t, J = 6.9 Hz, 3H, CH_3), 3.67 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.25 (q, J = 7.1 Hz, 2H, OCH_2), 6.91–6.92 (m, 3H, H_{Ar}), 7.11 (t, J = 7.3 Hz, 1H, H_{Ar}), 7.29 (t, J = 7.0 Hz, 1H, H_{Ar}), 7.42 (d, J = 8.1 Hz, 1H, H_{Ar}), 7.50 (d, J = 7.8 Hz, 1H, H_{Ar}), 9.06 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 14.1 (CH_3), 55.8 (OCH_3), 56.2 (OCH_3), 60.7 (OCH_2), 111.8 (CH), 112.0 (CH), 113.5 (CH), 117.9 (CH), 119.5 (Cq), 120.7 (CH), 121.9 (CH), 123.9 (Cq), 124.2 (Cq), 125.5 (CH), 128.1 (Cq), 135.8 (Cq), 151.9 (Cq), 153.2 (Cq),162.3 (CO); MS (IS^+) m/z 326 $[M + H]^+$.

6.11.4. Ethyl 3-(2-methoxy-6-(methoxymethoxy)phenyl)-1H-indole–2–carboxylate (**49**)

Compound **49** was synthesized using the general procedure for Suzuki reaction from **33** and boronic acid **44** and isolated after 7 h as an orange solid in a 74% yield. R_f : 0.2 (petroleum ether/EtOAc 8/2); Mp 124 °C; IR (Ge-ATR, cm^{-1}) ν 3314 (NH), 3020, 2961, 1700 (C=O), 1589, 1469, 1436, 1069; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.11 (t, J = 6.9 Hz, 3H, CH_3), 3.22 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 4.19 (q, J = 6.9 Hz, 2H, OCH_2), 4.92 (d, J = 7.5 Hz, 1H, OCH_2), 4.99 (d, J = 7.5 Hz, 1H, OCH_2), 6.70 (d, J = 8.1 Hz, 1H, H_{Ar}), 6.87 (d, J = 8.1 Hz, 1H, H_{Ar}), 6.07 (t, J = 7.2 Hz, 1H, H_{Ar}), 7.25–7.43 (m, 4H, H_{Ar}), 9.01 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 14.0 (CH_3), 55.9 (OCH_3), 56.0 (OCH_3), 60.5 (OCH_2), 95.0 (OCH_2), 104.9 (CH), 108.0 (CH), 111.8 (CH), 113.2 (Cq), 115.9 (Cq), 120.3 (CH), 122.2 (CH), 125.2 (CH), 128.3 (Cq), 129.1 (CH), 130.0 (Cq), 136.0 (Cq), 156.4 (Cq), 158.7 (Cq), 162.3 (CO); MS (IS^+) m/z 310 $[M + H]^+$.

6.11.5. Methyl 3-(2-methoxyphenyl)-4-(4-methoxyphenyl)-1H-indole-2-carboxylate (**50**)

Compound **50** was synthesized using the general procedure for Suzuki reaction from **39** and 2-methoxyphenylboronic acid **A** and isolated after 3 h as an orange solid in an 82% yield. Rf : 0.3 (petroleum ether/EtOAc 8/2); Mp 200 °C; IR (Ge-ATR, cm^{-1}) ν 3332, 3020, 3000, 1700, 1600–1460, 1439, 827, 751; ^{1}H NMR (DMSO-*d*6, 250 MHz) δ 3.34 (s, 3H, CH_3), 3.64 (s, 6H, $2CH_3$), 6.42–6.53 (m, 3H, H_{Ar}), 6.68 (t, J = 7.5 Hz, 1H, H_{Ar}), 6.78–6.88 (m, 5H, H_{Ar}), 7.02 (t,

J = 7.5 Hz, 1H, H_{Ar}), 7.47 (d, J = 10.0 Hz, 1H, H_{Ar}), 11.97 (br s, 1H, NH); ^{13}C NMR (DMSO-*d*6, 62.9 MHz) δ 51.3 (CH_3), 54.4 (CH_3), 54.9 (CH_3), 109.4 (CH), 111.2 (CH), 111.9 (2CH), 118.9 (CH), 119.6 (Cq), 121.3 (CH), 123.5 (Cq), 123.9 (Cq), 124.2(Cq), 124.3 (CH), 127.8 (CH), 129.3 (2CH), 131.5 (Cq), 131.7 (CH), 136.8 (Cq), 137.0 (Cq), 156.5 (Cq), 157.5 (Cq), 161.5 (CO); MS (IS^+) m/z 388 $[M + H]^+$.

6.11.6. Methyl 3-(2,5-dimethoxyphenyl)-4-(4-methoxyphenyl)-1H-indole-2-carboxylate (**51**)

Compound **51** was synthesized using the general procedure for Suzuki reaction from **39** to 2,5-dimethoxyphenylboronic acid **B** and isolated after 4 h as an orange solid in a 80% yield. R_f : 0.3 (petroleum ether/EtOAc 8/2); Mp 253 °C; IR (Ge-ATR, cm^{-1}) ν 3315, 3020, 3000, 1710, 1600, 1458, 1439, 837; ^{1}H NMR (DMSO-*d*6, 250 MHz) δ 3.46 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 3.72 (s, 6H, 2 × OCH_3), 6.44–6.48 (m, 4H, H_{Ar}), 6.63 (dd, J = 2.5 Hz, J' = 7.5 Hz, 1H, H_{Ar}), 6.92–7.01 (m, 3H, H_{Ar}), 7.31–7.43 (m, 2H, H_{Ar}), 9.35 (br s, 1H, NH); ^{13}C NMR (DMSO-*d*6, 62.9 MHz) δ 51.6 (OCH_3), 55.2 (OCH_3), 55.4 (OCH_3), 55.6 (OCH_3), 110.2 (CH), 110.5 (CH), 112.1 (2CH), 113.3 (CH), 117.7 (CH), 120.2 (Cq), 122.2 (CH), 123.9 (Cq), 124.5 (Cq), 125.0 (Cq), 125.1 (CH), 129.8 (2CH), 132.0 (Cq), 136.3 (Cq), 137.9 (Cq), 151.4 (Cq), 152.6 (Cq), 158.0 (Cq), 162.3 (CO); MS (IS^+) m/z 418 $[M + H]^+$.

6.11.7. Methyl 3-(2,5-Bis(methoxymethoxy)phenyl)-4-methyl-1H-indole-2-carboxylate. (**52**)

Compound **52** was synthesized using the general procedure for Suzuki reaction from **26** and **43** and isolated after 5 h as a cream solid in a 45% yield. R_f 0.20 (petroleum ether/EtOAc 80/20); Mp 133 °C; IR (Diamond-ATR, cm^{-1}) ν 3322, 1698, 1623, 1578, 1476, 1395, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.12 (s, 3H, CH_3), 3.20 (s, 3H, CH_3), 3.47 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 4.91 (d, J = 8.0 Hz, 1H, CH_2), 4.96 (d, J = 8.0 Hz, 1H, CH_2), 5.12 (s, 2H, CH_2), 6.84 (d, J = 4.0 Hz, 1H, H_{Ar}), 6.97 (d, J = 3.2 Hz, 1H, H_{Ar}), 7.01–7.04 (m, 1H, H_{Ar}), 7.11 (d, J = 8.0 Hz, 1H, H_{Ar}), 7.21 (t, J = 8.0 Hz, 1H, H_{Ar}), 7.28 (s, 1H, H_{Ar}), 8.94 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.3 (CH_3), 55.6 (CH_3), 55.6 (CH_3), 55.8 (CH_3), 95.2 (CH_2), 95.5 (CH_2), 109.5 (CH), 116.3 (CH), 116.7 (CH), 120.4 (CH), 120.5 (Cq), 121.9 (CH), 123.4 (Cq), 125.5 (CH), 126.6 (Cq), 127.4 (Cq), 133.7 (Cq), 135.9 (Cq), 150.7 (Cq), 151.4 (Cq), 162.2 (Cq). MS (IS^+) m/z 402 $[M + H]^+$.

6.11.8. Methyl 3-(2,5-bis(methoxymethoxy)phenyl)-4-methoxy-1H-indole-2-carboxylate (**53**)

Compound **53** was synthesized using the general procedure for Suzuki reaction from **24** and **43** and isolated after 5 h as a white solid in a 35% yield. R_f 0.2 (petroleum ether/EtOAc 8/2); Mp 113 °C; IR (Ge-ATR, cm^{-1}) ν 3275, 3020; 3000, 1700, 1578, 1433, 1065; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.26 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 4.91 (d, J = 8.0 Hz, 1H, OCH_2), 4.92 (d, J = 8.0 Hz, 1H, OCH_2), 5.11 (s, 2H, OCH_2), 6.44 (d, J = 8.0 Hz, 1H, H_{Ar}), 6.95–6.99 (m, 2H, H_{Ar}), 7.02 (t, J = 4.0 Hz, 1H, H_{Ar}), 7.10 (d, J = 8.0 Hz, 1H, H_{Ar}), 7.22 (t, J = 10.0 Hz, 1H, H_{Ar}), 8.95 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 51.6 (OCH_3), 55.1 (OCH_3), 55.6 (OCH_3), 55.8 (OCH_3), 95.4 (OCH_2), 96.0 (OCH_2), 100.3 (CH), 104.5 (CH), 116.0 (CH), 116.3 (CH), 118.4 (Cq), 119.4 (Cq), 120.6 (CH), 122.6 (Cq), 126.4 (CH), 126.8 (Cq), 137.2 (Cq), 151.0 (Cq), 151.2 (Cq), 155.9 (Cq), 162.2 (CO); MS (IS^+) m/z 402 $[M + H]^+$.

6.11.9. Methyl 3-(2,5-bis(methoxymethoxy)phenyl)-4-(trifluoromethyl)-1H-indole-2-carboxylate (**54**)

Compound **54** was synthesized using the general procedure for Suzuki reaction from **27** and **43** and isolated after 5 h as a yellow solid in a 60% yield. R_f 0.2 (petroleum ether/EtOAc 8/2); Mp 126 °C; IR (Ge-ATR, cm^{-1}) ν: 3334, 3020, 3000, 1700, 1583, 1346, 1078; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.28 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.91 (d, J = 12.0 Hz, 1H, OCH_2), 5.00 (d, J = 12.0 Hz, 1H, OCH_2), 5.16 (s, 2H, OCH_2), 7.06–7.08 (m, 2H, H_{Ar}), 7.21–7.25 (m, 1H, H_{Ar}), 7.48–7.55 (m, 2H, H_{Ar}), 7.81 (s, 1H, H_{Ar}), 9.37 (s, 1H, NH) ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 52.0 (CH_3), 55.8 (CH_3), 95.1 (CH_2), 95.7 (CH_2), 112.2 (CH), 116.4 (CH), 117.1 (CH), 120.2 (CH), 121.9 (CH), 122.0 (CH), 122.7 (Cq), 123.1 (q, J = 270 Hz, CF_3), 123.3 (Cq), 123.5 (Cq), 125.2 (Cq), 126.2 (Cq), 127.3 (Cq), 136.7 (Cq), 150.4 (Cq), 151.7 (Cq), 162.1 (Cq); MS (IS^+) m/z 440 $[M + H]^+$.

6.11.10. Methyl 3-(2,5-bis(methoxymethoxy)phenyl)-4-propoxy-1H-indole-2-carboxylate (**55**)

Compound **55** was synthesized using the general procedure for Suzuki reaction from **25** and **43** and isolated after 7 h as a white solid in a 77% yield. R_f 0.2 (petroleum ether/EtOAc 8/2); Mp 111 °C; IR (Ge-ATR, cm^{-1}) ν 3328, 3020, 3000, 1717, 1585, 1412, 1078; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.61 (t, J = 8.0 Hz, 3H, CH_3), 1.39–1.48 (m, 2H, CH_2), 3.23 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.78 (t, J = 8.0 Hz, 2H, OCH_2), 4.90 (s, 2H, OCH_2), 5.11 (s, 2H, OCH_2), 6.39 (d, J = 8.0 Hz, 1H, H_{Ar}), 6.96–6.99 (m, 3H, H_{Ar}), 7.06 (d, J = 8.0 Hz, 1H, H_{Ar}), 7.20 (d, J = 8.0 Hz, 1H, H_{Ar}), 8.88 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.5 (CH_3), 22.6 (CH_2), 51.6 (OCH_3), 55.7 (OCH_3), 55.9 (OCH_3), 70.0 (OCH_2), 95.1 (OCH_2), 96.0 (OCH_2), 102.7 (CH), 112.5 (CH), 116.5 (CH), 117.0 (CH), 117.7 (CH), 119.0 (Cq), 120.1 (CH), 124.1 (Cq), 125.3 (Cq), 128.3 (Cq), 130.9 (Cq), 150.6 (Cq), 151.8 (Cq), 154.2 (Cq), 162.3 (CO); MS (IS^+) m/z 430 $[M + H]^+$.

6.11.11. Ethyl 5-(benzyloxy)-3-(2,4-dimethoxyphenyl)-1H-indole-2-carboxylate (**56**)

Compound **56** was synthesized using the general procedure for Suzuki reaction from **35** to 2,4-dimethoxyphenyl boronic acid **B** and isolated after 8 h as a yellow solid in a 70% yield. Rf 0.3 (petroleum ether/EtOAc 8/2); Mp 143 °C; IR (Ge-ATR, cm^{-1}) ν 3020, 3000, 1721, 1503, 1074, 749; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.19 (t, J = 7.5 Hz, 3H, CH_3), 3.68 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.23 (q, J = 7.5 Hz, 2H, OCH_2), 5.00 (s, 2H, CH_2), 6.57–6.60 (m, 2H, H_{Ar}), 6.90 (s, 1H, H_{Ar}), 7.06 (dd, J = 2.1 Hz, J' = 8.9 Hz, 1H, H_{Ar}), 7.25–7.43 (m, 7H, H_{Ar}), 8.85 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 14.2 (CH_3), 55.4 (OCH_3), 55.4 (OCH_3), 60.6 (OCH_2), 70.6 (CH_2), 98.7 (CH), 103.6 (CH), 104.0 (CH), 112.7 (CH), 115.5 (Cq), 117.6 (CH), 119.4 (Cq), 124.5 (Cq), 127.6 (2CH), 127.8 (CH), 128.5 (2CH), 128.6 (Cq), 131.3 (Cq), 132.5 (CH), 137.5 (Cq), 153.8 (Cq), 158.5 (Cq), 160.5 (Cq), 162.1 (CO); MS (IS^+) m/z 432 $[M + H]^+$.

6.11.12. Ethyl 5-(benzyloxy)-3-(2,5 -dimethoxyphenyl) -1H-indole-2-carboxylate (**57**)

Compound **57** was synthesized using the general procedure for Suzuki reaction from **35** to 2,5-dimethoxyphenyl boronic acid **C** and isolated after 8 h as a yellow solid in a 63% yield. Rf : 0.3 (petroleum ether/EtOAc 8/2); Mp 143 °C; IR (Ge-ATR, cm^{-1}) ν 3310, 3020, 3000, 1722, 1505, 1073,748; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.17 (t, J = 7.5 Hz, 3H, CH_3), 3.65 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.23 (q, J = 7.5 Hz, 2H, OCH_2), 5.00 (s, 2H, CH_2), 6.92–6.95 (m, 4H, H_{Ar}), 7.08 (dd, J = 2.3 Hz, J' = 8.9 Hz, 1H, H_{Ar}), 7.25–7.40 (m, 6H, H_{Ar}), 9.12 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 14.1 (CH_3), 55.9 (OCH_3), 56.2 (OCH_3), 60.7 (OCH_2), 70.7 (CH_2), 103.4 (CH), 112.0 (CH), 112.8 (CH), 113.6 (Cq), 117.8 (CH), 117.9 (CH), 119.2 (Cq), 124.0 (Cq), 124.7 (Cq), 126.0 (Cq), 127.7 (2CH), 127.9 (CH), 128.6 (2CH), 131.3 (Cq), 137.4 (Cq), 151.9 (Cq), 153.2 (Cq), 154.0 (Cq), 162.1 (CO); MS (IS^+) m/z 432 $[M + H]^+$.

6.11.13. Ethyl 5-(benzyloxy)-3-[4-isopropoxy-5-methoxy-2-(methoxymethoxy) phenyl]-1H-indole-2-carboxylate (**58**)

Compound **58** was synthesized using the general procedure for Suzuki reaction from **35** and **41** and isolated after 7 h as a pale brown solid in a 76% yield. Rf 0.3 (petroleum ether/EtOAc 8/2); Mp 170 °C; IR (Ge-ATR, cm^{-1}) ν 3361, 3020, 2978, 1715, 1552, 1466, 1379,

1073, 766; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.19 (t, J = 7.0 Hz, 3H, CH_3), 1.42 (d, J = 6.0 Hz, 6H, $2CH_3$), 3.23 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.25 (q, J = 7.0 Hz, 2H, OCH_2), 4.57–4.62 (m, 1H, CH), 4.87 (d, 2H, OCH_2), 5.07 (s, 2H, CH_2), 6.80 (s, 1H, H_{Ar}), 6.92 (s, 1H, H_{Ar}), 6.96 (d, J = 2.0 Hz, 1H, H_{Ar}), 7.08 (dd, J = 2.0 Hz, J = 9.0 Hz, 1H, H_{Ar}), 7.25–7.34 (m, 6H, H_{Ar}), 9.05 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 14.1 (CH_3), 22.2 ($2CH_3$), 55.9 (OCH_3), 56.6 (OCH_3), 60.7 (OCH_2), 70.6 (CH_2), 96.6 (OCH_2), 103.4 (CH), 106.2 (CH), 112.8 (CH), 115.6 (CH), 116.6 (Cq), 117.7 (CH), 119.5 (Cq), 124.6 (Cq), 125.9 (Cq), 127.6 (2CH), 127.9 (CH), 128.6 (2CH), 131.3 (Cq), 137.4 (Cq), 145.3 (Cq), 147.4 (Cq), 149.8 (Cq), 153.9 (Cq), 162.1 (CO); MS (IS$^+$) m/z 520 $[M + H]^+$.

6.11.14. Methyl 3-(2,5-bis(methoxymethoxy)phenyl)-5-(trifluoromethyl)-1H-indole-2-carboxylate (**59**)

Compound **59** was synthesized using the general procedure for Suzuki reaction from **29** and **43** and isolated after 7 h as an orange solid in a 40% yield. R_f 0.2 (PE/EtOAc 8/2); mp 131 °C; IR (Ge-ATR, cm^{-1}) ν 3336, 3020, 3000, 1700, 1507, 1345, 1154; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.27 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.92 (d, J = 7.5 Hz, 1H, OCH_2), 4.99 (d, J = 7.5 Hz, 1H, OCH_2), 5.16 (s, 2H, CH_2), 7.06–7.08 (m, 2H, H_{Ar}), 7.20–7.25 (m, 1H, H_{Ar}), 7.48–7.57 (m, 2H, H_{Ar}), 7.81 (s, 1H, H_{Ar}), 9.31 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 52.0 (OCH_3), 55.8 (OCH_3), 95.1 (OCH_2), 95.7 (OCH_2), 112.2 (CH), 116.4 (CH), 117.1 (CH), 120.2 (CH), 120.3 (q, J = 270 Hz, CF_3), 121.9 (CH), 122.0 (CH), 122.7 (Cq), 122.9 (Cq), 123.4 (Cq), 123.5 (Cq), 125.2 (Cq), 127.3 (Cq), 136.6 (Cq), 150.4 (Cq), 151.7 (Cq), 162.0 (Cq); MS (IS$^+$) m/z 440 $[M + H]^+$.

6.11.15. Ethyl 3-(2,5-bis(methoxymethoxy)phenyl)-5-fluoro-1H-indole-2-carboxy late (**60**)

Compound **60** was synthesized using the general procedure for Suzuki reaction from **34** and **42** and isolated after 7 h as a brown solid in 82% yield. R_f 0.2 (petroleum ether/EtOAc 8/2); Mp 74 °C; IR (Ge-ATR, cm^{-1}) ν 3333, 3020, 3000, 1717,1548, 1235, 1077; ^{1}H NMR ($CDCl_3$, 250 MHz, F decoupled) δ 1.17 (t, J = 7.5 Hz, 3H, CH_3), 3.25 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 4.24 (q, J = 7.5 Hz, 2H, OCH_2), 4.88 (d, J = 7.5 Hz, 1H, OCH_2), 4.94 (d, J = 7.5 Hz, 1H, OCH_2), 5.15 (s, 2H, OCH_2), 7.02–7.19 (m, 5H, H_{Ar}), 7.34–7.39 (m, 1H, H_{Ar}), 8.96 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9 (CH_3), 55.9 ($2OCH_3$), 60.8 (OCH_2), 95.2 (OCH_2), 95.8 (OCH_2), 106.1 (CH), 106.3 (CH), 112.5 (CH), 112.6 (Cq), 114.5 (CH), 114.7 (Cq), 116.6 (CH), 120.1 (CH), 124.7 (Cq), 125.5 (Cq), 128.5 (Cq), 132.0 (Cq), 150.4 (Cq), 151.8 (Cq), 161.6 (CO); MS (IS$^+$) m/z 404 $[M + H]^+$.

6.11.16. Methyl 3-(2,5-dimethoxyphenyl)-6-(benzyloxy)-1H-indole-2-carboxylate (**61**)

Compound **61** was synthesized using the general procedure for Suzuki reaction from **31** to 2,5-dimethoxyphenyl boronic acid **C** and isolated after 7 h as a white solid in 60% yield. R_f 0.2 (petroleum ether/EtOAc 9/1); Mp 185 °C; IR (Ge-ATR, cm^{-1}) ν 3328, 3020, 3000, 1719, 1579, 1507, 1438, 733; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.68 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.16 (s, 3H, OCH_3), 5.13 (s, 2H, CH_2), 6.85–6.94 (m, 5H, H_{Ar}), 7.32–7.47 (m, 6H, H_{Ar}), 8.82 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 55.7 (OCH_3), 56.1 (OCH_3), 60.4 (OCH_3), 70.3 (OCH_2), 94.9 (CH), 111.8 (CH), 112.5 (CH), 113.4 (CH), 117.8 (CH), 119.9 (Cq), 122.6 (Cq), 122.7 (CH), 123.0 (Cq), 123.7 (Cq), 127.3 (2CH), 127.9 (CH), 128.5 (2CH), 136.5 (Cq), 136.9 (Cq), 151.7 (Cq), 153.0 (Cq), 158.0 (Cq), 161.9 (CO); MS (IS$^+$) m/z 478 $[M + H]^+$

6.11.17. Methyl 6-(benzyloxy)-3-(2,4-bis(methoxymethoxy) phenyl)-1H-indole-2-carboxylate (**62**)

Compound **62** was synthesized using the general procedure for Suzuki reaction from **31** and **45** and isolated after 7 h as pale brown oil in 68% yield. R_f 0.40 (petroleum ether/EtOAc: 60/40); IR (diamond-ATR, cm^{-1}) ν 2952, 1697, 1624, 1503, 1453, 1326 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.29 (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.94–5.07 (m, 2H, CH_2), 5.10 (s, 2H, OCH_2), 5.22 (s, 2H, OCH_2), 6.79 (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 6.83–6.87 (m, 2H), 6.96 (d, J = 2.4 Hz, 1H), 7.23–7.47 (m, 7H), 8.88 (br s, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 51.5 (OCH_3), 56.0 (OCH_3), 56.1 (OCH_3), 70.3 (CH_2), 94.6 (OCH_2), 94.8 (CH), 95.3 (OCH_2), 104.3 (CH), 108.7 (CH), 112.4 (CH), 117.3 (Cq), 120.5 (Cq), 122.5 (Cq), 122.9 (CH), 123.0 (Cq), 127.4 (2xCH), 127.9 (CH), 128.6 (2xCH), 132.4 (CH), 136.5 (Cq), 136.9 (Cq), 156.3 (Cq), 157.9 (Cq), 158.1 (Cq), 162.3 (CO). HRMS (ESI+) Calcd for $C_{27}H_{27}NO_7Na$: 500.16851. Found: 500.1697.

6.11.18. Methyl 3-(2,5-bis(methoxymethoxy)phenyl)-6-methyl-1H-indole-2-carboxylate (**63**)

Compound **63** was synthesized using the general procedure for Suzuki reaction from **32** and **43** and isolated after 7 h as a beige solid in 90% yield. R_f 0.2 (petroleum ether/EtOAc 9/1); Mp 127 °C; IR (Ge-ATR, cm^{-1}) ν 3366, 3303, 3020, 3000, 1713, 1468, 1077, 802; ^{1}H NMR (DMSO-d6, 250 MHz) δ : 2.47 (s, 3H, CH_3), 3.25 (s, 3H, CH_3), 3.49 (s, 3H, CH_3), 3.77 (s, 3H, CH_3), 4.91 (d, 2H, CH_2, J = 15.0 Hz), 5.14 (s, 2H, CH_2); 6.95–7.07 (m, 3H), 7.18 (d, J = 7.5 Hz, 2H); 7.39 (d, J = 10.0 Hz, 2H); 8.85 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 21.9 (CH_3), 51.6 (CH_3), 55.8 (CH_3), 55.9 (CH_3), 95.2 (CH_2), 96.0 (CH_2), 111.2 (CH), 116.5 (CH), 119.6 (Cq), 120.2 (CH), 121.5 (CH), 122.8 (CH), 123.0 (Cq), 125.2 (C), 126.0 (Cq), 135.8 (Cq), 136.0 (Cq), 150.6 (Cq), 151.8 (Cq), 162.4 (CO); MS (IS$^+$) m/z 386 $[M + H]^+$.

6.11.19. Methyl 3-(2,5-bis(methoxymethoxy)phenyl)-6-(4-methoxyphenyl)-1H-indole-2-carboxylate (**64**)

Compound **65** was synthesized using the general procedure for Suzuki reaction from **40** and **43** and isolated after 7 h as a beige solid in 60% yield. R_f 0.2 (petroleum ether/EtOAc 8/2); Mp 134 °C; IR (Ge-ATR, cm^{-1}) ν 3307, 3020, 3000, 1717, 1560, 1073, 829; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.27 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.93 (d, J = 12.5 Hz, 2H, OCH_2), 5.11 (s, 2H, OCH_2), 6.98–7.10 (m, 4H, H_{Ar}), 7.16–7.27 (m, 1H, H_{Ar}), 7.33–7.37 (m, 1H, H_{Ar}), 7.52–7.60 (m, 4H, H_{Ar}), 8.97 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 51.7 (OCH_3), 55.3 (OCH_3), 55.8 (OCH_3), 55.9 (OCH_3), 95.2 (OCH_2), 96.0 (OCH_2), 109.2 (CH), 114.2 (2CH), 116.9 (CH), 119.6 (Cq), 120.2 (CH), 120.3 (Cq), 120.6 (Cq), 122.1 (CH), 123.5 (Cq), 123.9 (Cq), 124.5 (Cq), 125.3 (Cq), 127.0 (Cq), 128.3 (CH), 134.1 (Cq), 136.2 (Cq), 138.7 (Cq), 150.6 (Cq), 151.8 (Cq), 159.1 (CO); MS (IS$^+$) m/z 478 $[M + H]^+$.

6.11.20. Ethyl 7-(2,5-Bis(methoxymethoxy)phenyl)-5H- [1,3]dioxolo [4,5-f]indole-6-carboxylate (**65**)

Compound **64** was synthesized using the general procedure for Suzuki reaction from **36** and **43** and isolated after 7 h as a grey solid in 60% yield. R_f 0.2 (petroleum ether/EtOAc 8/2); Mp 112 °C; IR (Ge-ATR, cm^{-1}) ν 3336, 3301, 3020, 3000, 1712, 1547, 1077; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.15 (t, J = 7.5 Hz, 3H, CH_3), 3.26 (s, 3H, CH_3), 3.49 (s, 3H, CH_3), 4.24 (q, J = 7.5 Hz, 2H, CH_2), 4.88 (d, J = 7.5 Hz, 1H, CH_2); 4.94 (d, J = 7.5 Hz, 1H, CH_2), 5.14 (s, 2H, CH_2), 5.94 (s, 2H, CH_2), 6.79 (s, 1H, H_{Ar}), 6.82 (s, 1H, H_{Ar}), 6.99–7.04 (m, 2H, H_{Ar}), 7.14–7.17 (m, 1H, H_{Ar}), 9.07 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 13.9 (CH_3), 55.8 ($2CH_3$), 60.4 (CH_2), 91.5 (CH), 95.1 (CH_2), 95.9 (CH_2), 99.2 (CH), 100.9 (CH_2), 116.4 (CH), 116.9 (CH), 120.1 (CH), 120.2 (Cq), 122.4 (Cq), 122.8 (Cq), 125.4 (Cq), 131.4 (Cq), 144.1 (Cq), 148.0 (Cq), 150.4 (Cq), 151.8 (Cq), 162.4 (CO); MS (IS$^+$) m/z 430 $[M + H]^+$.

6.12. General procedure for ether deprotection and lactonizations

Method ***A***: A mixture of ether derivative (1.0 mmol) in bromhydric solution in acetic acid (30%, 15 mL) was refluxed for the appropriate time. After cooling at room temperature, the mixture

was neutralized using a saturated aqueous solution of $NaHCO_3$. Extraction of the organic material was performed with EtOAc (3 × 60 mL), the combined organic layers were washed with water and then dried over $MgSO_4$ before evaporation to dryness. *Method* ***B***: A mixture of MOM protected derivative (1.0 mmol) in ethanol (45 mL) was saturated by HCl bubbling for 1 h and then refluxed overnight. *Method* ***C***: To a solution of **58a** in DCM (25 mL), a solution of BCl_3 (4.64 mL, 4.64 mmol, 10 eq.) in hexane was added at −78 °C. After stirring for 30 mn then 3 h at rt, DCM (150 mL) was added and the organic layer was washed with brine (2 × 30 mL) then water (2 × 30 mL). After drying over $MgSO_4$ and evaporation the solid residue was purified by chromatography on silica gel. *Method* ***D***. To a solution suspension containing derivative **62** (0.44 mmol) and Pd(C) 10% in EtOH (5 mL), hydrogen gas was bubbled for 30 min. The resulting mixture was stirred under an H_2-atmosphere overnight and then filtered through a pad of celite. The filtrate was concentrated and then dissolved in 4 mL of THF before the addition of potassium carbonate (1.76 mmol). The resulting mixture was stirred under reflux overnight, filtered and finally the filtrate was concentrated to afford the attempted product.

6.12.1. Chromeno[3,4-b]indol-6(7H)-one (**66**)

Compound **66** was synthesized using the general procedure for deprotection and lactonisation *Method* ***A*** from **46**. After 6 h a trituration with Et_2O of the crude material afforded **66** as a beige solid in 80% yield. Mp : >250 °C. IR (Ge-ATR, cm^{-1}) ν 3250, 3020, 1720, 1509, 1257; ^{1}H NMR (DMSO-*d*6, 250 MHz) δ 6.52 (t, J = 7.2 Hz, 1H), 6.6–6.7 (m, 4H) 6.80 (d, J = 8.4 Hz, 1H), 7.5–7.6 (m, 2H), 9.08 (br s, 1H, NH); ^{13}C NMR (DMSO-*d*6, 62.9 MHz) δ 113.3 (CH), 116.8 (CH), 118.2 (Cq), 119.7 (Cq), 121.1 (CH), 121.3 (Cq), 121.5 (CH), 122. (CH), 123.5 (CH), 124.8 (CH), 127.1 (CH), 127.3 (Cq), 139.6 (Cq), 150.2 (Cq), 155.1 (CO); MS (IS^+) m/z 236 $[M + H]^+$.

6.12.2. 3-Hydroxychromeno[3,4-b]indol-6(7H)-one (**67**)

Compound **67** was synthesized using the general procedure for deprotection and lactonisation *Method* ***A*** from **47** after 24 h and purification by flash chromatography (CH_2Cl_2/MeOH 1/1) as a white solid in 66% yield. Mp >250 °C. IR (Ge-ATR, cm^{-1}) ν 3314, 3020, 1679, 1520, 1472, 1258; ^{1}H NMR (DMSO-*d*6, 250 MHz) δ 6.89–6.94 (m, 1H, H_{Ar}), 7.30 (t, J = 7.5 Hz, 1H, H_{Ar}), 7.47–7.61 (m, 2H, H_{Ar}), 8.25 (d, J = 10.0 Hz, 1H, H_{Ar}), 8.39 (d, J = 7.5 Hz, 1H, H_{Ar}) 9.01 (br s, 1H, NH) 12.54 (s, 1H, OH); ^{13}C NMR (DMSO-*d*6, 62.9 MHz) δ 103.2 (CH), 110.2 (Cq), 113.1 (CH), 113.2 (CH), 119.3 (Cq), 120.3 (Cq), 121.0 (CH), 122.6 (CH), 124.4 (CH), 125.4 (Cq), 127.1 (CH), 139.8 (Cq), 151.8 (Cq), 155.5 (Cq), 157.3 (CO); MS (IS^+) m/z 252 $[M + H]^+$. HRMS (ESI-) cald for $C_{15}H_8NO_3$: 251.05097 found 250.0517.

6.12.3. 4-Hydroxychromeno[3,4-b]indol-6(7H)-one (**68**)

Compound **68** was synthesized using the general procedure for deprotection and lactonisation *Method* ***A*** from **48** after 24 h and purification by flash chromatography (CH_2Cl_2/MeOH 1/1) as a white solid in 74% yield. Mp > 250 °C; IR (Ge-ATR, cm^{-1}) ν 3314, 3020, 1679, 1520, 1472, 1258; ^{1}H NMR (DMSO-*d*6, 250 MHz) δ 6.87 (d, J = 2.5 Hz, 1H, H_{Ar}), 6.93–7.70 (m, 5H, H_{Ar}), 8.27 (d, J = 10.0 Hz, 1H, H_{Ar}), 9.68 (br s, 1H, NH), 12.66 (br s 1H, OH); ^{13}C NMR (DMSO-*d*6, 62.9 MHz) δ 108.1 (CH), 113.5 (CH), 115.0 (CH), 117.7 (CH), 118.8 (Cq), 119.7 (Cq), 121.4 (Cq), 121.5 (Cq), 121.6 (CH), 122.0 (CH), 127.0 (CH), 139.6 (Cq), 143.7 (Cq), 154.2 (Cq), 155.4 (CO); MS (IS^+) m/z 252 $[M + H]^+$. HRMS (ESI-) cald for $C_{15}H_8NO_3$: 250.05097 found 250.5116.

6.12.4. 1-Methoxychromeno[3,4-b]indol-6(7H)-one (**69**)

Compound **69** was synthesized using the general procedure for deprotection and lactonisation *Method* ***B*** from **49** after 12 h. After cooling, purification was achieved by simple filtration, washing of the crude material (water, EtOH and Et_2O) and drying under reduced pressure to afford **69** as a beige solid in 90% yield. R_f : 0.2 (petroleum ether/EtOAc 8/2) : Mp >250 °C; IR (Ge-ATR, cm^{-1}) ν 3243, 3020, 2967, 1716, 1515, 1417, 1216; ^{1}H NMR (DMSO-*d*6, 250 MHz) δ 4.11 (s, 3H, OCH_3), 7.08–7.50 (m, 5H, H_{Ar}), 7.59 (d, J = 8.1 Hz, 1H, H_{Ar}), 8.61 (d, J = 8.4 Hz, 1H, H_{Ar}); ^{13}C NMR (DMSO-*d*6, 62.9 MHz) δ 55.5 (OCH_3), 106.7 (CH), 109.1 (Cq), 109.7 (CH), 112.8 (CH), 118.6 (Cq), 120.7 (CH), 120.9 (Cq), 122.2 (Cq), 126.4 (CH), 126.7 (CH), 127.6 (CH), 140.0 (Cq), 151.2 (Cq), 155.0 (Cq), 155.1 (Cq); MS (IS^+) m/z 266 $[M + H]^+$. HRMS (ESI+) calcd for $C_{16}H_{12}N0_3$: 266.08117 found 266.08086.

6.12.5. 11-(4-Hydroxyphenyl)chromeno[3,4-b]indole-6(7H)-one (**70**)

Compound **70** was synthesized using the general procedure for deprotection and lactonisation *Method* ***A*** from **50** after 24 h and purification by flash chromatography (petroleum ether/EtOAc 8/2 to 1/1) as a yellow solid in 50% yield. R_f 0.3 (petroleum ether/EtOAc 8/2); Mp >250 °C; IR (Ge-ATR, cm^{-1}) ν 3332, 3020, 1700, 1583, 1497, 1228, 834; ^{1}H NMR (DMSO-*d*6, 250 MHz) δ 6.32 (d, J = 7.5 Hz, 1H, H_{Ar}), 6.75 (t, J = 7.5 Hz, 1H, H_{Ar}), 6.87 (d, J = 7.5 Hz, 2H, H_{Ar}), 7.15 (d, J = 7.5 Hz, 1H, H_{Ar}), 7.22–7.24 (m, 3H, H_{Ar}), 7.40 (d, J = 7.5 Hz, 1H, H_{Ar}), 7.52 (t, J = 7.5 Hz, 1H, H_{Ar}), 7.61 (d, J = 7.5 Hz, 1H, H_{Ar}), 9.67 (s, 1H, OH), 12.91 (s, 1H, NH); ^{13}C NMR (DMSO-*d*6, 62.9 MHz) δ 111.7 (CH), 115.2 (2CH), 116.4 (CH), 117.6 (Cq), 119.6 (Cq), 120.0 (Cq), 120.3 (Cq), 122.1 (Cq), 123.0 (CH), 123.3 (CH), 126.5 (CH), 126.6 (CH), 126.6 (CH), 130.2 (2CH), 133.1 (Cq), 137.8 (Cq), 140.4 (Cq), 150.1 (Cq), 155.3 (Cq), 157.2 (CO); MS (IS^+) m/z 328 $[M + H]^+$. HRMS (ESI-) cald for $C_{21}H_{12}NO_3$: 326.08227 found 326.08241.

6.12.6. 2-Hydroxy-11-(4-hydroxyphenyl)chromeno[3,4-b]indole-6(7H)-one (**71**)

Compound **71** was synthesized using the general procedure for deprotection and lactonisation *Method* ***A*** from **51** after 24 h and purification by flash chromatography (petroleum ether/EtOAc 8/2) as a yellow solid in 54% yield. R_f 0.3 (petroleum ether/EtOAc 8/2); Mp >250 °C. IR (Ge-ATR, cm^{-1}) ν 3317, 3020, 1671, 1583, 1497, 1218, 836; ^{1}H NMR (DMSO-*d*6, 250 MHz) δ 5.77 (d, J = 2.5 Hz, 1H, H_{Ar}), 6.72 (dd, J = 2.5 Hz, J = 7.5 Hz, 1H, H_{Ar}), 6.83–6.87 (m, 2H, H_{Ar}), 7.11–7.23 (m, 4H, H_{Ar}), 7.47–7.61 (m, 2H, H_{Ar}), 8.96 (br s, 1H, OH), 9.58 (br s, 1H, OH), 12.8 (br s, 1H, NH); ^{13}C NMR (DMSO-*d*6, 62.9 MHz) δ 111.5 (CH), 113.13 (CH), 113.8 (CH), 115.1 (2CH), 116.6 (CH), 118.4 (Cq), 120.18 (Cq), 122.2 (Cq), 123.4 (CH), 126.5 (CH), 129.9 (2CH), 132.7 (Cq), 137.9 (Cq), 140.3 (Cq), 143.4 (Cq), 152.8 (Cq), 155.6 (Cq), 157.3 (CO); MS (IS^+) m/z 344 $[M + H]^+$. HRMS (ESI-) cald for $C_{21}H_{12}NO_4$: 342.07718 found 342.07734. HRMS (ESI-) calcd for $C_{21}H_{12}NO_4$: 343.08446 found 343.08426.

6.12.7. 2-Hydroxy-11-methylchromeno[3,4-b]indol-6(7H)-one (**72**)

Compound **72** was synthesized using the general procedure for deprotection and lactonisation *Method* ***B*** from **52** after 12 h. After cooling, purification was achieved by simple filtration, washing of the crude material (water, EtOH and Et_2O) and drying under reduced pressure to afford **72** as a beige solid in 93% yield. R_f 0.3 (petroleum ether/EtOAc 9/1); Mp >250 °C; IR (Ge-ATR, cm^{-1}) ν 3290, 3020, 1676, 1569, 1239; ^{1}H NMR (DMSO-*d*6, 400 MHz) δ 3.04 (s, 3H, CH_3), 6.86 (dd, J = 2.4 Hz, J = 8.0 Hz, 1H, H_{Ar}), 7.09 (d, J = 8.0 Hz, 1H, H_{Ar}), 7.36 (t, J = 8.0 Hz, 1H, H_{Ar}), 7.45 (d, J = 8.0 Hz, 1H, H_{Ar}), 8.05 (d, J = 8.0 Hz, 1H), 8.45 (d, J = 2.4 Hz, 1H, H_{Ar}), 9.69 (br s, 1H, OH), 12.70 (br s, 1H, NH); ^{13}C NMR (DMSO-*d*6, 100.6 MHz) δ 25.9 (CH_3), 110.6 (CH), 111.2 (CH), 114.6 (CH), 118.0 (Cq), 118.8 (Cq), 120.5 (Cq), 121.8 (Cq), 122.0 (Cq), 123.7 (CH), 126.8 (CH), 132.2 (Cq), 143.4 (Cq), 153.7 (Cq), 155.5 (CO); MS (IS^+) m/z 266 $[M + H]^+$. HRMS (ESI-) calcd for $C_{16}H_{11}NO_3$: 264.06996 found 265.0739.

*6.12.8. 2-Hydroxy-11-methoxychromeno[3,4-b]indol-6(7H)-one (**73**)*

Compound **73** was synthesized using the general procedure for deprotection and lactonisation *Method **B*** from **53** after 12 h. After cooling, purification was achieved by simple filtration, washing of the crude material (water, EtOH and Et_2O) and drying under reduced pressure to afford **73** as a beige solid in 93% yield. R_f 0.2 (petroleum ether/EtOAc 9/1); Mp >250 °C; IR (Ge-ATR, cm^{-1}) ν 3343, 3020, 1673, 1571, 1438, 1236; ^{1}H NMR (DMSO-*d*6, 400 MHz) δ 4.10 (s, 3H, OCH_3), 6.78 (d, J = 8.0 Hz, 1H, H_{Ar}), 6.85 (dd, J = 4.0 Hz, J = 8.0 Hz, 1H, H_{Ar}), 7.18 (d, J = 8.0 Hz, 1H, H_{Ar}), 7.30 (d, J = 4.0 Hz, 1H, H_{Ar}), 7.42 (t, J = 8.0 Hz, 1H, H_{Ar}), 8.49 (d, J = 3.2 Hz, 1H, H_{Ar}), 9.61 (br s, 1H, OH), 12.60 (br s, 1H, NH); ^{13}C NMR (DMSO-*d*6, 100.6 MHz) δ 55.3 (OCH_3), 101.2 (CH), 105.9 (CH), 112.0 (CH), 112.6 (Cq), 115.0 (CH), 117.4 (CH), 118.5 (Cq), 120.8 (Cq), 128.3 (CH), 141.4 (Cq), 143.8 (Cq), 153.6 (Cq), 154.6 (Cq), 155.3 (CO); MS (IS^+) m/z 282 $[M + H]^+$. HRMS (ESI-) calcd for $C_{16}H_{10}NO_4$: 280.06098 found 280.06115.

*6.12.9. 2-Hydroxy-11-(trifluoromethyl)chromeno[3,4-b]indol-6(7H)-one (**74**)*

Compound **74** was synthesized using the general procedure for deprotection and lactonisation *Method **B*** from **54** after 12 h. After cooling, purification was achieved by simple filtration, washing of the crude material (water, EtOH and Et_2O) and drying under reduced pressure to afford **73** as a beige solid in 50% yield. R_f 0.2 (petroleum ether/EtOAc 9/1); Mp >250 °C; IR (Ge-ATR, cm^{-1}) ν 3384, 3020, 1676, 1549, 1289; ^{1}H NMR (DMSO-*d*6, 400 MHz) δ 6.92 (dd, J = 4.0 Hz, J = 13.5 Hz, 1H, H_{Ar}), 7.39 (d, J = 8.0 Hz, 1H, H_{Ar}), 7.74 (s, 1H, H_{Ar}), 7.81 (s, 2H, H_{Ar}), 8.56 (br s, 1H, H_{Ar}), 9.73 (s, 1H, OH), 13.10 (br s, 1H, NH); ^{13}C NMR (DMSO-*d*6, 100.6 MHz) δ 108.0 (CH), 114.5 (CH), 115.5 (CH), 117.8 (CH), 118.0 (Cq), 119.6 (CH), 120.2 (Cq), 120.5 (Cq), 121.8 (Cq), 122.2 (Cq), 123.0 (CH), 123.2 (q, CF_3, J = 268 Hz), 140.8 (Cq), 143.7 (Cq), 154.3 (Cq), 155.0 (CO); MS (IS^+) m/z 320 $[M + H]^+$.

*6.12.10. 2-Hydroxy-11-propoxychromeno[3,4-b]indol-6(7H)-one (**75**)*

Compound **75** was synthesized using the general procedure for deprotection and lactonisation *Method **B*** from **55** after 12 h. After cooling the purification was achieved by simple filtration, washing of the crude material (water, EtOH and Et_2O) and drying under reduced pressure to afford **75** as a beige solid in 76% yield. R_f 0.2 (petroleum ether/EtOAc 9/1); Mp 240 °C; IR (Ge-ATR, cm^{-1}) ν 3289, 3158, 3020, 1672, 1567, 1228; ^{1}H NMR (DMSO-*d*6, 400 MHz) δ 1.10 (t, J = 6.2 Hz, 3H, CH_3), 1.98–2.08 (m, 2H, CH_2), 4.25 (t, J = 6.2 Hz, 2H, OCH_2), 6.67–6.78 (m, 2H, H_{Ar}), 6.86–6.92 (m, 1H, H_{Ar}), 7.16 (d, J = 7.5 Hz, 1H, H_{Ar}), 7.29 (d, J = 7.5 Hz, 1H, H_{Ar}), 7.37 (d, J = 7.5 Hz, 1H, H_{Ar}), 9.36 (s, 1H, OH), 12.6 (br s, 1H, NH); ^{13}C NMR (DMSO-*d*6, 100.6 MHz) δ 10.5 (CH_3), 21.6 (CH_2), 69.9 (OCH_2), 101.9 (CH), 105.8 (CH), 112.6 (CH), 112.8 (Cq), 114.8 (CH), 117.1 (CH), 118.8 (Cq), 120.7 (Cq), 120.8 (Cq), 128.2 (CH), 141.5 (Cq), 143.8 (Cq), 153.7 (Cq), 153.9 (Cq), 155.3 (CO); MS (IS^+) m/z 310 $[M + H]^+$. HRMS (ESI-) calcd for $C_{18}H_{14}NO_4$: 308.09228 found 308.09256.

*6.12.11. 3,10-Dihydroxychromeno[3,4-b]indol-6(7H)-one (**76**)*

Compound **76** was synthesized using the general procedure for deprotection and lactonisation *Method **A*** from **56** after 24 h and purification by flash chromatography (CH_2Cl_2/MeOH 9/1) as a yellow solid in 70% yield. R_f 0.3 (CH_2Cl_2/MeOH 9/1); Mp >250 °C; IR (Ge-ATR, cm^{-1}) ν 3300, 3020, 1727, 1677, 1520–1472; 1211. ^{1}H NMR (DMSO-*d*6, 250 MHz) δ (ppm) : 6.87 (d, J = 2.3 Hz, 1H), 6.93 (dd, J = 8.3, 2.3 Hz, 1H), 7.07 (dd, J = 8.8 Hz, 1.8 Hz, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.57 (d, J = 1.8 Hz, 1H), 8.02 (d, J = 8.3 Hz, 1H), 9.29 (br s, 1H, OH), 10.03 (br s, 1H, OH), 12.19 (br s, 1H, NH); ^{13}C NMR (DMSO-*d*6, 62.9 MHz) δ 103.2 (CH), 105.1 (CH), 110.5 (Cq), 113.0 (CH), 113.9 (CH), 118.5 (CH) 119.5 (Cq), 119.8 (Cq), 121.6 (Cq), 123.8 (CH), 134.5 (Cq), 151.5 (Cq), 152.1 (Cq), 155.5 (Cq), 156.9 (CO); MS (IS^+) m/z 268 $[M + H]^+$. HRMS (ESI-) calcd for $C_{15}H_8NO_4$: 266.04588 found 266. 04594.

*6.12.12. 2,10-Dihydroxychromeno[3,4-b]indol-6(7H)-one (**77**)*

Compound **77** was synthesized using the general procedure for deprotection and lactonisation *Method **A*** from **57** after 24 h and purification by flash chromatography (CH_2Cl_2/MeOH 9/1) as a yellow solid in 65% yield. R_f 0.3 (CH_2Cl_2/MeOH 9/1); Mp >250 °C; IR (Ge-ATR, cm^{-1}) ν 3300, 3020; 1727, 1659, 1520, 1472, 1212, 748; ^{1}H NMR (DMSO-*d*6, 250 MHz) δ 6.86 (dd, J = 2.5 Hz, J = 7.5 Hz, 1H, H_{Ar}), 7.08 (dd, J = 2.5 Hz, J = 10.0 Hz, 1H, H_{Ar}), 7.34 (d, J = 7.5 Hz, 1H, H_{Ar}), 7.45–7.53 (m, 3H, H_{Ar}), 9.38 (br s, 1H, OH), 9.67 (br s, 1H, OH), 12.41 (br s, 1H, NH), ^{13}C NMR (DMSO-*d*6, 62.9 MHz) δ 104.7 (CH), 107.7 (CH), 114.2 (CH), 114.5 (CH), 117.7 (CH), 118.4 (CH), 118.5 (Cq), 119.2 (Cq), 121.5 (Cq), 122.0 (Cq), 134.3 (Cq), 143.4 (Cq), 152.5 (Cq), 154.2 (Cq), 155.4 (CO); MS (IS^+) m/z 268 $[M + H]^+$. HRMS (ESI-) calcd for $C_{15}H_8NO_4$: 266. 04588 found 266.04599.

*6.12.13. 2,3,10-Trihydroxychromeno[3,4-b]indol-6(7H)-one (**78**)*

Compound **78** was obtained in two steps. Starting from **58**, application of the general *Method **B*** in order to remove the MOM group and to achieve lactonisation led to 10-benzyloxy-3-isopropoxy-2-methoxychromeno[3,4-*b*]indol-6(7*H*)-one (**58a**) as a white solid after 12 h and trituration with water in a 40% yield. Compound **58a** was next used in the deprotection procedure *Method **C*** to achieve synthesis. Compound ***78*** was isolated as a white solid after 3 h and a flash chromatography (CH_2Cl_2/MeOH 8/2) as a white solid in 32% yield. Compound **58a** : R_f 0.2 (petroleum ether 7/3); Mp >250 °C; IR (Ge-ATR, cm^{-1}) ν 3258, 2977; 1698, 1569, 1483, 1106; ^{1}H NMR (DMSO-*d*6, 250 MHz) δ 1.31 (d, J = 5.0 Hz, 6H, $2CH_3$), 3.97 (s, 3H, OCH_3), 4.70–4.74 (m, 1H, CH), 5.33 (s, 2H, CH_2), 7.20 (s, 1H, H_{Ar}), 7.26–7.43 (m, 4H, H_{Ar}), 7.51–7.58 (m, 4H, H_{Ar}), 7.73 (s, 1H, H_{Ar}), 12.42 (br s, 1H, NH); ^{13}C NMR (DMSO-*d*6, 100.6 MHz) δ 21.6 ($2CH_3$), 56.2 (OCH_3), 69.6 (CH_2), 70.5 (Cq), 99.4 (Cq), 103.7 (CH), 104.4 (CH), 105.4 (CH), 105.43 (Cq), 110.5 (Cq), 114.2 (CH), 118.8 (CH), 119.8 (Cq), 120.3 (Cq), 120.9 (CH), 127.4 (CH), 127.6 (CH), 128.3 (CH), 135.1 (Cq), 137.4 (Cq), 139.0 (CH), 144.8 (Cq), 146.4 (Cq), 147.1 (Cq), 153.3 (Cq), 155.4 (CO); MS (IS^+) m/z 430 $[M + H]^+$. Compound **78** : R_f 0.2 (DCM/MeOH 8/2); Mp >250 °C; IR (Ge-ATR, cm^{-1}) ν 3249, 1772, 1659, 1598, 1484, 1212, 779; ^{1}H NMR (DMSO-*d*6, 250 MHz) δ 6.89 (s, 1H, H_{Ar}), 7.06 (d, J = 8.0 Hz, 1H, H_{Ar}), 7.41–7.52 (m, 3H, H_{Ar}), 9.32 (s, 1H, OH), 9.62 (s, 1H, OH), 12.13 (br s, 1H, NH); ^{13}C NMR (DMSO-*d*6, 100.6 MHz) δ 104.3 (CH), 105.2 (CH), 108.3 (CH), 110.4 (Cq), 114.4 (CH), 118.8 (CH), 120.2 (Cq), 120.3 (Cq), 122.0 (Cq), 134.9 (Cq), 143.5 (Cq), 144.5 (Cq), 145.9 (Cq), 152.5 (Cq), 156.2 (CO); MS (IS^+) m/z 284 $[M + H]^+$. HRMS (ESI-) calcd for $C_{15}H_8NO_5$: 282.04080 found 282.04090.

*6.12.14. 2-Hydroxy-10-(trifluoromethyl)chromeno[3,4-b]indol-6(7H)-one (**79**)*

Compound **79** was synthesized using the general procedure for deprotection and lactonisation *Method **B*** from **59** after 12 h. After cooling, purification was achieved by simple filtration, washing of the crude material (water, EtOH and Et_2O) and drying under reduced pressure to afford **79** as a beige solid in 50% yield. R_f 0.2 (petroleum ether/EtOAc 9/1); Mp >250 °C; IR (Ge-ATR, cm^{-1}) ν 3369, 3020, 1662, 1549, 1228; ^{1}H NMR (DMSO-*d*6, 250 MHz) δ 6.92 (d, J = 8.0 Hz, 1H, H_{Ar}), 7.39 (d, J = 8.0 Hz, 1H, H_{Ar}), 7.75 (s, 1H, H_{Ar}), 7.81 (s, 2H, H_{Ar}), 8.57 (br s, 1H, H_{Ar}), 9.74 (s, 1H, OH), 13.1 (br s, 1H, NH); ^{13}C NMR (DMSO-*d*6, 100.6 MHz) δ 108.0 (CH), 114.5 (CH), 115.5 (CH), 117.8 (CH), 117.9 (Cq), 119.6 (Cq), 119.6 (CH), 120.2 (Cq), 120.5 (2Cq), 123.0 (CH), 123.2 (Cq), 140.8 (Cq), 143.7 (Cq), 154.3 (Cq), 155.0 (Cq); MS (IS^+) m/z 320 $[M + H]^+$.

*6.12.15. 2-Hydroxy-10-fluorochromeno[3,4-b]indol-6(7H)-one (**80**)*

Compound **80** was synthesized using the general procedure for deprotection and lactonisation *Method **B*** from **60** after 12 h. After cooling, purification was achieved by simple filtration, washing of the crude material (water, EtOH and Et_2O) and drying under reduced pressure to afford **80** as a pale brown solid in 80% yield. R_f 0.2 (petroleum ether/EtOAc 9/1); Mp >250 °C; IR (Ge-ATR, cm^{-1}) ν 3305, 3020, 1719, 1673, 1523, 1253, 1236; ^1H NMR (DMSO-*d*6, 250 MHz) δ 6.90 (d, J = 5.0 Hz, 1H, H_{Ar}), 7.39 (dd, J = 8.0 Hz, J = 24.0 Hz, 2H, H_{Ar}),7.64–7.66 (m, 3H, H_{Ar}), 8.01 (br s, 1H, OH), 9.6 (br s, 1H, NH); ^{13}C NMR (DMSO-*d*6, 100.6 MHz) δ 106.3 (CH), 106.5 (CH), 107.9 (CH), 114.7 (Cq), 114.8 (Cq), 115.7 (CH), 115.9 (CH), 117.5 (CH), 118.3 (Cq), 119.3 (Cq), 122.7 (Cq), 136.1 (Cq), 143.3 (Cq), 154.1 (Cq), 155.0 (CO); MS (IS^+) m/z 270 $[M + H]^+$. HRMS (ESI-) calcd for $C_{15}H_7FNO_3$: 268.04154 found 268.04200.

*6.12.16. 2,9-Dihydroxychromeno[3,4-b]indol-6(7H)-one (**81**)*

Compound **81** was synthesized using the general procedure for deprotection and lactonisation *Method **A*** from **61** after 24 h. After cooling purification was achieved by simple filtration, washing of the crude material (water, EtOH and Et_2O) and drying under reduced pressure to afford **81** as a pale grey solid in 22% yield. R_f 0.2 (petroleum ether/EtOAc 9/1); Mp >250 °C; IR (Ge-ATR, cm^{-1}) ν 3325, 3020, 1692, 1544, 1491, 1244, 1220; ^1H NMR (DMSO-*d*6, 250 MHz) δ 6.86–6.94 (m, 3H, H_{Ar}), 7.32 (d, J = 10.0 Hz, 1H, H_{Ar}), 7.62 (s, 1H, H_{Ar}), 8.07 (d, J = 10.0 Hz, 1H, H_{Ar}), 9.66 (br s, 1H, OH), 9.89 (br s, 1H, OH), 12.23 (sl, 1H, NH); ^{13}C NMR (DMSO-*d*6, 100.6 MHz) δ 97.1 (CH), 107.9 (CH), 113.2 (CH), 114.7 (Cq), 114.9 (CH), 117.6 (CH), 118.7 (Cq), 120.0 (Cq), 120.4 (Cq), 122.8 (CH), 141.6 (Cq), 143.7 (Cq), 154.0 (Cq), 155.1 (Cq), 157.5 (Cq); MS (IS^+) m/z 268 $[M + H]^+$. (ESI-) calcd for $C_{15}H_8NO_4$: 266.04588 found 266.04556.

*6.12.17. 3,9-Dihydroxychromeno[3,4-b]indol-6(7H)-one (**82**)*

Compound **82** was synthesized using the general procedure for deprotection and lactonisation *Method **D*** from **87** after 12 h for hydrogenolysis and 12 h for basic treatment. After cooling purification was achieved by simple filtration, washing of the crude material (water, EtOH and Et_2O) and drying under reduced pressure to afford **82** as a beige solid in 51% yield. R_f 0.2 (petroleum ether/EtOAc 9/1); Mp >250 °C; IR (Diamond ATR, cm^{-1}) ν 3302, 1721, 1589, 1456, 1245; ^1H NMR (DMSO-*d*6, 250 MHz) δ 6.85–6.91 (m, 2H, H_{Ar}), 7.56–7.63 (m, 3H, H_{Ar}), 8.17 (dd, J = 8.8 Hz, J = 3.5 Hz, 1H, H_{Ar}), 8.18 (br s, 1H, OH), 10.05 (br s, 1H, OH), 12.00 (br s, 1H, NH); ^{13}C NMR (DMSO-*d*6, 62.9 MHz) δ 98.8 (CH), 104.9 (CH), 112.1 (CH), 114.9 (CH), 116.4 (Cq), 119.6 (CH), 123.7 (Cq), 125.4 (Cq), 126.3 (Cq), 134.0 (CH), 143.8 (Cq), 153.9 (Cq), 157.2 (Cq), 159.2 (Cq), 159.6 (Cq); MS (IS^+) m/z 268 $[M + H]^+$. HRMS (ESI-) calcd for $C_{15}H_8NO_4$: 267.04588 found 267.04563.

*6.12.18. 2-Hydroxy-9-methylchromeno[3,4-b]indol-6(7H)-one (**83**)*

Compound **83** was synthesized using the general procedure for deprotection and lactonisation *Method **B*** from **63** after 12 h. After cooling, purification was achieved by simple filtration, washing of the crude material (water, EtOH and Et_2O) and drying under reduced pressure to afford **83** as a beige solid in 73% yield. R_f 0.2 (petroleum ether/EtOAc 9/1); Mp > 250 °C; IR (Ge-ATR, cm^{-1}) ν 3325, 3020; 1666, 1598; 1245; ^1H NMR (DMSO-*d*6, 250 MHz) δ 2.56 (s, 3H, CH_3), 6.89 (dd, J = 1.5 Hz, J = 5.0 Hz, 1H, H_{Ar}), 7.21 (d, J = 5.0 Hz, 1H, H_{Ar}), 7.36 (d, J = 5.0 Hz, 1H, H_{Ar}), 7.42 (s, 1H, H_{Ar}), 7.67 (d, J = 2.5 Hz, 1H, H_{Ar}), 8.14 (d, J = 5.0 Hz, 1H, H_{Ar}), 9.67 (br s, 1H, OH), 12.52 (br s, 1H, NH); ^{13}C NMR (DMSO-*d*6, 100.6 MHz) δ 21.4 (CH_2), 108.0 (CH), 112.8 (CH), 114.8 (CH), 117.6 (CH), 118.7 (Cq), 119.2 (Cq), 119.7 (Cq), 120.8 (Cq), 121.5 (CH), 123.5 (CH), 136.9 (Cq), 140.1 (Cq), 143.6 (Cq), 154.0 (Cq), 155.3 (CO);. MS (IS^+) m/z 266 $[M + H]^+$. HRMS (ESI-) calcd for $C_{16}H_{11}NO_3$: 264.06996 found 265.06957.

*6.12.19. 2-Hydroxy-9-(4-methoxyphenyl)chromeno[3,4-b]indol-6(7H)-one (**84**)*

Compound **84** was synthesized using the general procedure for deprotection and lactonisation *Method **B*** from **64** after 12 h. After cooling, purification was achieved by simple filtration, washing of the crude material (water, EtOH and Et_2O) and drying under reduced pressure to afford **84** as a pale grey solid in 80% yield. R_f 0.2 (petroleum eter/EtOAc 9/1); Mp >250 °C; IR (Ge-ATR, cm^{-1}) ν 3255, 3020, 1692, 1544, 1491, 1244, 1220, 824; ^1H NMR (DMSO-*d*6, 400 MHz) δ 3.81 (s, 3H, CH_3), 6.91 (d, J = 8.0 Hz, 1H, H_{Ar}), 7.07 (d, J = 8.0 Hz, 2H, H_{Ar}), 7.37 (d, J = 8.0 Hz, 1H, H_{Ar}), 7.62–7.76 (m, 4H, H_{Ar}), 8.30 (d, J = 8.0 Hz, 1H, H_{Ar}), 8.14 (d, J = 8.0 Hz, 1H, H_{Ar}), 9.74 (br s, 1H, OH), 12.6 (br s, 1H, NH); ^{13}C NMR (DMSO-*d*6, 100.6 MHz) δ 55.1 (OCH_3), 108.1 (CH), 110.1 (CH), 114.4 (2CH), 115.0 (CH), 117.7 (CH), 118.7 (Cq), 119.7 (Cq), 120.1 (Cq), 120.8 (CH), 121.7 (Cq), 122.3 (CH), 128.0 (2CH), 132.4 (Cq), 138.9 (Cq), 140.3 (Cq), 143.7 (Cq), 154.2 (Cq), 155.2 (Cq), 159.0 (CO); MS (IS^+) m/z 358 $[M + H]^+$. HRMS (ESI-) calcd for $C_{22}H_{15}NO_4$: 356.09283 found 356.09295.

*6.12.20. 2-Hydroxy- [1,3]dioxolochromeno[3,4-b]indol-6(7H)-one (**85**)*

Compound **85** was synthesized using the general procedure for deprotection and lactonisation *Method **B*** from **65** after 12 h. After cooling, purification was achieved by simple filtration, washing of the crude material (water, EtOH and Et_2O) and drying under reduced pressure to afford **85** as a white solid in 70% yield. R_f 0.2 (petroleum ether/EtOAc 9/1); Mp > 250 °C; IR (Ge-ATR, cm^{-1}) ν 3366–3300, 3020, 1712–1671, 1547, 1244, 1220, 1051; ^1H NMR (DMSO-*d*6, 250 MHz) δ 6.14 (s, 2H, CH_2), 6.68 (dd, J = 2.5 Hz, J = 7.5 Hz, 1H, H_{Ar}), 7, 6.89 (s, 1H, H_{Ar}), 7.32 (d, J = 7.5 Hz, 1H, H_{Ar}), 7.60 (d, J = 2.5 Hz, 1H, H_{Ar}), 7.64 (s, 1H, H_{Ar}), 9.58 (br s, 1H, OH), 12.5 (br s, 1H, NH); ^{13}C NMR (DMSO-*d*6, 62.9 MHz) δ 92.7 (CH), 99.0 (CH), 101.0 (OCH_2), 107.9 (CH), 114.6 (CH), 114.9 (Cq), 117.5 (CH), 118.6 (Cq), 119.9 (2Cq), 136.1 (Cq), 143.5 (Cq), 144.5 (Cq), 148.6 (Cq), 154.0 (Cq), 154.8 (Cq); MS (IS^+) m/z 296 $[M + H]^+$. HRMS (ESI-) calcd for $C_{16}H_8NO_5$: 294.04080 found 294.04092.

*6.13. 2-(2,4-Bis(benzyloxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**86**)*

This compound was synthesized as described for **45** from 2,4-bis(benzyloxy)bromobenzene. The crude product was subjected to silica gel flash chromatography (petroleum ether/EtOAc 95/5 to 10/90) to afford **86** as colourless oil in 62% yield. R_f 0.80 (petroleum ether/EtOAc 90/10); IR (Ge-ATR, cm^{-1}) ν 1454, 1499, 1570, 1602, 2976, 3031; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.35 (s, 12H, CH_3), 5.06 (s, 2H, CH_2), 5.08 (s, 2H, CH_2), 6.57–6.64 (m, 2H, H_{Ar}), 7.17–7.41 (m, 8H, H_{Ar}), 7.60–7.69 (m, 3H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 24.9 (4CH), 69.8 (CH_2), 69.9 (CH2), 83.1 (2xCq), 100.3 (CH), 105.9 (CH), 126.6 (2CH), 127.2 (CH), 127.5 (2CH), 128.0 (CH), 128.1 (2CH), 128.5 (2CH), 136.7 (Cq), 137.5 (CH), 138.1 (Cq), 162.7 (Cq), 164.9 (Cq); HRMS (ESI) calcd for $C_{26}H_{29}O_4NaB$: 439.2057. Found: 439.2037.

*6.14. Methyl 6-(benzyloxy)-3-(2,4-bis(benzyloxy)phenyl)-1H-indole-2-carboxylate (**87**)*

This compound was synthesized according to the typical procedure for the Suzuki reaction leading to a type **II** compound starting from the indole derivative **31** and boron derivative **86** to afford after a silica gel flash chromatography (petroleum ether/EtOAc 80/20) compound **87** as an orange oil in 55% yield. R_f 0.30 (petroleum ether/EtOAc 80/10); IR (Ge-ATR, cm^{-1}) ν 1453, 1502, 1555, 1612, 1696, 3031, 3329; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.70 (s,

3H, CH_3), 4.98 (s, 2H, CH_2), 5.10 (s, 2H, CH_2), 5.13 (s, 2H, CH_2), 6.67–6.75 (m, 2H, H_{Ar}), 6.85–6.90 (m, 2H, H_{Ar}), 7.12–7.50 (m, 17H, H_{Ar}), 8.80 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 51.5 (CH), 70.2 (CH_2), 70.3 (CH_2), 70.4 (CH_2), 94.8 (CH), 101.3 (CH), 105.6 (CH), 112.4 (CH), 116.2 (Cq), 119.9 (Cq), 122.6 (Cq), 123.0 (CH), 123.1 (Cq), 126.8 (2xCH), 127.4 (2CH), 127.7 (2CH), 127.8 (CH), 127.9 (CH), 128.0 (CH), 128.2 (2xCH), 128.6 (4CH), 132.4 (CH), 136.5 (Cq), 136.9 (Cq), 137.0 (Cq), 137.1 (Cq), 157.5 (Cq), 158.1 (Cq), 159.6 (Cq), 162.3 (Cq); HRMS (ESI) calcd for $C_{37}H_{32}NO_5$: 570.2280. Found: 570.2287.

6.15. Kinase assays

Were performed as previously described [26].

6.16. DNA binding measurements

Were performed as previously described [27].

6.17. Topoisomerase inhibition assays and cell culture and survival assays

Were performed as previously described [28].

6.18. Molecular modelling

Hardware and software: all molecular modelling studies were performed with Schrodinger Molecular Modelling Suite 2011 [25]. Maestro is the interface piloting the diverse modules. Glide was used to dock ligands. Calculations were run on a Linux station: Intel® Core ™ i7 CPU 950 @ 3.07 GHz.

Structures preparation: DYRK1A in complex with 7-methoxy-1-methyl-9*H*-pyrido[3,4-*b*]indole (HRM) was retrieved from the protein data bank, PDB code 3anr [29]. Subunit B was conserved and subunits A, C and D were removed in DYRK1A because of more missing residues or atoms than in subunit A. Structure was next prepared using the workflow Protein Preparation Wizard of the Schrodinger Molecular Modelling Suite 2011. The protein was pre-processed (hydrogen atoms added, incomplete residues filled …), bond orders and connections of ligands were manually corrected. An exhaustive sampling was conducted regarding hydrogen bond assignment and the complex was finally refined by a minimization stage with a constraint to converge to a structure with an RMSD of 0.3 Å (OPLS2005 force field), essentially in order to remove steric clashes. Ligands, other than the one co-crystallized, were built within Marvin [30] and were submitted to Corina [31], a 3D structure generator. Next 3D structures were submitted to the LigPrep module of the Schrodinger Molecular Modelling Suite 2011 in order to take into account tautomerization and ionization *via* the Ionizer module. The resulting structures became the starting point for docking simulations.

Docking parameters: docking calculations were performed with extra precision. Ligand flexibility was taken into account and the option of sampling of ring conformation was activated.

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Appendix. Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejmech.2012.01.040.

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